International consensus statement on the diagnosis and management of phaeochromocytoma and paraganglioma in children and adolescents

Ruth T. Casey[1,2†], Emile Hendriks[3], Cheri Deal[4], Steven G. Waguespack[5], Verena Wiegering[6], Antje Redlich[7], Scott Akker[8], Rathi Prasad[9], Martin Fassnacht[10], Roderick Clifton-Bligh[11], Laurence Amar[12], Stefan Bornstein[13], Letizia Canu[14, 15], Evangelia Charmandari[16], Alexandra Chrisoulidou[17], Maria Currás Freixes[18], Ronald de Krijger[19,20], Luisa de Sanctis[21], Antonio Fojo[22], Amol Ghia[23], Angela Huebner[24], Vasilis Kosmoliaptsis[25,,26], Michaela Kuehlen[27], Marco Raffaelli[28,29], Charlotte Lussey-Lepoutre[30], Stephen D. Marks[31], Naris Nilubol[32], Mirko Parasiliti-Caprino[33], Henri H.J.L.M. Timmers[34], Anna Lena Zietlow[35], Mercedes Robledo[18], Anne-Paule Gimenez-Roqueplo[36,,37], Ashley Grossman[38,39,40], David Taïeb[41], Eamonn R. Maher[1], Jacques W.M. Lenders[34], Graeme Eisenhofer[13], Camilo Jimenez[5], Karel Pacak[42] and Christina Pamporaki[13†]

1. Department of Medical Genetics, University of Cambridge and NIHR Cambridge Biomedical Research Centre, Cambridge, UK

2. Department of Endocrinology,Cambridge Cancer Centre and Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.

3. Department of Paediatric Diabetes and Endocrinology, Cambridge Cancer Centre and Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.

4. Endocrine and Diabetes Service, CHU Sainte-Justine and University of Montreal, Montreal, Québec, Canada.

5. Department of Endocrine Neoplasia and Hormonal Disorders, the University of Texas MD Anderson Cancer Center, Houston, TX, USA.

6. University Children's Hospital, Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, University of Wuerzburg, Wuerzburg, Germany.

7. Pediatric Oncology Department, Otto von Guericke University Children's Hospital, Magdeburg, Germany.

8. St Bartholomew's Hospital, Barts Health NHS Trust, London, UK.

9. Centre for Endocrinology, William Harvey Research Institute, Queen Mary University of London, London, UK.

10. Department of Medicine, Division of Endocrinology and Diabetes, University Hospital, University of Würzburg, Würzburg, Germany.

11. Department of Diabetes and Endocrinology, Royal North Shore Hospital, Sydney, NSW, Australia.

12. Université de Paris, Paris, France; Hypertension Unit, Hôpital Européen Georges Pompidou, Assistance Publique - Hôpitaux de Paris, Paris, France.

13. Department of Medicine III, University Hospital Carl Gustav Carus, Medical Faculty Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany.

14. Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy.

15. Centro di Ricerca e Innovazione sulle Patologie Surrenaliche, Azienda Ospedaliera Universitaria (AOU) Careggi, Florence, Italy.

16. Division of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, National and Kapodistrian University of Athens Medical School, 'Aghia Sophia' Children's Hospital, Athens, Greece.

17. Unit of Endocrinology, Theagenio Hospital, Thessaloniki, Greece.

Commented [RC1]: This is the one institution so not two affiliations

Commented [RC2]: This is the one institution so not two affiliations

18. Hereditary Endocrine Cancer Group, Spanish National Cancer Research Centre (CNIO) & Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Institute of Health Carlos III (ISCIII), Madrid, Spain.

19. Princess Maxima Center for Pediatric Oncology, Utrecht, Netherlands

20. Department of Pathology, University Medical Center Utrecht, Utrecht, Netherlands.

21. Department of Public Health and Pediatric Sciences, University of Turin, Turin, Italy.

22. Division of Hematology/Oncology, Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY, USA.

23. Department of Radiation Oncology, University Hospital of Texas, MD Anderson Cancer Center, Houston, TX, USA.

24. Department of Pediatrics, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany.

25. Department of Surgery, University of Cambridge and National Institute for Health Research Cambridge Biomedical Research Centre, Addenbrooke's Hospital, Cambridge, UK.

26. Blood and Transplant Research Unit in Organ Donation and Transplantation, National Institute for Health Research, University of Cambridge, Cambridge, UK.

27. Paediatrics and Adolescent Medicine, Faculty of Medicine, University of Augsburg, Augsburg, Germany.

28. U.O.C. Chirurgia Endocrina e Metabolica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy

29. Istituto di Semeiotica Chirurgica, Università Cattolica del Sacro Cuore, Roma, Italy.

30. Service de médecine nucléaire, Inserm U970, Sorbonne université, Groupe hospitalier Pitié-Salpétrière, Paris, France.

31. Department of Paediatric Nephrology, Great Ormond Street Hospital for Children NHS Foundation Trust and NIHR GOSH Biomedical Research Centre, University College London Great Ormond Street Institute of Child Health, London, UK.

32. Surgical Oncology Program, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

33. Endocrinology, Diabetes and Metabolism, Department of Medical Sciences, University of Turin, Corso Dogliotti, Turin, Italy.

34. Department of Internal Medicine, Radboud University Medical Centre, Nijmegen, Netherlands.

35. Clinical Child and Adolescent Psychology, Institute of Clinical Psychology and Psychotherapy, Department of Psychology, TU Dresden, Dresden, Germany.

36. Université Paris Cité, PARCC, INSERM, F-75006 Paris, France

37. Service de Génétique, Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France.

38. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK.

39. Centre for Endocrinology, Barts and the London School of Medicine, London, UK

40. ENETS Centre of Excellence, Royal Free Hospital, London, UK.

41. Department of Nuclear Medicine, La Timone University Hospital, CERIMED, Aix-Marseille University, Marseille, France.

42. Section on Medical Neuroendocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Rockville, MD, USA.

†**Email:** rc674@cam.ac.uk, Christina.Pamporaki@ukdd.de

[H1] Abstract

Phaeochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumours that arise not only in adulthood but also in childhood and adolescence. Up to 70–80% of childhood PPGLs are hereditary, accounting for a higher incidence of metastatic and/or multifocal PPGL in paediatric patients compared with adult patients. Key differences in the tumour biology and management, together with rare disease incidence and therapeutic challenges in paediatric compared with adult patients, mandate close expert cross-disciplinary teamwork. Teams should ideally include adult and paediatric endocrinologists, oncologists, cardiologists, surgeons, geneticists, pathologists, radiologists, clinical psychologists and nuclear medicine physicians. Provision of an international Consensus Statement should improve care and outcomes for children and adolescents with these tumours.

[H1] Introduction

Phaeochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumours arising from the adrenal medulla or extra-adrenal sympathetic and parasympathetic paraganglia. PPGLs are more frequently diagnosed in adult than paediatric populations; paediatric cases account for only 10–20% of all detected cases of PPGL with an estimated annual incidence of 0.5–2.0 per million children[1–4]. Due to the slow growing nature of the tumours and usual delays in diagnosis, the true prevalence of PPGLs in childhood is likely to be much higher than currently estimated. The median age at presentation is 11–15 years[5,6] and PPGLs are exceedingly rare in children under 5 years.

The management of PPGL in childhood is complicated by the high incidence of multifocality and/or recurrence and metastatic disease[5,6], together with the limited evidence base and paucity of international guidance and the lack of clinical trials. Approximately 35% of PPGLs in adults

and 70–80% in children are caused by an inherited pathogenic variant in one of at least 25 tumour susceptibility genes[6–9]. Thus, germline genetic testing has high priority in the diagnostic work up and guides personalised diagnostic, management, therapeutic and surveillance strategies for children and adolescents with PPGL.

As with adults, paediatric PPGL susceptibility genes can be divided into two main clinically relevant clusters defined by specific transcriptomic profiles, and a third cluster encompassing predominately somatic gene variants[10]. Cluster 1 tumours include those caused by pathogenic variants in the von Hippel-Lindau (*VHL*) suppressor gene, multiple Krebs cycle genes (including the succinate dehydrogenase complex genes (*SDHA, SDHB, SDHC* and *SDHD*)) and somatic gain-of-function pathogenic variants in the hypoxia-inducible factor 2 alpha gene (*HIF2A* or *EPAS1*). Cluster 2 tumours include those driven by pathogenic variants in neurofibromatosis type 1 (*NF1*) tumour suppressor gene, the rearranged during transfection (*RET*) proto-oncogene and the genes encoding transmembrane protein 127 (*TMEM127*) and MYC-associated factor X (*MAX*)[10,11]

PPGLs typically present with symptoms and signs of catecholamine excess, including hypertension, palpitations, sweating, nervousness and headaches. However, in children, the signs and symptoms of catecholamine excess are often overlooked. Absence of signs and symptoms is particularly relevant for children who undergo screening because of a known familial PPGL predisposition gene; in this population, tumours are commonly detected when they are reasonably small[12]. The higher incidence of hereditary PPGL in children requires multidisciplinary care and life-long follow-up, with surveillance tailored to the specific gene variant or clinical phenotype. Paediatric patients with metastatic PPGL have a disease-related 5-year and 10-year survival rate of 78% and 31%, respectively[13]. The choice of therapy for paediatric patients with metastatic PPGL is best guided by symptoms and/or signs, tumour and catecholamine burden and the sites of metastases, as well as the rate of tumour progression. Therapeutic selection should also be guided by paediatric-specific considerations, including the effect on growth, pubertal development, fertility preservation and psychosocial factors for the patient and family.

Early diagnosis and therapeutic intervention are expected to reduce morbidity and mortality[14,15]. Therefore, family-based identification of children with disease-causing variants followed by enrolment into surveillance programmes is likely to improve the detection of the

initial tumours at a time and size that allows resection, and is likely to minimise, if not avoid, metastatic progression. An outstanding problem is the wider institution of such programmes, which can, in part, be facilitated by several patient support groups that have emerged over the past 20 years. Patient advocacy groups also play a crucial role in empowering children, young adults and families to become experts in their rare tumour and genetic diagnosis where applicable and should be considered part of the wider multidisciplinary team focus. This Consensus Statement aims to guide clinicians in the diagnosis and management of paediatric patients with abdominal and pelvic PPGL (**Supplementary Box 2** provides a brief overview of head and neck paragangliomas in children).

[H1] Methods

[H2] Participants

Participants were identified by their expertise in the field of PPGL management, through membership of the European Network for the Study of Adrenal Tumours (ENSAT) and/or the Phaeochromoctyoma and Paraganglioma Research Support Organization (PRESSOR). The task force included five paediatric oncologists, seven paediatric endocrinologists, 14 adult endocrinologists and/or internists, one adult oncologist, one radiation oncology specialist, two nuclear imaging specialists, three surgeons, three geneticists, one clinical chemist, one paediatric psychologist and two pathologists. Participants are from eleven different countries across three continents (Europe, North America (USA) and Oceana (Australia)). Survey participation was voluntary with no financial incentive.

[H2] Delphi consensus formation

A Delphi process was applied to establish consensus about the diagnosis and management of paediatric patients with PPGL. R.T.C. and C.P. planned the workflow according to the Delphi recommendations. Consensus was defined prior to the study as ≥75% for agreement (Likert Scale 1, 2) or disagreement (Likert Scale 4, 5). Responses with >75% agreement in one round were removed from the next round as consensus was considered reached. For the final round, the statements were graded as A (strong) or B (weak) if they had agreement of ≥85% or 75–84% of the responders, respectively.

[H2] Delphi questionnaire

The first questionnaire was designed by R.T.C. and C.P. The survey was conducted using the online platform REDCap. Prior to the project, R.T.C. and C.P. performed a literature review for the working group. The questions were divided into six sections: general remarks, diagnosis, management, surveillance, metastatic disease and transition. The Delphi process contained four rounds, including the first round with the online questionnaire. The questionnaire consisted of two open and 73 multiple choice questions with free text for comments. The list of questions was provided online in REDCap and sent to participants via an online link. Participants were requested to answer the questionnaire in a timeline of 30 days (from 01.07.2022 until 01.08.2022) and were encouraged to comment in free text to facilitate further discussion. All participants responded and provided their answers in the first round-online survey questionnaire. Then, the two moderators, R.T.C. and C.P., analysed their answers and translated them into a series of statements. These statements were reviewed and approved by six subcommittees for each of the six sections described above.

In the second round of the Delphi process, 44 statements (**Supplementary Tables 1–6**) were rated in a timeline of 30 days (from 27.10.2022 until 26.11.2022) and commented on by each participant independently using the 5-point Likert scale (1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree). Participants also had the option to abstain from answering a question if they felt unqualified to answer. Statements that did not reach consensus were reviewed at a virtual subcommittee meeting, adjusted, and reformulated for the next round of rating. Five statements did not reach consensus after three consecutive rounds and were removed from the consensus **(Supplementary Table 7**). The responses and comments remained anonymous, except to moderators. The aim of this methodology was to facilitate an unbiased consensus.

[H2] Grading of evidence-based data

After completion of the Delphi process the task force, and later the subcommittees and chairpersons graded the evidence of the statements that reached consensus based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group[16,17]. For each recommendation, the quality of evidence was rated as very low, low, moderate or high **(Supplementary Table 8**).

[H1] General remarks

- **S1. The management of paediatric patients with PPGL requires specialist multidisciplinary input and should ideally be performed in a centre with expertise in managing PPGL.** (Agreement A; Evidence, low)

Evidence: Due to the rare nature of PPGL and its variable clinical presentation in children and adolescents, diagnosis, and management (including therapies) can be delayed in centres where physicians lack expertise and the support of an experienced specialist multidisciplinary team[18–20]. A cumulative body of literature has advocated the implementation of a multidisciplinary approach in the treatment and management of cancers, for adherence to clinical guidelines, outcome improvement and cancer patient management[21]. Similarly, among patients with neuroendocrine tumours (including PPGL), it has been established that management of patients in multidisciplinary referral centres was associated with improved patient outcomes compared with those managed without the support of a dedicated multidisciplinary team[22–24]. Multidisciplinary teams should have expertise in PPGL and other tumours in the differential diagnosis including neuroblastoma and composite tumours (Supplementary Box 1). Members of the multidisciplinary team should include paediatric endocrinologists and oncologists, surgeons, geneticists, genetic counsellors, radiologists, nuclear medicine specialists, clinical psychologists and paediatric ancillary services (see statement S38). Specialists such as cardiologists, anaesthesiologists and intensive care physicians as well as the pain management team should also be involved to oversee perioperative patient-tailored treatment. Finally, referral to specialised centres can also provide the opportunity for patients and their families to participate in clinical trials.

[H1] Diagnosis

- **S2. Clinical suspicion of PPGL should be raised in paediatric patients with a) signs and symptoms of catecholamine excess and b) incidentally discovered adrenal or extra-adrenal mass. The risk of PPGL is higher in children with pathogenic variants in tumour susceptibility genes and or a previous history of PPGL compared with those without.** (Agreement A; Evidence, moderate)

Evidence: Outside of surveillance programmes, PPGL typically presents with signs and symptoms of catecholamine excess, often paroxysmal in nature. Hyperhidrosis, palpitations, pallor, tremor and nausea and/or vomiting are among the most common presenting complaints

in paediatric patients with PPGL[2,5,25–28]. Occasionally, children with PPGL can experience anxiety and/or nervousness, distraction, sleep disturbance or impaired school performance. In such cases, diagnosis can be even more challenging, as clinical presentation of PPGL can overlap with other disorders often encountered among paediatric patients, such as attention deficit hyperactivity disorder (ADHD)[29]. Finally, polyuria and visual disturbances have been also reported among paediatric patients with PPGL[30].

Hypertension (defined as an average systolic and diastolic blood pressure >95th percentile for age, sex and height) in childhood is uncommon compared with in adults,[31] in whom hypertension is often associated with other comorbidities. Nevertheless, the presence of hypertension alone is not usually sufficient to justify a search for PPGL until other, more common forms of secondary hypertension are excluded.[3,31] The possibility of PPGL should be considered when hypertension is paroxysmal or accompanied by other signs or symptoms of catecholamine excess.[5,32]. On the other hand, as hypertension can be paroxysmal[33,34], paediatricians should not discount a diagnosis of PPGL in a paediatric patient with normal blood pressure in the outpatient clinic if other signs and symptoms of catecholamine excess are reported in the medical history, as tumours can be non-secretory or too small to produce sufficient catecholamines to induce hypertension. Finally, paediatric patients tested for PPGL should be evaluated for weight loss and tachycardia and, if present, these symptoms should be documented in the clinical evaluation[5].

Today, in the era of widespread accessibility to genetic testing, paediatric patients diagnosed with PPGL as part of surveillance programmes, are usually normotensive and asymptomatic when first diagnosed with their tumours[11,15]. In such cases, tumours are at an early stage of development, too small to release enough catecholamines to present with manifestations of catecholamine excess. Similarly, children in follow-up due to a previous history of PPGL, or less commonly, due to incidental adrenal or extra-adrenal masses discovered on imaging studies performed for unrelated reasons, might also be asymptomatic. Finally, clinical evaluation of children with suspicion of PPGL or enrolled into surveillance programmes should include complete physical examination, history of signs and symptoms of presumed catecholamine excess, family history, weight, height, BMI, blood pressure and heart rate measurements. The results of this initial evaluation should guide the decision for subsequent biochemical testing.

[H2] Biochemical

- **S3. Biochemical testing for patients with suspicion of PPGL should include plasma free or urine (spot or 24-hour) levels of normetanephrine and metanephrine, and should be performed using liquid chromatography assay.** (Agreement A; Evidence, moderate)

Evidence: Data based mainly on adult cohorts indicate that plasma levels of free metanephrines or 24-hour urinary levels of deconjugated metanephrines should be the screening test of choice for patients with suspected PPGL[20,35] . Importantly, plasma levels of free metanephrines offer higher diagnostic accuracy than urinary levels of free or deconjugated metabolites in patients at high risk of PPGL, such as those screened as part of surveillance programmes[36]. Inclusion of methoxytyramine in the panel of metabolites is also important, but only in plasma[36]. In urine, methoxytyramine has limited utility in the identification of dopamine-producing tumours[37,38]. Metanephrines can be measured in (overnight) first morning[39] or random spot urine samples[40] that could offer an alternative to 24-hour urine collections. It has been previously reported that both first morning and random spot urine levels of metanephrines present with a similar diagnostic accuracy to 24-hour urine levels of metanephrines[39–42], although with inferior sensitivity compared with plasma measurements[39].

Two studies documented a high diagnostic accuracy of plasma levels of free metanephrines for paediatric patients[43,44]. Considering that 24-hour urine collections can be troublesome in children, and blood sampling procedures followed in paediatric settings are stressful for children (see statement S4), assessment of plasma levels of free metanephrines is preferred in children with high pretest probability of the disease (for example, germline pathogenic variant in a tumour susceptibility gene) over 24-hour urinary levels of metanephrines. First morning spot urine could be an alternative option for the exclusion of PPGL among young children with low risk of PPGL (for example, children tested only due to signs and symptoms) and needle phobia, but additional prospective studies are needed to validate the diagnostic value of first morning spot urine.

For older children, 24-hour urine collections provide an alternative to blood samples. Due to a lack of evidence to indicate whether plasma or 24-hour urine metanephrine measurements are more accurate in children, the choice of biochemical testing should be guided by availability of the test, experience of the clinician and practical considerations (see statement S4).

Commented [OT3]: Au: In the sentence starting 'Considering that 24-hour urine collections', removal of 'minimally' to improve clarity, OK? Additionally, in the same sentence, addition of 'over 24-hour urinary levels of metanephrines' to improve clarity, OK?

Commented [PC4R3]: OK

Metabolites should be measured using a procedure that includes chromatographic separation[45,46], which provides superior diagnostic performance compared with immunoassays, especially when using the cutoffs provided by the manufacturer[47,48]. Liquid chromatography with tandem mass spectrometry is preferred to liquid chromatography with electrochemical detection, as it has greater overall freedom from analytical interference[48].

- **S4. Blood sampling for measurements of plasma levels of metanephrines and methoxytyramine should be carried out with appropriate consideration of preanalytics**. (Agreement: A; Evidence, moderate)

Evidence: Sympathoadrenal activation can be triggered by multiple physiological and psychological stressors and activities of daily life, leading to increases in plasma levels of catecholamines and their metabolites[49]. A typical example is the increase of sympathoadrenal activity by the upright posture that in turn increases plasma concentrations of normetanephrine, leading to higher rates of false positive results when assessing plasma levels of metanephrines[50–52]. In this context, it is recommended that blood should be drawn after at least 20 minutes of supine rest for the assessment of plasma metanephrines[20].

Apart from posture, sympathoadrenal activation can be triggered by distress associated with venepuncture, often encountered among young children. Distress-triggered sympathoadrenal activation is apparent for direct venepuncture and less apparent for sampling via intravenous cannula[53–56]. Placement of paediatric intravenous cannulas by providers experienced in paediatric phlebotomy[57,58], and application of various distractions for children during this procedure[59], can help to minimise further distress associated with needle phobia, and blood sampling through intravenous cannula is preferred to direct venepuncture. Finally, blood sampling should be performed in a warm and relaxed environment, as acclimatisation of the sympathetic nervous system to warmer inside temperatures over a long time period (such as overnight) is associated with a statistically significant reduction of plasma metabolites, and particularly of normetanephrine[56,60].

The influence of dietary catecholamines on levels of metanephrines is negligible[61] but dietary dopamine and tyramine do affect plasma methoxytyramine levels[61,62]. Therefore, if methoxytyramine is included in the plasma panel, children should be instructed to fast overnight. Nicotine and caffeine potently stimulate sympathoadrenal secretion of catecholamines and teenage patients should be instructed to abstain from caffeine and nicotine overnight, and in the morning before blood sampling or during urine collections[48]. Drugs such

as noradrenaline reuptake blockers, or amphetamines and methylphenidate (which is used for treatment of ADHD can artificially elevate blood levels of normetanephrine and so affect the diagnostic test results[48]. Discontinuation of the interfering medication could be considered in the case of positive biochemical test results. The time interval of interfering drug discontinuation should be calculated according to the drug's half-life, the concept of exponential decay, as well as the patient´s renal and hepatic function as per the local hospital protocol.

- **S5. In situations of acute physical illness or intense emotional stress, biochemical test results should be interpreted with caution.** (Agreement A; Evidence, low)

Evidence: While metanephrines are less responsive to acute sympathoadrenal activation[63] compared with catecholamines, acute illness or intense emotional stress can lead to increases in plasma and urinary levels of metanephrines, as shown mainly in studies focused on adult cohorts[64–67]. Such increases are particularly apparent for patients hospitalised due to severe illness, where levels of metanephrines can even be indistinguishable from patients with PPGL[68,69]. Thus, and despite lack of studies on paediatric cohorts, biochemical assessment of metanephrines in children under such conditions should be interpreted with caution. A positive biochemical test result in a child with acute illness or intense emotional stress should be repeated after full recovery and under appropriate preanalytical conditions. For children at high risk of PPGL, however, clinicians could proceed directly to imaging studies in case of a positive biochemical test.

- **S6. For plasma or urine normetanephrine and metanephrine testing, laboratories should employ appropriate reference intervals.** (Agreement A; Evidence, moderate)

Evidence: Plasma levels of metanephrines vary according to age and sex. Levels of normetanephrine and methoxytyramine are high in neonates and drop dramatically after the first year of age, remaining constant throughout childhood.[70] By contrast, plasma concentrations of metanephrine increase during early infancy and are higher in younger children than in adolescents[70]. Thus, age-specific reference intervals for plasma concentrations of metanephrines in children are important for the correct interpretation of test results[44,71,72]. Apart from age, sex differences are also apparent in plasma concentrations of metanephrines, with boys showing higher concentrations of metanephrine than girls[70]. A nomogram of upper cut-offs for plasma levels of free metanephrines in children and adolescents is presented in **Table 1**.

24-hour urinary outputs of normetanephrine and metanephrine are up to four times higher in older adolescents compared with young children[73–75], rendering age-specific reference intervals for urinary metabolites crucial[76–78]. Finally, as with plasma metabolites, sex contributes to variable differences in urine metabolites, with boys showing higher 24-hour urinary outputs of normetanephrine and metanephrine than girls[79]. Establishment of reference intervals for spot urine metanephrines is even more challenging than for the 24-hour urine samples, as measurements of spot urine specimens require dilution correction of urinary outputs for creatinine excretion. Creatinine excretion, however, is influenced by muscle mass and as such, it increases during child growth and is higher in boys than in girls[39,80]. Thus, reference intervals for spot urine, unlike those for 24-hour urine levels of metanephrines, show decreases throughout childhood[81]. Due to the practical difficulties of laboratories to establish appropriate reference intervals, the use of spot urine levels of metanephrines is currently limited in paediatric settings.

- **S7. In case of borderline elevations (less than a twofold increase above the upper cut-off) of only one catecholamine metabolite in a paediatric patient with low degree of suspicion for PPGL (for example, tested due to signs and symptoms of catecholamine excess), biochemical testing should be repeated.** (Agreement A; Evidence, low)

Evidence: Data from the Prospective Monoamine-producing Tumor Study (PMT-Study), based mainly on adult patients, has shown that 21% of patients diagnosed with PPGL presented with borderline elevations of a single metabolite, (less than twofold above the upper cut-off)[36]. Thus, all patients with positive biochemical test results should receive follow-up. The nature of follow-up, however, depends on the extent of increases of each metabolite and on the pretest clinical suspicion of PPGL. Although there is a lack of evidence for paediatric patients, elevations of one or more metabolites greater than twofold above the upper cut-offs should prompt consideration for imaging studies regardless of the pre-test clinical suspicion for PPGL[36,82]. By contrast, for elevations of a single metabolite lower than two-fold above the upper cut-off, the nature of follow-up should be decided based on the pretest clinical suspicion of the disease. For patients with low risk of PPGL (for example, tested due to signs and symptoms of catecholamine excess) and borderline elevations of a single catecholamine metabolite, a wait and retest approach (for example, in 6 months) is usually preferable to

immediate retesting[83]. Clinicians should ensure that follow-up measurements are performed with mass spectrometric methods and adhere to preanalytical precautions[48].

[H2] Radiology

- **S8. In paediatric patients with biochemically confirmed PPGL, either MRI or CT can be performed to localise a tumour.** (Agreement B; Evidence, low)

Evidence: Anatomical imaging for tumour localization and staging is the next diagnostic step after biochemical confirmation of PPGL. Contrast-enhanced CT or MRI are two initial imaging modalities of choice for PPGL in children[13,84–85] given their similar diagnostic performance[86]. Contrast-enhanced CT or MRI of the abdomen and pelvis should be considered as the first step in patients with biochemically confirmed PPGL (**Supplementary Table 9**). If this initial imaging is negative, contrast-enhanced CT or MRI of the chest and dedicated MRI of the neck should be considered[87].

Phaeochromocytomas can be difficult to distinguish from neuroblastomas (the most common type of extracranial solid tumours in young children) radiologically, as both tumour types can show similar characteristics on both contrast-enhanced CT and MRI and tracer uptake on ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy. Therefore, the interpretation of cross-sectional imaging must be made in the context of symptoms and signs of catecholamine excess confirmed by positive biochemical testing (elevated levels of metanephrines). Interpreting imaging results requires careful consideration of whether the patient had high or low pretest probability of PPGL (for example, an adrenal mass in a carrier of a PPGL predisposition gene versus an incidentally discovered adrenal mass).

Overall, MRI shows 95% sensitivity and 70% specificity for phaeochromocytomas and abdominal or pelvic PGLs, and it is the preferred imaging modality for head and neck paragangliomas (HNPGL) due the excellent contrast-to-noise ratio within soft tissue. MRI should also be preferred as the initial imaging modality in paediatric patients with suspected PPGL due to the lack of ionising radiation exposure[84]. In addition, dedicated discussion between surgeons and radiologists in multidisciplinary boards can help to interpret MRI findings correctly without the need for an additional ionising examination. MRI is also the imaging modality of choice for the surveillance of asymptomatic carriers of a PPGL predisposition gene (for example, *SDHx* carriers)[87]. Non-contrast MRI is usually suboptimal in

the evaluation in PPGL patients, although it can be used for surveillance in carriers of PPGL pathogenic variants [15,88]. Nevertheless, MRI is more time intensive (and costly) compared with CT and young children often require sedation, which is associated with additional risks and costs[89,90].

CT is an excellent alternative anatomical imaging modality to MRI, with very high spatial resolution and sensitivity (100%) for PPGL. Simultaneous imaging of the chest, abdomen and pelvis is possible, it is much less time intensive than MRI, and sedation is seldom required. Nevertheless, CT is typically reserved as a second line option in children due to the associated risks of ionising irradiation[89–93]. Estimating the actual radiation risk is challenging, as children are not, in fact, more radiosensitive than adults in the radiologic imaging dose range, rendering dose reduction for children potentially unjustifiable[94]. Nevertheless, caution should be taken to use the lowest possible radiation dose during a specific CT examination (for example, weight adjusted doses) with adequate imaging quality. Taking these factors into account, CT might be favoured in the preoperative work-up of a child or adolescent in whom a PPGL has been confirmed, to provide the most accurate tumour staging and anatomical assessment of the tumour(s) and adjacent structures to strive for complete tumour resection. Finally, ultrasound is considered the safest imaging modality in children as there is no ionising radiation, contrast dye or sedation involved. However, abdominal or pelvic ultrasound is overall suboptimal (sensitivity about 89%)[95]. Its role is therefore limited as a primary anatomical imaging modality to search for biochemically confirmed PPGL (**Supplementary Table 9**).

- **S9. Functional imaging should be considered preoperatively if multiple tumours or metastatic disease is suspected.** (Agreement A; Evidence, moderate)

Evidence: Functional imaging is currently considered a very useful adjunct to anatomical imaging due to its high PPGL specificity and whole-body imaging sequences. Indications for considering functional imaging include disease staging pre-operatively, detection of occult metastases or recurrent and/or multiple tumours, characterisation of incidental lesions highly suspicious for PPGL (for example, in patients with inconclusive biochemical testing) and for the selection of targeted molecular radiotherapies as well as post-therapy follow-up. Commonly used functional imaging modalities for PPGL include: [^{68}Ga]-DOTATATE, [^{18}F]-fluorodopa (FDOPA), and [^{18}F]-fluorodeoxyglucose (FDG) PET–CT as well as [^{123}I]-MIBG scintigraphy. The indication for functional imaging and the potential benefit for the individual

child or adolescent must be carefully balanced against the radiation risk, cost and the availability of a particular functional imaging modality. Based on imaging guidelines from the past 5 years, the choice of functional imaging modality needs to be guided by the clinical question (for example, staging versus selection of a targeted molecular radiotherapy) and by the genetic status of the patient (**Table 2**), as the genotype influences the tumour biology and can affect the sensitivity of certain functional imaging tracers[96,97].

As PPGL typically exhibit strong somatostatin receptor type 2 expression, somatostatin-receptor (SSTR)-guided PET–CT using ^{68}Ga radiolabelled somatostatin analogues have demonstrated very good sensitivity in both adult and paediatric cohorts with PPGL. SSTR PET–CT has been shown to be particularly sensitive in patients with metastatic disease, with *SDHx* pathogenic variants, as well as with HNPGLs[96,98-100]. For example, its sensitivity approaches 100% for HNPGL, paragangliomas and metastatic lesions. Therefore, SSTR PET–CT, if available, is recommended as the first line molecular imaging modality for whole body staging for paediatric patients with PPGL[96,100].

[^{18}F]-FDG PET–CT is more available than SSTR PET–CT worldwide as a molecular imaging modality and has good sensitivity in PPGLs, particularly for patients harbouring germline pathogenic variants in cluster 1 genes[101], and for patients with metastatic PPGL. [^{18}F]-FDG PET–CT should be considered if SSTR PET–CT and [^{18}F]-FDOPA PET–CT are not available. The sensitivity and specificity of [^{18}F]-FDG PET–CT is affected by brown adipose tissue activation in patients with catecholamine excess and [^{18}F]-FDG uptake by other non-PPGL tumours and non-malignant pathologies (such as inflammation or infection)[102]. Other paediatric-specific variations need to be considered when interpreting [^{18}F]-FDG PET–CT in children, including increased thymic and skeletal growth plate [^{18}F]-FDG uptake compared with adult patients, which might affect the detection of small tumours in these locations. [^{123}I]-MIBG has lower sensitivity as a staging test for patients with cluster 1 PPGL[103–105] compared with patients with cluster 2 or sporadic PPGL. Considering that most children with PPGL harbour cluster 1 gene variants, [^{123}I]-MIBG should be typically reserved for patients with metastatic disease in whom radiolabelled [^{131}I]-MIBG therapy is being considered[96].

[H2] Genetic testing

- **S10. Germline genetic testing is recommended for all children presenting with PPGL as well as all children with first degree relatives in whom germline pathogenic variants have been detected.** (Agreement A; Evidence, moderate)

Evidence: PPGL has a strong hereditary basis, with more than 25 susceptibility genes identified to date. The predisposition genes can be subdivided into three main categories or 'clusters', determined by their effect on downstream tumour signalling pathways[10]. Cluster 1 (the 'pseudohypoxic cluster') includes *VHL*, *SDHx, MDH2*, *FH* and *EPAS1* genes and is characterised by transcriptional upregulation of genes implicated in angiogenesis, and cellular proliferation secondary to hypoxia-inducible factor (HIF) complex stabilisation[10,106]. Cluster 2 genes include *RET*, *NF1*, *TMEM127*, *MAX* and *HRAS*, which activate kinase pathways. Cluster 3 genes include somatic *CSDE1* mutations and *MAML3* fusion variants implicated in *Wnt*-pathway signal alterations[10]. The prevalence of hereditary PPGL is notably higher in paediatric (~80%) compared with adult populations (~50%)[6], and genetic testing can inform tailored surveillance and management strategies[107]. Genetic testing using conventional Sanger sequencing is still useful in select instances, particularly in syndromic patients, and might be the only option available in some centres. However, single gene testing has largely been replaced by next generation sequencing methods using small to medium sized gene panels, as PPGLs show a high degree of heterogeneity in clinical presentation and genotype cannot always be reliably predicted by phenotype. Furthermore, the *NF1* gene is not always included on targeted gene panels because germline pathogenic variants in this gene are rare in non-syndromic patients with PPGL[108–110]. Finally, immunohistochemistry using antibodies directed against the SDHB protein is a cost effective and sensitive screening tool for the early detection of an underlying *SDHx* mutation[111] and should be considered in all patients with PPGL.

- **S11. If routine testing does not identify a germline pathogenic or probable pathogenic variant, consider referral to a specialist genetic centre for genetic analyses on tumoral DNA for detection of somatic variants (or mosaic constitutional variants) by large panel sequencing. If somatic sequencing is not available, consider additional germline genetic analysis using an extended panel, whole exome or whole genome sequencing.** (Agreement A; Evidence, low)

Evidence: For those children in whom germline genetic testing has not identified a pathogenic variant, a somatic driver variant can be identified in approximately 30–40% of tumours[10,112] Tumour sequencing should therefore be considered if germline genetic testing is negative, as mosaic or somatic driver variants can be identified in paediatric patients with PPGL without

an identifiable germline pathogenic variant. Furthermore, tumour sequencing can provide additional, important prognostic information regarding the presence of possible mosaic variants, and therapeutic information for patients with metastatic PPGL and a specific driver somatic variant.[113,114]. Cluster 1 gene somatic variants are more common in paediatric compared with adult tumours[6] and the early development of multifocal PPGL in children also suggests that dysregulated molecular signalling might occur in early embryogenesis before neural crest development. This hypothesis is supported by the finding of somatic mosaic variants in cluster 1 genes such as *EPAS1*, *SDHB* and *VHL* in approximately 6% of paediatric patients with PPGL[6,112,115]. Inactivating somatic variants in *NF1* are detected in both adult and paediatric patients with PPGL[6,109,112].

[H1] Management

[H2] Surgical management and preoperative and perioperative optimisation

- **S12. The decision for surgery and the surgical approach should be discussed at a specialist multidisciplinary team meeting and surgery should be performed by a surgeon experienced in PPGL surgery.** (Agreement A; Evidence, low)

Evidence: Surgery is the only curative treatment option for PPGL. The main objectives of surgical resection are to improve symptoms and/or signs by removing the source of catecholamine excess and mass effect-related symptoms and/or signs, and to minimise the risk of tumour recurrence and/or metastasis by prioritising a complete resection of the PPGL without disrupting the tumour capsule. If there are no contraindications, all children and adolescents with PPGL, and their parents, should be offered surgical consultation with a surgeon knowledgeable of this disease. In some centres, this might require close collaboration between paediatric and adult surgeons of different subspecialties with expertise in PPGL surgery.

- **S13. A minimally invasive approach should be favoured, when feasible, for children with abdominal and pelvic PPGL.** (Agreement A; Evidence, very low)

Evidence: For relatively small (usually up to 5 cm in diameter) non-invasive PPGL without evidence of local invasion, or nodal metastases or spread on preoperative imaging, a minimally invasive surgery is usually safe and can be preferable to open surgery, due to the shorter recovery time[116–120]. The minimally invasive surgical approach should be selected based on the

expertise of the surgical team. There are no prospective clinical trials directly comparing laparoscopic versus open adrenalectomy approaches for PPGL in adult or paediatric patients. An open approach should be considered for paediatric patients with an aggressive or potentially aggressive PPGL as indicated by tumour size (>5 cm in diameter), presence of locoregional lymph node metastases on pre-operative imaging, multifocality in the same location or tumours invading or abutting adjacent organs or vascular structures.

Incomplete resection of the primary PPGL in children is associated with increased risk of recurrence or metastatic spread[8]. The priority of surgery should be complete margin negative resection of the primary tumour and locoregional metastases at the time of surgery. Therefore, the surgical approach should be selected with this goal in mind, based on the expertise of the local surgical team. When margin-negative surgery is not deemed feasible or is outweighed by the risk of substantial surgery related morbidity, de-bulking surgery can be considered on an individualised basis, especially for children with localised tumours who are affected by symptoms due to compression or catecholamine secretion. Surveillance versus adjuvant treatment for patients with R1 resection status requires careful consideration and should be guided by patient symptoms and multidisciplinary team discussion.

- **S14. Cortical-sparing partial adrenalectomies should be considered for children with bilateral phaeochromocytomas, or those in whom the presence of a germline pathogenic variant carries a high risk of bilateral phaeochromocytomas but a low metastatic potential.** (Agreement A; Evidence, low)

Evidence: Bilateral phaeochromocytomas, occurring either synchronously or metachronously, are more common in children than in adults, reflecting the higher incidence of hereditary PPGLs in paediatric patients[6]. Total bilateral adrenalectomy performed for bilateral phaeochromocytoma results in definitive glucocorticoid and mineralocorticoid deficiency in all patients, compared with a risk of glucocorticoid and mineralocorticoid deficiency of approximately 23% in patients treated with a subtotal or cortical sparing adrenalectomy [121]. Cortical-sparing adrenalectomy is typically reserved for phaeochromocytomas <5 cm in diameter, and should ideally be performed by an experienced adrenal surgeon. This procedure can be performed by a minimally invasive or open approach[117,121]. The long-term morbidity (including adrenal crises or iatrogenic Cushing syndrome) associated with glucocorticoid and mineralocorticoid deficiency resulting from bilateral total adrenalectomy[121] needs to be carefully balanced against the risk of potential local or metastatic tumour recurrence in patients

undergoing cortical-sparing adrenal resections. There is a higher potential risk of parenchymal spillage and local seeding during a cortical-sparing adrenalectomy compared with a total adrenalectomy. Therefore, for tumours with higher metastatic potential (such as in those patients with *SDHB* pathogenic variants), a total adrenalectomy is preferred, especially if the risk for bilateral phaeochromocytomas and, therefore, adrenal insufficiency, is very low.

A large multicentre cohort study investigating outcomes following total versus cortical-sparing adrenalectomy in adult patients has demonstrated low rates of local recurrence (5.6%) and metastatic disease (1.3%) in patients undergoing cortical sparing adrenalectomies. Most patients in this study had germline pathogenic variants in either the *RET* or *VHL* gene and only one patient with an *SDHB* pathogenic variant was included[121]. There are no modalities to ensure complete removal of the medullary tissue unless the entire gland is removed. Therefore, a cortical-sparing technique might not be recommended for patients with pathogenic gene variants, in whom the potential for metastatic spread is significant (for example, *SDHB)*[122]. Bilateral phaeochromocytomas are more common in patients with *SDHD* versus *SDHB* pathogenic variants, but due to a lack of longitudinal data to inform the risks and benefits of total versus cortical sparing adrenalectomy, an individualised approach is advised after careful counselling and multidisciplinary discussion.

- **S15. Pre-operative optimisation with α-adrenoceptor blockers and/or calcium channel blockers, together with maintenance fluid intake of 1–2 times a weight-appropriate fluid intake, should be considered in all children with PPGL ahead of a planned surgery or intervention. β-Adrenoceptor blockers can be reserved for those patients with persistent tachycardia not caused by α-adrenoceptor blockers that persists despite optimal fluid intake.** (Agreement B; Evidence, low)

Evidence: International guidelines continue to support preoperative α-adrenoceptor blockade to ensure the best possible outcomes for adult patients with catecholamine-producing PPGL.[20] α-Adrenoceptor blockers (including non-selective ones such as phenoxybenzamine and selective α1-adrenoceptor blockers such as doxazosin or prazosin) are widely used as primary treatment in adult and paediatric patients with PPGL and are helpful in managing the symptoms of catecholamine excess. Once α-adrenoceptor blockade has been established, β-adrenoceptor blockers can be added, but only if tachycardia persists in the absence of adrenoceptor blocker or hypovolemia-induced hypotension. β-Adrenoceptor blockers should not be started before α-adrenoceptor blockers have been initiated for a minimum of 2–3 days, and the patient is

haemodynamically optimised, to minimise the risk of a hypertensive crisis[20,123–125]. The β1-cardioselective adrenoceptor blockers atenolol and metoprolol are preferred to non-selective β-adrenoceptor blockers (such as, propranolol), due to much lower risk of bronchial constriction and other systemic effects.[20] Monotherapy with calcium channel blockers can be considered in paediatric patients presenting with mild hypertension and borderline biochemistry or extensive adverse events from α-adrenoceptor blockade[20,126].

The Endocrine Society guidelines advise that α-adrenoceptor blockade is initiated at least 7–14 days in advance of planned surgical intervention for a patient with PPGL[20] (**Table 3**), but it should be noted that it can take longer (2–3 weeks) to pre-operatively optimise haemodynamic parameters in children and adolescents[126]. Adrenoceptor blockers should be titrated as tolerated by the patient to achieve optimum blood pressure and heart rate targets ahead of surgery (**Table 3**). Clinical targets to guide titration of medication include blood pressure <90th percentile using age and height-based reference charts; heart rate between 10th and 90th percentile using age-based reference charts, and minimal or asymptomatic postural hypotension.[31,127]. We would also like to acknowledge that a minority of our panel was not in favour of administering α-adrenoceptor blockers pre-operatively to all patients with PPGL.

Symptomatic patients with catecholamine-secreting metastatic PPGL should be treated with adrenergic blockade long-term to minimise complications related to catecholamine release. If symptomatic control of catecholamine excess is difficult to achieve with α-adrenoceptor blockers alone, metyrosine, a selective tyrosine hydroxylase inhibitor, can improve haemodynamic stability before and after intervention[126,128,129]. Standard weight-based dosing is recommended for all the medications discussed when used in the paediatric setting[126] (**Table 3**). Finally, patients with catecholamine producing PPGL should be advised to avoid medication at risk of precipitating a catecholamine crisis (such as, steroids, ephedrine and metoclopramide)[91].

[H2] Postoperative follow-up

- **S16. Plasma or urinary levels of normetanephrine and metanephrine and plasma levels of 3-methoxytyramine (if available) should be repeated between 2–8 weeks after surgery. For patients for whom pre-operative staging was not performed, post-operative imaging (at 3–6 months) should be considered to determine surgical remission.** (Agreement A; Evidence, low)

Evidence: For children with localised, biochemically positive PPGL and adequate pre-operative staging, post-operative remission can be determined by normalisation of plasma or urinary levels of normetanephrine and metanephrine, and plasma levels of methoxytyramine (if available) on repeat measurement 2–8 weeks postoperatively. These measurements should be timed in line with the child's post-operative recovery[20,130]. Due to the high incidence of metastatic and multifocal tumours in paediatric patients with PPGL[6], full body staging, by either whole-body MRI or functional imaging, is advised pre-operatively (see statement S9). For patients with non-secretory tumours, interval whole-body imaging using MRI should be considered at 12 weeks post-surgery and at 1–2-year intervals thereafter if stable (**Table 4**).

[H2] Long-term follow-up

- **S17. Children with PPGL should ideally have post-operative follow-up in a dedicated specialist clinic and surveillance strategies should be tailored based on individual clinical factors, including the presence of metastases, germline variant status, family history, tumour size and location as well as tumour biochemical phenotype.** (Agreement A; Evidence, low)

Evidence: The reported prevalence of metastatic PPGL in children and adolescents presenting with PPGL ranges between studies (2.4–85.7%), owing to potential referral bias and lack of longer-term follow-up[1,6,122,131,132]. Importantly, studies have demonstrated that paediatric patients are more likely to develop metachronous metastatic tumours rather than initially presenting with metastatic disease when compared with adult patients, highlighting the need for very close postoperative follow-up[6]. A 2020 study reported a median time of 2 years from surgery to local recurrence (range 0–26 years) and a median time from diagnosis of primary tumour to diagnosis of metastatic disease of 4 years (range 0–26 years) in their study of paediatric patients with *SDHB* pathogenic variants[122]. There is a recognised risk of late relapse or metastatic recurrence for paediatric patients with PPGL and a notable rate of metastatic recurrence later than 5 years after initial surgery has been reported[8,131].

A 2011 study reported on 32 patients who presented with PPGL in childhood or adolescence and subsequently developed metastatic recurrence and identified that extra-adrenal tumours in the abdomen or pelvis, a noradrenergic biochemical phenotype and germline pathogenic variants in the *SDHB* were the most statistically significant risk factors for metastatic recurrence in this patient population[131]. A primary tumour size >5 cm in diameter in paediatric patients has also been associated with increased risk of early metastatic recurrence and reduced

overall survival compared with tumours <5 cm in diameter[122]. The need for consensus on long-term follow-up was highlighted in a French study of paediatric patients with PPGL spanning over two decades,[8] which identified that 7% of patients were lost to follow-up after surgery. In children with hereditary PPGL or risk factors for metastatic recurrence, surveillance should include interval anatomical imaging using MRI as the preferred imaging modality. Imaging should be reviewed by an experienced radiologist or reviewed at a specialist multidisciplinary team meeting (**Table 4**).

- **S18. Children with a germline pathogenic or probable pathogenic variant in a PPGL predisposition gene should be offered life-long clinical follow-up.** (Agreement A; Evidence, moderate)

Evidence: In paediatric patients with confirmed hereditary PPGL, lifelong follow-up is essential to screen for both recurrent metastatic disease and synchronous tumours or syndrome-related pathologies[1]. In one of the largest studies to date evaluating long-term prognosis for paediatric patients with PPGL, 38% of patients developed a second primary PPGL after a mean interval of 25 years from initial presentation, and the incidence of second tumours increased over time (25% at 9 years to 50% at 31 years)[1]. The long-term surveillance protocols should be tailored to the specific pathogenic variant, although for some hereditary syndromes, PPGL might be the less penetrant tumour type (**Table 4** and **Table 5**).

- **S19. For children with a history of PPGL but without a germline pathogenic variant in a PPGL predisposition gene or evidence of a somatic or mosaic somatic pathogenic variant, the duration of follow-up should be a minimum of 10 years.** (Agreement A; Evidence, very low)

Evidence: The risk of metastatic disease is lower in patients with sporadic PPGL compared with patients with pathogenic variants in the cluster 1 genes (such as *SDHx*), but a rate of recurrence of 14.7% in adult patients with sporadic PPGL was identified in one large multi-centre study[133]. In this same study, just over half of the patients with sporadic PPGL presented with recurrence within ten years of initial surgery and the remainder of cases of recurrence occurred later than 10 years after development of the initial PPGL. These findings highlight the need to consider surveillance for a period longer than ten years for patients with sporadic PPGL[133]. For children with apparently sporadic PPGL, we advise follow-up for a minimum of 10 years. A review of the genetic testing results at an expert centre should be considered for those patients in whom initial genetic testing was negative but who develop recurrent PPGL or

synchronous tumours, or patients in whom discharge from clinical follow-up is being considered. Life-long surveillance should be considered for select patients including those with risk factors[131] (**Table 4**).

- **S20. Children with a somatic or somatic mosaic pathogenic or probable pathogenic variants in *EPAS1, VHL* or *SDHB* should be offered life-long clinical surveillance.** (Agreement A; Evidence, very low)

Evidence: Germline cluster 1 gene pathogenic variants are detected in paediatric patients with PPGL at a higher frequency compared with adult patients. Furthermore, postzygotic somatic pathogenic variants in cluster 1 genes, including *EPAS1,* have been reported at a frequency of 1–4% in paediatric patients. Patients with postzygotic *EPAS1* mutations are at high risk of multifocal, recurrent and metastatic PPGL, polycythaemia and somatostatinomas[134–137] and therefore long-term surveillance is advisable (**Table 4**). Somatic and mosaic pathogenic variants in *VHL* and *SDHB* have also been reported in paediatric patients[6,138] and, although rare, studies suggest that patients could be at risk of a similar phenotype to those with germline mutations in the same genes[139,140].

[H1] Identification and surveillance of asymptomatic PPGL predisposition gene carriers

Commented [OT5]: Au: The heading 'Identification and surveillance of asymptomatic…' has been edited to fit the character limit of 82 characters (including spaces), OK?

Commented [RC6R5]: OK

- **S21. Surveillance in children with a pathogenic germline variant in the *SDHx* genes (*SDHA*, *SDHB*, *SDHC* and *SDHD*) should ideally include: i) Annual clinical symptoms review from the time of presentation or from age 5 years for asymptomatic *SDHB* carriers and age 10 for *SDHA*, *SDHC* or *SDHD* carriers. ii) Annual blood pressure check, biannual measurements of either plasma or urinary levels of metanephrines and plasma levels of methoxytyramine and interval MRI of neck, thorax, abdomen and pelvis every 2–5 years.** (Agreement A; Evidence, low)

- **S22. Surveillance for new or recurrent PPGL (as part of systemic *VHL* surveillance) in children with a pathogenic germline variant in *VHL* should ideally include: Annual clinical symptoms review from the time of presentation or from age 5 years for asymptomatic *VHL* carriers. ii) Annual blood pressure check, annual measurements of either plasma or urinary levels of metanephrines and annual MRI from the age of 16 years.** (Agreement A; Evidence, low)

- **S23. Surveillance for new or recurrent PPGL (as part of systemic *RET* surveillance) in children with a pathogenic germline variant in *RET* should ideally include: i) Annual clinical symptoms review from the time of presentation or from age 11 years for high-to-moderate-risk *RET* gene mutation carriers and 16 years for low-risk RET gene mutation carriers. ii) Annual blood pressure check, annual measurements of either plasma or urinary levels of metanephrines. MRI is not required routinely and can be reserved for patients with clinical symptoms or high or rising plasma or urinary levels of metanephrines to inform early partial adrenalectomy and to reduce morbidity.** (Agreement A; Evidence, low)

- **S24. Surveillance in children with a pathogenic germline mosaic *VHL* variant should ideally be carried out as per the guidelines for patients with germline *VHL* gene pathogenic variants.** (Agreement A; Evidence, very low)

- **S25. Surveillance for PPGL in children with a pathogenic or probably pathogenic mosaic or somatic variant in *EPAS1* should ideally include: i) Annual clinical symptoms review from the age of presentation. ii) Annual blood pressure check, annual measurement of plasma or urinary levels of normetanephrine and metanephrine. Interval MRI of the abdomen and pelvis can be considered at 2–3-year intervals.** (Agreement B; Evidence, very low)

- **S26. Children with a pathogenic or probable pathogenic mosaic variant in *VHL* should be offered life-long clinical surveillance.** (Agreement A; Evidence, very low)

- **S27. Surveillance in children and adolescents with pathogenic germline variants in *TMEM127* and children and adolescents with paternally inherited pathogenic variants in *SDHAF2* should ideally include: i) Annual or biannual clinical symptoms review from the age at presentation or from age 10–15 years for**

asymptomatic carriers. ii) Annual or biannual blood pressure check and measurement of either plasma or urinary levels of metanephrines. (Agreement B; Evidence, very low)

- **S28. MRI of the neck, thorax, abdomen and pelvis should be performed at the first screening visit and, if negative, interval MRI of the neck, thorax, abdomen and pelvis should be performed every 3–5 years for *TMEM127* variant carriers.** (Agreement B; Evidence, very low)

- **S29. MRI of the neck should be performed at intervals of 3–5 years for *SDHAF2* carriers.** (Agreement B; Evidence, very low)

- **S30. Surveillance in children without a pathogenic germline variant in a PPGL predisposition gene or evidence of a germline mosaic variant in *EPAS1* or *VHL* should be tailored to the individual case and more frequent surveillance might be required for patients with extra adrenal tumours, a history of a large tumour (>5 cm in diameter), synchronous or recurrent tumours or a family history of PPGL.** (Agreement B; Evidence, very low)

- **S31. Surveillance in children with a pathogenic germline variant in *MAX* should ideally include: i) Annual clinical symptoms review from the age of presentation or from age 10 years. ii) Annual blood pressure check, annual or two-yearly check of plasma or urinary levels of normetanephrine and metanephrine and interval MRI of the neck, thorax, abdomen and pelvis every 2–3 years from presentation or from age 15 years.** (Agreement B; Evidence, very low)

Evidence: For precision medicine strategies to improve population health, targeted approaches must be considered, not only for disease treatment, but also for early diagnosis and prevention of PPGL related morbidity and mortality[141]. An important component of precision medicine in paediatrics is the identification through genetic testing of children at risk of PPGL because of pathogenic germline variants. As the prevalence of hereditary disease among adult patients with PPGL is up to 35%, genetic testing is currently recommended by the Endocrine Society guidelines for all patients[20]. For those with germline pathogenic variants, cascade screening should be offered to first degree relatives, including children. This process offers a way of identifying children at risk for PPGL within a family, allowing them to enter timely surveillance programs to facilitate early tumour detection. Despite wide acceptance of cascade screening[142–144], PPGL in children remains underdiagnosed[72], indicating that implementation of effective interventions to improve testing in clinical practice is crucial. Assistance in

identifying at-risk relatives in endocrinology and/or oncology settings, design of dissemination plans, updated digitised materials to pass on to parents, incorporation of psychological support for children and their families throughout the whole process, as well as interventions focused on enhancing family support and communication should be implemented in family-based programs. Such programs are already in place in many centres with expertise on PPGL[145,146]. Finally, the success of these programs is likely to be enhanced through the support of advocacy support groups (**Supplementary Table 10**) who strive to reduce patient-reported barriers to effective care[145,146].

Once identified, long-term surveillance strategies for asymptomatic gene carriers should be specifically tailored to the genetic diagnosis and should consider the anticipated phenotype and penetrance of the gene. The surveillance strategy, if commenced in childhood, should also focus on minimising radiation exposure to a genetically vulnerable population, as well as aiming to minimise anxiety and inconvenience for patients and families (**Table 5**). We advise that asymptomatic children identified as carriers for PPGL predisposition genes are monitored, as per already existing guidelines or through this Consensus Statement, for the more common or well-described predisposition genes[15,147,148]. It is important to note that existing guidelines focused on surveillance for asymptomatic carriers of PPGL predisposition genes are based on low quality evidence documenting the penetrance of the most common PPGL predisposition genes in childhood and/or data on PPGL in childhood, as well as expert opinion. Well-designed multi centre prospective studies are required to determine the clinical, psychological and economic impacts of asymptomatic screening and long-term surveillance in and from childhood.

[H1] Management of metastatic PPGL

- **S32. Treatment of metastatic PPGL in paediatric patients should be considered on an individualised basis according to tumour burden, location and progression rate as well as the presence of signs and symptoms related to catecholamine excess or mass effects.** (Agreement A; Evidence, low)

Evidence: Systemic treatment options for adult and paediatric patients with metastatic PPGL are limited and, therefore, the choice of therapeutic selection for paediatric patients should be individualised, directed by a multidisciplinary specialist team and discussed with the patient's family. The definition of metastatic disease is provided in **Supplementary Box 3**[111]. The natural history of metastatic PPGL is variable and can range from slow growing indolent to rapidly progressive tumours. The rate of tumour progression, burden and sites of metastatic disease are key considerations when deciding on a therapeutic strategy, as are the clinical symptoms and/or signs, and the wishes of the patient and their family (**Figure 1**).

Findings from retrospective adult cohorts have shown that approximately 50% of all treatment-naïve patients with metastatic PPGL have stable disease at one year[149]. These findings indicate that active surveillance with regular radiological monitoring could be considered for asymptomatic or minimally symptomatic patients with low tumour burden and a slow progression rate,.

Surgery is the only curative treatment option for metastatic PPGL . If complete resection is not possible, debulking surgery or metastasectomy can be considered in children with metastatic PPGL. Debulking is defined as the incomplete resection of tumour tissue in the context of metastatic disease, aimed at improving patient signs and symptoms. In a 2022 study, adults and children with metastatic PPGL and low tumour burden showed longer disease-specific survival compared with those with high tumour burden[150]. Importantly, studies including adults and a small cohort of children with metastatic PPGL showed that resection of the primary tumour improved signs and symptoms of catecholamine excess and overall survival[151,152]. Finally, debulking surgery can prevent complications related to compression of adjacent organs or vascular structures[153,154], increase the efficacy of subsequent systemic therapy and improve the uptake of radiopharmaceutical agents in the remaining tumour(s)[155,156].

Systemic treatment options are typically considered for patients with high tumour burden usually associated with rapid tumour progression rate, to prolong survival or as an adjunct to debulking surgery (**Figure 1**). Targeted molecular radiotherapies are a treatment option for paediatric patients with metastatic PPGL when tumour lesions have avidity for the corresponding diagnostic radionuclides and do not have rapid progression. The radioactive compound that is most studied amongst adult[157–160] and paediatric patients with metastatic PPGL[159,160] is radioactive [^{131}I]-MIBG. A systematic review and meta-analysis of 17 studies showed that tumour response following [^{131}I]-MIBG could be achieved in 82% of patients[161]. Application of high-specific-activity [^{131}I]-MIBG molecules (that administer lower mass doses) was associated with 92% partial response or stable disease in two studies from the past 5 years[162,163] and was approved in 2018 by the FDA for the treatment of children with metastatic PPGL older than 12 years[164]. However, the production of high-specific-activity [^{131}I]-MIBG was announced to be terminating in the US in early 2024 due to high costs and lack of commercial demand[232]. Finally, clinicians should not discount that some children with metastatic PPGL could be expected to lack avidity for MIBG[163,165].

The use of peptide receptor radionuclide therapy (PRRT) targeting SSTR2 and SSTR5 (usually expressed on PPGL cells) shows promising results in adult patients with metastatic PPGL, especially among those with *SDHx* pathogenic variants[166,167]. In addition, treatment with PRRT has been applied with effectiveness and minimal adverse effects in paediatric patients with metastatic neuroendocrine tumours[168]. For children with metastatic PPGL and SSTR-expressing lesions, PRRT has not yet been approved[169]. However, several clinical trials (**Supplementary Table 11**) are currently evaluating PRRT for children with metastatic PPGL[132], so this option can be explored in the setting of a clinical trial or as an 'off-label' option under local governance and multidisciplinary team guidance. Despite their promising performance, all currently available systemic radionuclide therapies are associated with adverse events[168,170,171] in children and there are limited data on potential adverse effects that appear later in life.

Systemic chemotherapy consisting of cyclophosphamide, vincristine and dacarbazine (CVD) is currently used for rapidly progressive metastatic PPGL or high tumour burden[172–174], or for patients who have progressive disease despite previous treatment using targeted radionuclide therapies (**Figure 1**). Although there are no prospective clinical trials to establish the effectiveness of CVD in children, and retrospective studies include mainly small cohorts of

adults without systematic follow-up, cumulative findings indicate that CVD can delay tumour growth, and improve symptoms/signs of catecholamine excess[156,172,175]. Disease control rates with CVD chemotherapy are estimated at approximately 40%, but a notable number of patients experience therapeutic failure after a short period of remission[172,173,175–177]. CVD chemotherapy is associated with adverse effects such as myelosuppression, peripheral neuropathy and gastrointestinal toxicity[173,178].

As with other paediatric cancers[179], preliminary studies show promising results for the treatment of metastatic PPGL with temozolomide, especially among patients with *SDHB* pathogenic variants[180–183]. Notably, temozolomide is an oral analogue of dacarbazine and therefore is not advised for patients following failure of treatment with CVD[180]. Anti-angiogenic agents such as tyrosine kinase inhibitors are currently studied for the treatment of metastatic PPGL[184]. Despite their increasing application in other paediatric cancers[185–187], tyrosine kinase inhibitors have not yet been approved for treatment in paediatric patients with metastatic PPGL. Similarly, HIF2α inhibitors are currently under evaluation as a potential treatment of paediatric PPGL[188,189]. Prospective clinical trials, however, are needed to validate the efficiency and long-term safety of targeted therapies[190].

- **S33. In paediatric patients with oligometastases or metastasis-related pain, ablation treatment including radiotherapy can be considered.** (Agreement A; Evidence, low)

Evidence: In patients with metastatic PPGL, the goal of treatment with localised therapies is to reduce symptoms and/or signs of catecholamine excess, palliate metastasis-related pain, treat oligometastases and improve prognosis. Given the rarity of metastatic PPGL and the concern for fatal cardiovascular instability due to ablation-related catecholamine release, data on ablative treatment for metastatic PPGL come from small retrospective studies on adult cohorts[191–196]. In particular, thermal ablation in metastatic bone lesions can delay severe skeletal events[191–194]. Similarly, radiofrequency ablation (RFA) of hepatic lesions can lead to radiological disease response[191,195–197]. In a 2019 study, application of local therapies, such as RFA, cryoablation and percutaneous ethanol injections, in patients with metastatic PPGL was associated with an 86% radiological and 92% biochemical control[198]. Although children older than 8 years were included in this latest study,[198] most data on the efficacy and safety of local therapies in children come from studies on RFA to control pain in paediatric patients with sarcoma[199,200].

Data on the use of local radiotherapy in paediatric cohorts with metastatic PPGL is sparse[201–203]. It is traditionally used for the management of pain and compressive symptoms/signs from localised disease not amenable to other therapies[204–206]. Nevertheless, apart from palliative purposes, targeted radiotherapies, such as external beam radiation or stereotactic body radiation therapy, are increasingly used to improve prognosis for oligometastases, with promising results for long-term local tumour[207,208] and tumour-related control of symptoms and/or signs[209,210] in adults and children older than 11 years. Finally, antiresorptive treatments including zolendronic acid or denosumab can be considered for children with symptomatic bone metastases or skeletal-related events such as hypercalcaemia, a high burden of skeletal disease or those with a history of pathological fractures[211].

- **S34. Pre-ablation treatment with adrenoceptor blocking agent should be initiated to reduce haemodynamic variability in case of catecholamine release during the procedure. Post-ablation cardiovascular monitoring should be initiated in all paediatric patients for at least 24 hours.** (Agreement A; Evidence, low)

Evidence: Pre-ablation treatment with adrenoceptor blockade is essential and should be initiated before an ablative procedure (such as RFA) of functional tumours according to the titration schema shown in **Table 4**, to minimise the risks of a catecholamine crisis[191,192,195] Other procedural risks include haemorrhage, infection, injury to surrounding organs, seeding of the ablation probe, procedural pain and transitory neurological deficiencies. Additionally, post-RFA syndrome with fever and flu-like symptoms has been reported[192]. Children who undergo ablative procedures should be monitored post-procedure for at least 24 hours[192]. For symptomatic paediatric patients with catecholamine secreting metastatic PPGL, adrenoreceptor blockade should be continued for as long as tolerated to minimise complications related to catecholamine release in doses prior to pre-ablation titration interval. In patients with oligometastatic disease confined to the skeleton and treated with radiation therapy, the dose of the adrenoreceptor blockade can be reduced over time, provided the patient is responding to therapy. For asymptomatic patients with metastatic PPGL but negative biochemistry, adrenoreceptor blockade can be stopped after discharge from the hospital and discussion of clinical and tumour-related aspects in a multidisciplinary team.

- **S35. For paediatric patients with newly diagnosed metastatic disease, radiological follow-up should be initiated within 3–6 months, depending on clinical judgement**

as well as tumour burden and location of lesion(s). (Agreement A; Evidence, very low)

Evidence: The role of imaging in metastatic PPGL includes an initial evaluation of the extent of metastatic disease (staging) and surveillance of disease progression and response to treatment (re-staging). Although evidence-based literature to support the frequency of monitoring is limited[212–215], a time interval of approximately 3 months for establishing the rate of disease progression after the initial diagnosis of metastatic disease is usually suggested[123,216,217]. This interval, however, can vary according to clinical judgement, the patient's clinical presentation, the size and location of lesion(s) (for example, organs *versus* bones), and planning of specific treatment strategies.

- **S36. The option of fertility preservation should be discussed with teenage patients with advanced metastatic disease before cytotoxic treatment or radiotherapy of the pelvic area.** (Agreement: A; Evidence, low)

Gonadal dysfunction and infertility are major points of concern for young patients and their families, causing additional fear and anxiety related to cancer treatment. Careful consideration of this issue and appropriate patient and family counselling is imperative.

Evidence: Supplementary Box 4.

[H1] Transition to adult services

- **S37. Transition from paediatric to adult care is essential and should be initiated sometime after the patient turns 16 years old.** (Agreement: A; Evidence, very low)

Transitioning clinical care from paediatric to adult services requires adequate resources and coordination. An excellent transition process is dependent on the education of adult physicians alongside the appropriate preparation of the paediatric patient and family.

Evidence: Supplementary Box 5.

- **S38. Psychological support should be offered to the children and their relatives at the time of initial PPGL diagnosis and genetic counselling, any PPGL-related procedures, as well as during follow-up.** (Agreement A; Evidence, very low)

Evidence: The diagnosis and treatment of cancer in childhood and adolescence can have psychological effects on all aspects of a child's life and compromise a young person's physical, social, emotional and cognitive development[218]. The PPGL diagnosis influences not only the

child but the entire family unit[219]. It can affect adherence to treatment, engagement with services, willingness to participate in patient directed care models and overall well-being and quality of life[220]. An ideal transition process to adult care should include clinical psychologists as part of the multidisciplinary approach to assess psychological and psychosocial needs and offer psychological support for all family members[221]. The Standards of Care for Children with Cancer guidelines of the European Society for Paediatric Oncology, as well as the Psychosocial Standards of Care Project for Childhood Cancer (PSCPCC) recommend that every child with cancer and their families should be offered psychological support through all stages of illness, with long-term monitoring and interventions to reintegrate the child into society and education as individually needed [221,222]. Such psychological interventions have been shown to be effective at reducing anxiety and depressive symptoms as well as enhancing quality of life and should be adapted according to the child's age and developmental stage[218,223].

- **S39. Children and their families should be offered participation in national and international registries with pseudonymised databases and tissue biobanks to promote research on disease diagnosis, management, and treatment.** (Agreement A; Evidence, very low)

Evidence: Historically, enrolment of children (<15 years old) to research protocols has been higher than for adults[224–226]. This high enrolment has led to the publication of evidence-based guidelines that, in turn, have contributed to advances in paediatric cancer prevention, diagnosis and treatment strategies[227]. Apart from the long-term benefits associated with the promotion of clinical and scientific research, participation in clinical trials is also associated with improved survival of participating children, young adolescents and young adults compared with paediatric patients not enrolled in clinical trials [228,229]. The development of national and international data registries and better collaboration between existing research and advocacy groups should improve understanding of these tumours by combining traditional randomised controlled clinical trials with the power of large cohort data[230].

[H1] Conclusions

A Delphi process was applied to establish consensus across 40 experts from 11 countries and we have provided 39 statements of recommendations for the diagnosis, management and long-

term surveillance for children with or at risk of PPGL. Of note, not all of the recommendations are supported by high quality evidence and some recommendations are provided based on low quality evidence but expert consensus opinion (**Box 1**).

This Consensus Statement serves as a catalyst to further promote close working relationships between paediatric and adult specialists managing patients with PPGL, and between specialists and national and international patient support and advocacy groups.

This Consensus Statement has highlighted the strong hereditary basis of PPGL and the requirement for surveillance of asymptomatic genetic carriers from childhood or early adulthood and the need for life-long follow-up. Additionally, this Consensus Statement supports a role for wide-scale adoption of 'family clinic' models for families affected by PPGL or families with individuals carrying a PPGL predisposition gene. Future research should focus on specific recommendations to guide the paediatric anaesthesia team with intra-operative management of catecholamine producing tumours.

Finally, this international and collaborative work has emphasised the need for novel treatment options and the need for children and young adults to be included in local, national and international data registries of PPGL and in the design of clinical trials.

References

1. Bausch, B. *et al.* Long-term prognosis of patients with pediatric pheochromocytoma. *Endocr Relat Cancer* **21**, 17–25 (2014).
2. Ciftci, A. O., Tanyel, F. C., Şenocak, M. E. & Büyükpamukçu, N. Pheochromocytoma in children. *J Pediatr Surg* **36**, 447–452 (2001).
3. HUME, D. M. Pheochromocytoma in the adult and in the child. *Am J Surg* **99**, 458–496 (1960).
4. Wyszyńska, T., Cichocka, E., Wieteska-Klimczak, A., Jobs, K. & Januszewicz, P. A single pediatric center experience with 1025 children with hypertension. *Acta Paediatr* **81**, 244–246 (1992).
5. Barontini, M., Levin, G. & Sanso, G. Characteristics of pheochromocytoma in a 4- to 20-year-old population. *Ann N Y Acad Sci* **1073**, 30–37 (2006).
6. Pamporaki, C. *et al.* Characteristics of Pediatric vs Adult Pheochromocytomas and Paragangliomas. *J Clin Endocrinol Metab* **102**, 1122–1132 (2017).
7. Neumann, H. P. H. *et al.* Germ-Line Mutations in Nonsyndromic Pheochromocytoma. *New England Journal of Medicine* **346**, 1459–1466 (2002).

8. de Tersant, M. *et al.* Pheochromocytoma and Paraganglioma in Children and Adolescents: Experience of the French Society of Pediatric Oncology (SFCE). *J Endocr Soc* **4**, bvaa039 (2020).
9. Redlich, A. *et al.* Pseudohypoxic pheochromocytomas and paragangliomas dominate in children. *Pediatr Blood Cancer* **68**, e28981 (2021).
10. Fishbein, L. *et al.* Comprehensive Molecular Characterization of Pheochromocytoma and Paraganglioma. *Cancer Cell* **31**, 181–193 (2017).
11. Dahia, P. L. M. Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. *Nat Rev Cancer* **14**, 108–119 (2014).
12. Michałowska, I. *et al.* Growth Rate of Paragangliomas Related to Germline Mutations of the SDHx Genes. *Endocrine Practice* **23**, 342–352 (2017).
13. Pham, T. H. *et al.* Pheochromocytoma and paraganglioma in children: a review of medical and surgical management at a tertiary care center. *Pediatrics* **118**, 1109–17 (2006).
14. Davidoff, D. F. *et al.* Surveillance Improves Outcomes for Carriers of *SDHB* Pathogenic Variants: A Multicenter Study. *J Clin Endocrinol Metab* **107**, e1907–e1916 (2022).
15. Amar, L. *et al.* International consensus on initial screening and follow-up of asymptomatic SDHx mutation carriers. *Nat Rev Endocrinol* **17**, 435–444 (2021).
16. Atkins D *et al.* Grading quality of evidence and strength of recommendations. *BMJ* **328**, 1490 (2004).
17. Swiglo, B. A. *et al.* A Case for Clarity, Consistency, and Helpfulness: State-of-the-Art Clinical Practice Guidelines in Endocrinology Using the Grading of Recommendations, Assessment, Development, and Evaluation System. *J Clin Endocrinol Metab* **93**, 666–673 (2008).
18. Fassnacht, M. *et al.* Adrenocortical carcinomas and malignant phaeochromocytomas: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* **31**, 1476–1490 (2020).
19. PDQ Pediatric Treatment Editorial Board. Childhood Pheochromocytoma and Paraganglioma Treatment (PDQ®): Health Professional Version. In: PDQ Cancer Information Summaries. Bethesda (MD): National Cancer Institute (US); June 8, (2022).
20. Lenders, J. W. M. *et al.* Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* **99**, 1915–1942 (2014).
21. Croke, J. M. & El-Sayed, S. Multidisciplinary Management of Cancer Patients: Chasing a Shadow or Real Value? An Overview of the Literature. *Current Oncology* **19**, 232–238 (2012).
22. Magi, L. *et al.* Multidisciplinary Management of Neuroendocrine Neoplasia: A Real-World Experience from a Referral Center. *J Clin Med* **8**, 910 (2019).
23. Metz, D. C. *et al.* A rationale for multidisciplinary care in treating neuroendocrine tumours. *Curr Opin Endocrinol Diabetes Obes* **19**, 306–313 (2012).
24. Taïeb, D. *et al.* Clinical consensus guideline on the management of phaeochromocytoma and paraganglioma in patients harbouring germline SDHD pathogenic variants. *Lancet Diabetes Endocrinol* **11**, 345–361 (2023).
25. Révillon, Y. *et al.* Pheochromocytoma in children: 15 cases. *J Pediatr Surg* **27**, 910–911 (1992).
26. Virgone, C. *et al.* Pheochromocytomas and paragangliomas in children: Data from the Italian Cooperative Study (TREP). *Pediatr Blood Cancer* **67**, e28332 (2020).

27. Geroula, A. *et al.* Pheochromocytoma and paraganglioma: clinical feature-based disease probability in relation to catecholamine biochemistry and reason for disease suspicion. *Eur J Endocrinol* **181**, 409–420 (2019).
28. King, K. S., Darmani, N. A., Hughes, M. S., Adams, K. T. & Pacak, K. Exercise-induced nausea and vomiting: another sign and symptom of pheochromocytoma and paraganglioma. *Endocrine* **37**, 403–407 (2010).
29. Batsis, M. *et al.* Attention Deficit Hyperactivity Disorder in Pediatric Patients with Pheochromocytoma and Paraganglioma. *Hormone and Metabolic Research* **48**, 509–513 (2016).
30. Sullivan, J., Groshong, T. & Tobias, J. D. Presenting Signs and Symptoms of Pheochromocytoma in Pediatric-aged Patients. *Clin Pediatr (Phila)* **44**, 715–719 (2005).
31. Flynn, J. T. *et al.* Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics* **140**, e20171904 (2017).
32. Chandar, J. & Zilleruelo, G. Hypertensive crisis in children. *Pediatric Nephrology* **27**, 741–751 (2012).
33. Lenders, J. W., Eisenhofer, G., Mannelli, M. & Pacak, K. Phaeochromocytoma. *The Lancet* **366**, 665–675 (2005).
34. Reddy, V. S. *et al.* Twenty-five-year surgical experience with pheochromocytoma in children. *Am Surg* **66**, 1085–91 (2000).
35. Eisenhofer, G. *et al.* Plasma Normetanephrine and Metanephrine for Detecting Pheochromocytoma in von Hippel–Lindau Disease and Multiple Endocrine Neoplasia Type 2. *New England Journal of Medicine* **340**, 1872–1879 (1999).
36. Eisenhofer, G. *et al.* 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* **64**, 1646–1656 (2018).
37. Brown, M. J. & Allison, D. J. Renal conversion of plasma DOPA to urine dopamine. *Br J Clin Pharmacol* **12**, 251–3 (1981).
38. Patin, F. *et al.* Low specificity of urinary 3-methoxytyramine in screening of dopamine-secreting pheochromocytomas and paragangliomas. *Clin Biochem* **49**, 1205–1208 (2016).
39. Peitzsch, M. *et al.* Overnight/first-morning urine free metanephrines and methoxytyramine for diagnosis of pheochromocytoma and paraganglioma: is this an option? *Eur J Endocrinol* **182**, 499–509 (2020).
40. Zuo, M. *et al.* High specificity of spot urinary free metanephrines in diagnosis and prognosis of pheochromocytomas and paragangliomas by HPLC with electrochemical detection. *Clin Chim Acta* **478**, 82–89 (2018).
41. Sbardella, E. & Grossman, A. B. Pheochromocytoma: An approach to diagnosis. *Best Pract Res Clin Endocrinol Metab* **34**, 101346 (2020).
42. Wang, K. *et al.* Stability and reference intervals of spot urinary fractionated metanephrines and methoxytyramine by tandem mass spectrometry as a screening method for pheochromocytoma and paraganglioma. *Endocrine* **69**, 188–195 (2020).
43. Sarathi, V. *et al.* Performance of plasma fractionated free metanephrines by enzyme immunoassay in the diagnosis of pheochromocytoma and paraganglioma in children. *Endocr Pract* **18**, 694–9 (2012).
44. Weise, M., Merke, D. P., Pacak, K., Walther, M. M. & Eisenhofer, G. Utility of Plasma Free Metanephrines for Detecting Childhood Pheochromocytoma. *J Clin Endocrinol Metab* **87**, 1955–1960 (2002).
45. Lenders, J. W. *et al.* Determination of metanephrines in plasma by liquid chromatography with electrochemical detection. *Clin Chem* **39**, 97–103 (1993).

46. Peitzsch, M. *et al.* Analysis of plasma 3-methoxytyramine, normetanephrine and metanephrine by ultraperformance liquid chromatography-tandem mass spectrometry: utility for diagnosis of dopamine-producing metastatic phaeochromocytoma. *Ann Clin Biochem* **50**, 147–55 (2013).
47. Weismann, D. *et al.* Measurements of plasma metanephrines by immunoassay vs liquid chromatography with tandem mass spectrometry for diagnosis of pheochromocytoma. *Eur J Endocrinol* **172**, 251–60 (2015).
48. Eisenhofer, G., Pamporaki, C. & Lenders, J. W. M. Biochemical Assessment of Pheochromocytoma and Paraganglioma. *Endocr Rev* **44**, 862–909 (2023).
49. Robertson, D. *et al.* Comparative assessment of stimuli that release neuronal and adrenomedullary catecholamines in man. *Circulation* **59**, 637–43 (1979).
50. Deutschbein, T. *et al.* Influence of various confounding variables and storage conditions on metanephrine and normetanephrine levels in plasma. *Clin Endocrinol (Oxf)* **73**, 153–60 (2010).
51. Därr, R. *et al.* Biochemical diagnosis of phaeochromocytoma using plasma-free normetanephrine, metanephrine and methoxytyramine: importance of supine sampling under fasting conditions. *Clin Endocrinol (Oxf)* **80**, 478–86 (2014).
52. Boyd, J. *et al.* A high rate of modestly elevated plasma normetanephrine in a population referred for suspected PPGL when measured in a seated position. *Eur J Endocrinol* **181**, 301–309 (2019).
53. Cook, L. S. Needle Phobia. *J Infus Nurs* **39**, 273–9 (2016).
54. Netter, P. Psychological aspects of catecholamine response patterns to pain and mental stress in essential hypertensive patients and controls. *J Clin Hypertens* **3**, 727–42 (1987).
55. Eijkelenkamp, K. *et al.* Blood sampling for metanephrines comparing venipuncture vs. indwelling intravenous cannula in healthy subjects. *Clin Chem Lab Med* **58**, 1681–1686 (2020).
56. Pommer, G. *et al.* Preanalytical Considerations and Outpatient Versus Inpatient Tests of Plasma Metanephrines to Diagnose Pheochromocytoma. *J Clin Endocrinol Metab* **107**, e3689–e3698 (2022).
57. Berger-Achituv, S., Budde-Schwartzman, B., Ellis, M. H., Shenkman, Z. & Erez, I. Blood sampling through peripheral venous catheters is reliable for selected basic analytes in children. *Pediatrics* **126**, e179-86 (2010).
58. Lee, S. U. *et al.* Factors associated with difficult intravenous access in the pediatric emergency department. *J Vasc Access* **21**, 180–185 (2020).
59. Kuo, H.-C., Pan, H.-H., Creedy, D. K. & Tsao, Y. Distraction-Based Interventions for Children Undergoing Venipuncture Procedures: A Randomized Controlled Study. *Clin Nurs Res* **27**, 467–482 (2018).
60. Pamporaki, C. *et al.* Seasonal variation in plasma free normetanephrine concentrations: implications for biochemical diagnosis of pheochromocytoma. *Eur J Endocrinol* **170**, 349–57 (2014).
61. de Jong, W. H. A. *et al.* Dietary influences on plasma and urinary metanephrines: implications for diagnosis of catecholamine-producing tumors. *J Clin Endocrinol Metab* **94**, 2841–9 (2009).
62. Goldstein, D. S. *et al.* Sources and physiological significance of plasma dopamine sulfate. *J Clin Endocrinol Metab* **84**, 2523–31 (1999).
63. Eisenhofer, G. *et al.* Plasma metadrenalines: do they provide useful information about sympatho-adrenal function and catecholamine metabolism? *Clin Sci (Lond)* **88**, 533–42 (1995).

64. Jéquier, E. & Perret, C. Urinary excretion of catecholamines and their main metabolites after myocardial infarction; relationahip to the clinical syndrome. *Eur J Clin Invest* **1**, 77–83 (1970).
65. Leow, M. K. S., Loh, K. C., Kiat Kwek, T. & Ng, P. Y. Catecholamine and metanephrine excess in intracerebral haemorrhage: revisiting an obscure yet common 'pseudophaeochromocytoma'. *J Clin Pathol* **60**, 583–4 (2007).
66. Syed, A. A., Wheatley, H. A., Badminton, M. N. & McDowell, I. F. W. Urinary catecholamines and metabolites in the immediate postoperative period following major surgery. *J Clin Pathol* **57**, 548–50 (2004).
67. Chamorro, A. *et al.* Catecholamines, infection, and death in acute ischemic stroke. *J Neurol Sci* **252**, 29–35 (2007).
68. Kline, G. A., Boyd, J., Sadrzadeh, H. S. M. & Leung, A. A. Inpatient Measurements of Urine Metanephrines are Indistinguishable from Pheochromocytoma: Retrospective Cohort Study. *Am J Med* **134**, 1039-1046.e3 (2021).
69. Eisenhofer, G., Januszewicz, A., Pamporaki, C., Lenders , J. W. M. Chapter 22. Endocrine Hypertensive Emergencies. In: Endocrine and Metabolic Medical Emergencies. A clinician´s Guide, 2nd Edition, (2018)
70. Peitzsch, M., Mangelis, A., Eisenhofer, G. & Huebner, A. Age-specific pediatric reference intervals for plasma free normetanephrine, metanephrine, 3-methoxytyramine and 3-O-methyldopa: Particular importance for early infancy. *Clinica Chimica Acta* **494**, 100–105 (2019).
71. Franscini, L. C. *et al.* Pediatric reference intervals for plasma free and total metanephrines established with a parametric approach: Relevance to the diagnosis of neuroblastoma. *Pediatr Blood Cancer* **62**, 587–593 (2015).
72. Eisenhofer, G., Peitzsch, M., Bechmann, N. & Huebner, A. Biochemical Diagnosis of Catecholamine-Producing Tumors of Childhood: Neuroblastoma, Pheochromocytoma and Paraganglioma. *Front Endocrinol (Lausanne)* **13**, 901760 (2022).
73. MODI, N. & HUTTON, J. L. Urinary Creatinine Excretion and Estimation of Muscle Mass in Infants of 25-34 Weeks Gestation. *Acta Paediatr* **79**, 1156–1162 (1990).
74. Al-Dahhan, J., Stimmler, L., Chantler, C. & Haycock, G. B. Urinary creatinine excretion in the newborn. *Arch Dis Child* **63**, 398–402 (1988).
75. Skinner, A. M., Addison, G. M. & Price, D. A. Changes in the urinary excretion of creatinine, albumin and N-acetyl-β-D-glucosaminidase with increasing age and maturity in healthy schoolchildren. *Eur J Pediatr* **155**, 596–602 (1996).
76. Pussard, E., Neveux, M. & Guigueno, N. Reference intervals for urinary catecholamines and metabolites from birth to adulthood. *Clin Biochem* **42**, 536–539 (2009).
77. Griffin, A., O'Shea, P., FitzGerald, R., O'Connor, G. & Tormey, W. Establishment of a paediatric age-related reference interval for the measurement of urinary total fractionated metanephrines. *Annals of Clinical Biochemistry: International Journal of Laboratory Medicine* **48**, 41–44 (2011).
78. Fitzgibbon, M. C. & Tormey, W. P. Paediatric Reference Ranges for Urinary Catecholamines/Metabolites and Their Relevance in Neuroblastoma Diagnosis. *Annals of Clinical Biochemistry: International Journal of Laboratory Medicine* **31**, 1–11 (1994).
79. Eisenhofer, G. *et al.* Reference intervals for LC-MS/MS measurements of plasma free, urinary free and urinary acid-hydrolyzed deconjugated normetanephrine, metanephrine and methoxytyramine. *Clinica Chimica Acta* **490**, 46–54 (2019).

80. Haap, M., Blaschka, F., Lehmann, R., Hoyer, A. & Müssig, K. Association Between Urinary Catecholamine Excretion and Urine Volume. *Hormone and Metabolic Research* **51**, 531–538 (2019).
81. Davidson, D. F., Hammond, P. J., Murphy, D. & Carachi, R. Age-related medical decision limits for urinary free (unconjugated) metadrenalines, catecholamines and metabolites in random urine specimens from children. *Annals of Clinical Biochemistry: International Journal of Laboratory Medicine* **48**, 358–366 (2011).
82. Hirsch, D., Grossman, A., Nadler, V., Alboim, S. & Tsvetov, G. Pheochromocytoma: Positive predictive values of mildly elevated urinary fractionated metanephrines in a large cohort of community-dwelling patients. *J Clin Hypertens (Greenwich)* **21**, 1527–1533 (2019).
83. Eisenhofer, G. *et al.* Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. *J Clin Endocrinol Metab* **88**, 2656–66 (2003).
84. Hanafy, A. K. *et al.* Imaging features of adrenal gland masses in the pediatric population. *Abdom Radiol (NY)* **45**, 964–981 (2020).
85. Melo-Leite, A. F. de *et al.* Adrenocortical neoplasms in adulthood and childhood: distinct presentation. Review of the clinical, pathological and imaging characteristics. *Journal of Pediatric Endocrinology and Metabolism* **30**, 253-276 (2017).
86. Goldstein, R. E. *et al.* Clinical experience over 48 years with pheochromocytoma. *Ann Surg* **229**, 755–64 (1999).
87. Ilias, I. & Pacak, K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. *J Clin Endocrinol Metab* **89**, 479–91 (2004).
88. Daniel, E., Jones, R., Bull, M. & Newell-Price, J. Rapid-sequence MRI for long-term surveillance for paraganglioma and phaeochromocytoma in patients with succinate dehydrogenase mutations. *Eur J Endocrinol* **175**, 561–570 (2016).
89. Tufton, N., White, G., Drake, W. M., Sahdev, A. & Akker, S. A. Diffusion-weighted imaging (DWI) highlights SDHB -related tumours: A pilot study. *Clin Endocrinol (Oxf)* **91**, 104-109 (2019)
90. Weiser, D. A., Kaste, S. C., Siegel, M. J. & Adamson, P. C. Imaging in childhood cancer: a Society for Pediatric Radiology and Children's Oncology Group Joint Task Force report. *Pediatr Blood Cancer* **60**, 1253–60 (2013).
91. Eisenhofer, G. *et al.* Adverse drug reactions in patients with phaeochromocytoma: incidence, prevention and management. *Drug Saf* **30**, 1031–62 (2007).
92. Chong, A. L. *et al.* Imaging in pediatric patients: time to think again about surveillance. *Pediatr Blood Cancer* **55**, 407–13 (2010).
93. Ahmed, B. A. *et al.* Cumulative effective doses from radiologic procedures for pediatric oncology patients. *Pediatrics* **126**, e851-8 (2010).
94. Siegel, J. A., Sacks, B., Pennington, C. W. & Welsh, J. S. Dose Optimization to Minimize Radiation Risk for Children Undergoing CT and Nuclear Medicine Imaging Is Misguided and Detrimental. *Journal of Nuclear Medicine* **58**, 865–868 (2017).
95. Linet, M. S., Kim, K. P. & Rajaraman, P. Children's exposure to diagnostic medical radiation and cancer risk: epidemiologic and dosimetric considerations. *Pediatr Radiol* **39 (Suppl 1)**, S4-26 (2009).
96. Taïeb, D. *et al.* European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of phaeochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging* **46**, 2112–2137 (2019).
97. Jha, A. *et al.* Sporadic Primary Pheochromocytoma: A Prospective Intraindividual Comparison of Six Imaging Tests (CT, MRI, and PET/CT Using ^{68} Ga-DOTATATE,

FDG, ^{18} F-FDOPA, and ^{18} F-FDA). *American Journal of Roentgenology* **218**, 342–350 (2022).
98. Jha, A. *et al.* Superiority of 68Ga-DOTATATE over 18F-FDG and anatomic imaging in the detection of succinate dehydrogenase mutation (SDHx)-related pheochromocytoma and paraganglioma in the pediatric population. *Eur J Nucl Med Mol Imaging* **45**, 787–797 (2018).
99. Janssen, I. *et al.* Superiority of [68Ga]-DOTATATE PET/CT to Other Functional Imaging Modalities in the Localization of *SDHB* -Associated Metastatic Pheochromocytoma and Paraganglioma. *Clinical Cancer Research* **21**, 3888–3895 (2015).
100. Janssen, I. *et al.* ^{68} Ga-DOTATATE PET/CT in the Localization of Head and Neck Paragangliomas Compared with Other Functional Imaging Modalities and CT/MRI. *Journal of Nuclear Medicine* **57**, 186–191 (2016).
101. Jaiswal, S. K. *et al.* The utility of ^{68} Ga-DOTATATE PET/CT in localizing primary/metastatic pheochromocytoma and paraganglioma in children and adolescents – a single-center experience. *Journal of Pediatric Endocrinology and Metabolism* **34**, 109–119 (2021).
102. Rahman, W. T. *et al.* The impact of infection and inflammation in oncologic 18F-FDG PET/CT imaging. *Biomedicine & Pharmacotherapy* **117**, 109168 (2019).
103. Timmers, H. J. L. M. *et al.* Superiority of Fluorodeoxyglucose Positron Emission Tomography to Other Functional Imaging Techniques in the Evaluation of Metastatic *SDHB* -Associated Pheochromocytoma and Paraganglioma. *Journal of Clinical Oncology* **25**, 2262–2269 (2007).
104. Fiebrich, H.-B. *et al.* 6-[F-18]Fluoro- <scp>l</scp> -Dihydroxyphenylalanine Positron Emission Tomography Is Superior to Conventional Imaging with 123I-Metaiodobenzylguanidine Scintigraphy, Computer Tomography, and Magnetic Resonance Imaging in Localizing Tumors Causing Catecholamine Excess. *J Clin Endocrinol Metab* **94**, 3922–3930 (2009).
105. Fonte, J. S. *et al.* False-negative 123I-MIBG SPECT is most commonly found in SDHB-related pheochromocytoma or paraganglioma with high frequency to develop metastatic disease. *Endocr Relat Cancer* **19**, 83–93 (2012).
106. Jochmanova, I. & Pacak, K. Genomic Landscape of Pheochromocytoma and Paraganglioma. *Trends Cancer* **4**, 6–9 (2018).
107. Horton, C. *et al.* Universal Germline Panel Testing for Individuals With Pheochromocytoma and Paraganglioma Produces High Diagnostic Yield. *J Clin Endocrinol Metab* **107**, e1917–e1923 (2022).
108. López-Jiménez, E. *et al.* Research Resource: Transcriptional Profiling Reveals Different Pseudohypoxic Signatures in SDHB and VHL-Related Pheochromocytomas. *Molecular Endocrinology* **24**, 2382–2391 (2010).
109. Burnichon, N. *et al.* Somatic NF1 inactivation is a frequent event in sporadic pheochromocytoma. *Hum Mol Genet* **21**, 5397–5405 (2012).
110. Welander, J., Söderkvist, P. & Gimm, O. The NF1 gene: a frequent mutational target in sporadic pheochromocytomas and beyond. *Endocr Relat Cancer* **20**, C13–C17 (2013).
111 Mete, O. *et al*. Overview of the 2022 WHO Classification of Paragangliomas and Pheochromocytomas. *Endocrine pathology* **33,** 90-114 (2022).
112. Currás-Freixes, M. *et al.* PheoSeq. *The Journal of Molecular Diagnostics* **19**, 575–588 (2017).

113. Dahia, P. L. M. The Genetic Landscape of Pheochromocytomas and Paragangliomas: Somatic Mutations Take Center Stage. *J Clin Endocrinol Metab* **98**, 2679–2681 (2013).
114. Toledo, R. A. *et al.* Consensus Statement on next-generation-sequencing-based diagnostic testing of hereditary phaeochromocytomas and paragangliomas. *Nat Rev Endocrinol* **13**, 233–247 (2017).
115. Pacak, K. *et al.* New Syndrome of Paraganglioma and Somatostatinoma Associated With Polycythemia. *Journal of Clinical Oncology* **31**, 1690–1698 (2013).
116. Walz, M. K. *et al.* Minimally Invasive Surgery (MIS) in Children and Adolescents with Pheochromocytomas and Retroperitoneal Paragangliomas: Experiences in 42 Patients. *World J Surg* **42**, 1024–1030 (2018).
117. Heloury, Y. *et al.* Minimally invasive adrenalectomy in children. *J Pediatr Surg* **47**, 415–421 (2012).
118. Chen, Y. *et al.* Risk Factors Associated With Perioperative Complications and Prolonged Length of Stay After Laparoscopic Adrenalectomy. *JAMA Surg* **153**, 1036 (2018).
119. Peyton, A. J. Circuit for Monitoring the Median Frequency of the Spectrum of the Surface EMG Signal. *IEEE Trans Biomed Eng* **BME-34**, 391–394 (1987).
120. Takata, M. C., Kebebew, E., Clark, O. H. & Duh, Q.-Y. Laparoscopic bilateral adrenalectomy: results for 30 consecutive cases. *Surg Endosc* **22**, 202–207 (2008).
121. Neumann, H. P. H. *et al.* Comparison of Pheochromocytoma-Specific Morbidity and Mortality Among Adults With Bilateral Pheochromocytomas Undergoing Total Adrenalectomy vs Cortical-Sparing Adrenalectomy. *JAMA Netw Open* **2**, e198898 (2019).
122. Jochmanova, I. *et al.* Clinical characteristics and outcomes of SDHB-related pheochromocytoma and paraganglioma in children and adolescents. *J Cancer Res Clin Oncol* **146**, 1051–1063 (2020).
123. Lenders, J. W. M. *et al.* Genetics, diagnosis, management and future directions of research of phaeochromocytoma and paraganglioma: a position statement and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension. *J Hypertens* **38**, 1443–1456 (2020).
124. Yip, L. *et al.* American Association of Endocrine Surgeons Guidelines for Adrenalectomy. *JAMA Surg* **157**, 870 (2022).
125. Fishbein, L. *et al.* The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Management of Metastatic and/or Unresectable Pheochromocytoma and Paraganglioma. *Pancreas* **50**, 469–493 (2021).
126. Seamon, M. L. & Yamaguchi, I. Hypertension in Pheochromocytoma and Paraganglioma: Evaluation and Management in Pediatric Patients. *Curr Hypertens Rep* **23**, 32 (2021).
127. Fleming, S. *et al.* Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *The Lancet* **377**, 1011–1018 (2011).
128. Ludwig, A. D. *et al.* Recent advances in the diagnosis and treatment of pheochromocytoma in children. *Am J Surg* **194**, 792–6 (2007).
129. Gruber, L. M. *et al.* The Role for Metyrosine in the Treatment of Patients With Pheochromocytoma and Paraganglioma. *J Clin Endocrinol Metab* **106**, e2393–e2401 (2021).
130. Zelinka, T. *et al.* Biochemical Testing After Pheochromocytoma Removal: How Early? *Hormone and Metabolic Research* **47**, 633–636 (2015).

131. King, K. S. *et al.* Metastatic Pheochromocytoma/Paraganglioma Related to Primary Tumor Development in Childhood or Adolescence: Significant Link to *SDHB* Mutations. *Journal of Clinical Oncology* **29**, 4137–4142 (2011).
132. Kuo, M. J. M., Nazari, M. A., Jha, A. & Pacak, K. Pediatric Metastatic Pheochromocytoma and Paraganglioma: Clinical Presentation and Diagnosis, Genetics, and Therapeutic Approaches. *Front Endocrinol (Lausanne)* **13**, 936178 (2022).
133. Li, M. *et al.* Recurrent Disease in Patients With Sporadic Pheochromocytoma and Paraganglioma. *J Clin Endocrinol Metab* **108**, 397–404 (2023).
134. Lorenzo, F. R. *et al.* A novel EPAS1/HIF2A germline mutation in a congenital polycythemia with paraganglioma. *J Mol Med* **91**, 507–512 (2013).
135. Zhuang, Z. *et al.* Somatic HIF2A Gain-of-Function Mutations in Paraganglioma with Polycythemia. *New England Journal of Medicine* **367**, 922–930 (2012).
136. Rosenblum, J. S., Wang, H., Nazari, M. A., Zhuang, Z. & Pacak, K. Pacak–Zhuang syndrome: a model providing new insights into tumor syndromes. *Endocr Relat Cancer* **30**, e230050 (2023).
137. Därr, R. *et al.* Novel insights into the polycythemia–paraganglioma–somatostatinoma syndrome. *Endocr Relat Cancer* **23**, 899–908 (2016).
138. Winzeler, B. *et al.* Investigating the role of somatic sequencing platforms for phaeochromocytoma and paraganglioma in a large UK cohort. *Clin Endocrinol (Oxf)* **97**, 448–459 (2022).
139. Wu, P. *et al.* Mosaicism in von Hippel-Lindau disease with severe renal manifestations. *Clin Genet* **84**, 581–4 (2013).
140. Coppin, L. *et al.* VHL mosaicism can be detected by clinical next-generation sequencing and is not restricted to patients with a mild phenotype. *Eur J Hum Genet* **22**, 1149–52 (2014).
141. Khoury, M. J., Iademarco, M. F. & Riley, W. T. Precision Public Health for the Era of Precision Medicine. *Am J Prev Med* **50**, 398–401 (2016).
142. Bednar, E. M., Sun, C. C., McCurdy, S. & Vernon, S. W. Assessing relatives' readiness for hereditary cancer cascade genetic testing. *Genetics in Medicine* **22**, 719–726 (2020).
143. Teutsch, S. M. *et al.* The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group. *Genetics in Medicine* **11**, 3–14 (2009).
144. Courtney, E. *et al.* Impact of free cancer predisposition cascade genetic testing on uptake in Singapore. *NPJ Genom Med* **4**, 22 (2019).
145. Srinivasan, S., Won, N. Y., Dotson, W. D., Wright, S. T. & Roberts, M. C. Barriers and facilitators for cascade testing in genetic conditions: a systematic review. *European Journal of Human Genetics* **28**, 1631–1644 (2020).
146. Roberts, M. C. *et al.* Delivery Of Cascade Screening For Hereditary Conditions: A Scoping Review Of The Literature. *Health Aff* **37**, 801–808 (2018).
147. American Thyroid Association Guidelines Task Force *et al.* Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid* **19**, 565–612 (2009).
148. Rednam, S. P. *et al.* Von Hippel–Lindau and Hereditary Pheochromocytoma/Paraganglioma Syndromes: Clinical Features, Genetics, and Surveillance Recommendations in Childhood. *Clinical Cancer Research* **23**, e68–e75 (2017).

149. Hescot, S. *et al.* One-Year Progression-Free Survival of Therapy-Naive Patients With Malignant Pheochromocytoma and Paraganglioma. *J Clin Endocrinol Metab* **98**, 4006–4012 (2013).
150. Pamporaki, C. *et al.* Determinants of disease-specific survival in patients with and without metastatic pheochromocytoma and paraganglioma. *Eur J Cancer* **169**, 32–41 (2022).
151. Roman-Gonzalez, A. *et al.* Impact of Surgical Resection of the Primary Tumor on Overall Survival in Patients With Metastatic Pheochromocytoma or Sympathetic Paraganglioma. *Ann Surg* **268**, 172–178 (2018).
152. Strajina, V. *et al.* Surgical Treatment of Malignant Pheochromocytoma and Paraganglioma: Retrospective Case Series. *Ann Surg Oncol* **24**, 1546–1550 (2017).
153. Immergut, M. A., Boldus, R., Köllin, C. P. & Rohlf, P. The Management of Ectopic Pheochromocytoma Producing Ureteral Obstruction. *Journal of Urology* **104**, 337–341 (1970).
154. Nonaka, K., Makuuchi, H., Naruse, Y., Kobayashi, T. & Goto, M. Surgical excision of malignant pheochromocytoma in the left atrium. *The Japanese Journal of Thoracic and Cardiovascular Surgery* **48**, 126–128 (2000).
155. Ohshima, Y. *et al.* Antitumor effects of radionuclide treatment using α-emitting meta-211At-astato-benzylguanidine in a PC12 pheochromocytoma model. *Eur J Nucl Med Mol Imaging* **45**, 999–1010 (2018).
156. Ayala-Ramirez, M. *et al.* Clinical benefits of systemic chemotherapy for patients with metastatic pheochromocytomas or sympathetic extra-adrenal paragangliomas. *Cancer* **118**, 2804–2812 (2012).
157. Nastos, K. *et al.* Peptide Receptor Radionuclide Treatment and (131)I-MIBG in the management of patients with metastatic/progressive phaeochromocytomas and paragangliomas. *J Surg Oncol* **115**, 425–434 (2017).
158. Loh, K.-C., Fitzgerald, P. A., Matthay, K. K., Yeo, P. P. B. & Price, D. C. The treatment of malignant pheochromocytoma with Iodine-131 metaiodobenzylguanidine (131I-MIBG): A comprehensive review of 116 reported patients. *J Endocrinol Invest* **20**, 648–658 (1997).
159. Thorpe, M. P. *et al.* Long-Term Outcomes of 125 Patients With Metastatic Pheochromocytoma or Paraganglioma Treated With 131-I MIBG. *J Clin Endocrinol Metab* **105**, e494–e501 (2020).
160. Wakabayashi, H. *et al.* A phase I clinical trial for [131I]meta-iodobenzylguanidine therapy in patients with refractory pheochromocytoma and paraganglioma. *Sci Rep* **9**, 7625 (2019).
161. van Hulsteijn, L. T., Niemeijer, N. D., Dekkers, O. M. & Corssmit, E. P. M. ^{131} I-<scp>MIBG</scp> therapy for malignant paraganglioma and phaeochromocytoma: systematic review and meta-analysis. *Clin Endocrinol (Oxf)* **80**, 487–501 (2014).
162. Pryma, D. A. *et al.* Efficacy and Safety of High-Specific-Activity ^{131} I-MIBG Therapy in Patients with Advanced Pheochromocytoma or Paraganglioma. *Journal of Nuclear Medicine* **60**, 623–630 (2019).
163. Noto, R. B. *et al.* Phase 1 Study of High-Specific-Activity I-131 MIBG for Metastatic and/or Recurrent Pheochromocytoma or Paraganglioma. *J Clin Endocrinol Metab* **103**, 213–220 (2018).
164. United States Food and Drug Administration. AZEDRA (iobenguane I 131) injection, for intravenous use Initial U.S. Approval: 2018. United States Food and Drug Administration. *accessdata.fda.gov*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209607s000lbl.pdf (2018).

165. FITZGERALD, P. A. *et al.* Malignant Pheochromocytomas and Paragangliomas. *Ann N Y Acad Sci* **1073**, 465–490 (2006).
166. Ziegler, C. G. *et al.* Expression of neuropeptide hormone receptors in human adrenal tumors and cell lines: Antiproliferative effects of peptide analogues. *Proceedings of the National Academy of Sciences* **106**, 15879–15884 (2009).
167. Van Essen, M., Krenning, E. P., De Jong, M., Valkema, R. & Kwekkeboom, D. J. Peptide Receptor Radionuclide Therapy with radiolabelled somatostatin analogues in patients with somatostatin receptor positive tumours. *Acta Oncol (Madr)* **46**, 723–734 (2007).
168. Foster, J. H. *et al.* Peptide receptor radionuclide therapy for treatment of metastatic neuroendocrine tumors in children. *Pediatr Blood Cancer* **68**, e29056 (2021).
169. Strosberg, J. *et al.* Phase 3 Trial of ^{177} Lu-Dotatate for Midgut Neuroendocrine Tumors. *New England Journal of Medicine* **376**, 125–135 (2017).
170. Huibregtse, K. E. *et al.* Incidence and risk factors for secondary malignancy in patients with neuroblastoma after treatment with 131I-metaiodobenzylguanidine. *Eur J Cancer* **66**, 144–152 (2016).
171. Weiss, B., Vora, A., Huberty, J., Hawkins, R. A. & Matthay, K. K. Secondary Myelodysplastic Syndrome and Leukemia Following 131I-Metaiodobenzylguanidine Therapy for Relapsed Neuroblastoma. *J Pediatr Hematol Oncol* **25**, 543–547 (2003).
172. Asai, S., Katabami, T., Tsuiki, M., Tanaka, Y. & Naruse, M. Controlling Tumor Progression with Cyclophosphamide, Vincristine, and Dacarbazine Treatment Improves Survival in Patients with Metastatic and Unresectable Malignant Pheochromocytomas/Paragangliomas. *Horm Cancer* **8**, 108–118 (2017).
173. Huang, H. *et al.* Treatment of malignant pheochromocytoma/paraganglioma with cyclophosphamide, vincristine, and dacarbazine. *Cancer* **113**, 2020–2028 (2008).
174. Jawed, I. *et al.* Continued Tumor Reduction of Metastatic Pheochromocytoma/Paraganglioma Harboring Succinate Dehydrogenase Subunit B Mutations with Cyclical Chemotherapy. *Cell Mol Neurobiol* **38**, 1099–1106 (2018).
175. Niemeijer, N. D., Alblas, G., van Hulsteijn, L. T., Dekkers, O. M. & Corssmit, E. P. M. Chemotherapy with cyclophosphamide, vincristine and dacarbazine for malignant paraganglioma and pheochromocytoma: systematic review and meta-analysis. *Clin Endocrinol (Oxf)* **81**, 642–651 (2014).
176. Averbuch, S. D. Malignant Pheochromocytoma: Effective Treatment with a Combination of Cyclophosphamide, Vincristine, and Dacarbazine. *Ann Intern Med* **109**, 267 (1988).
177. Tanabe, A. *et al.* Combination Chemotherapy with Cyclophosphamide, Vincristine, and Dacarbazine in Patients with Malignant Pheochromocytoma and Paraganglioma. *Horm Cancer* **4**, 103–110 (2013).
178. Berthold, F., Spix, C., Kaatsch, P. & Lampert, F. Incidence, Survival, and Treatment of Localized and Metastatic Neuroblastoma in Germany 1979–2015. *Pediatric Drugs* **19**, 577–593 (2017).
179. Bartels, U. *et al.* The Use and Effectiveness of Temozolomide in Children with Central Nervous System Tumours: A Survey from the Canadian Paediatric Brain Tumour Consortium. *Current Oncology* **18**, 675 (2011).
180. Urquhart, C. *et al.* The use of temozolomide in paediatric metastatic phaeochromocytoma/paraganglioma: A case report and literature review. *Front Endocrinol (Lausanne)* **13**, 1066208 (2022).
181. Perez, K. *et al.* SDHx mutations and temozolomide in malignant pheochromocytoma and paraganglioma. *Endocr Relat Cancer* **29**, 533–544 (2022).

182. Sait, S., Kobos, R., LaQuaglia, M. P., Pandit-Taskar, N. & Modak, S. Acute myeloid leukemia therapy elicits durable complete response in chemoradio-resistant metastatic paraganglioma. *Pediatr Blood Cancer* **64**, e26314 (2017).
183. Singh, C., Bindra, R. S., Glazer, P. M., Vasquez, J. C. & Pashankar, F. Metastatic and multiply relapsed SDH-deficient GIST and paraganglioma displays clinical response to combined poly ADP-ribose polymerase inhibition and temozolomide. *Pediatr Blood Cancer* **70**, e30020 (2023).
184. O'Kane, G. M. *et al.* A phase 2 trial of sunitinib in patients with progressive paraganglioma or pheochromocytoma: the SNIPP trial. *Br J Cancer* **120**, 1113–1119 (2019).
185. Carofiglio, F. *et al.* Bcr-Abl Tyrosine Kinase Inhibitors in the Treatment of Pediatric CML. *Int J Mol Sci* **21**, 4469 (2020).
186. Chen, M., Zhu, Y., Lin, Y., Tengwang, T. & Zhang, L. Use of tyrosine kinase inhibitors for paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia: a systematic review and meta-analysis. *BMJ Open* **11**, e042814 (2021).
187. Tragiannidis, A. & Mantadakis, E. Effects of Tyrosine Kinase Inhibitors on Growth and Bone Metabolism in Children with Haematologic Malignancies. *Cardiovasc Hematol Agents Med Chem* **20**, 175–177 (2022).
188. Kamihara, J. *et al.* Belzutifan, a Potent HIF2α Inhibitor, in the Pacak–Zhuang Syndrome. *New England Journal of Medicine* **385**, 2059–2065 (2021).
189. Toledo, R. A. *et al.* Hypoxia-Inducible Factor 2 Alpha (HIF2α) Inhibitors: Targeting Genetically Driven Tumor Hypoxia. *Endocr Rev* **44**, 312–322 (2023).
190. Kaczmarska, A., Śliwa, P., Lejman, M. & Zawitkowska, J. The Use of Inhibitors of Tyrosine Kinase in Paediatric Haemato-Oncology—When and Why? *Int J Mol Sci* **22**, 12089 (2021).
191. Venkatesan, A. M. *et al.* Radiofrequency Ablation of Metastatic Pheochromocytoma. *Journal of Vascular and Interventional Radiology* **20**, 1483–1490 (2009).
192. McBride, J. F. *et al.* Minimally Invasive Treatment of Metastatic Pheochromocytoma and Paraganglioma: Efficacy and Safety of Radiofrequency Ablation and Cryoablation Therapy. *Journal of Vascular and Interventional Radiology* **22**, 1263–1270 (2011).
193. Pacak, K. *et al.* Radiofrequency Ablation: a Novel Approach for Treatment of Metastatic Pheochromocytoma. *JNCI Journal of the National Cancer Institute* **93**, 648–649 (2001).
194. Gravel, G. *et al.* Prevention of serious skeletal-related events by interventional radiology techniques in patients with malignant paraganglioma and pheochromocytoma. *Endocrine* **59**, 547–554 (2018).
195. Mamlouk, M. D., vanSonnenberg, E., Stringfellow, G., Smith, D. & Wendt, A. Radiofrequency Ablation and Biopsy of Metastatic Pheochromocytoma: Emphasizing Safety Issues and Dangers. *Journal of Vascular and Interventional Radiology* **20**, 670–673 (2009).
196. Ohkawa, S. *et al.* [Examination of percutaneous microwave coagulation and radiofrequency ablation therapy for metastatic liver cancer]. *Gan To Kagaku Ryoho* **29**, 2149–51 (2002).
197. Tepel, J., Hinz, S., Klomp, H.-J., Kapischke, M. & Kremer, B. Intraoperative radiofrequency ablation (RFA) for irresectable liver malignancies. *Eur J Surg Oncol* **30**, 551–5 (2004).
198. Kohlenberg, J. *et al.* Efficacy and Safety of Ablative Therapy in the Treatment of Patients with Metastatic Pheochromocytoma and Paraganglioma. *Cancers (Basel)* **11**, 195 (2019).

199. Chahal, A. *et al.* CT-guided percutaneous radiofrequency ablation of osteoid osteoma: Our experience in 87 patients. *Indian J Radiol Imaging* **27**, 207–215 (2017).
200. Arıkan, Y. *et al.* Percutaneous radiofrequency ablation for osteoid osteoma under guidance of threedimensional fluoroscopy. *J Orthop Surg (Hong Kong)* **24**, 398–402 (2016).
201. Tucker, T. L., Samant, R. S. & Fitzgibbon, E. J. Knowledge and Utilization of Palliative Radiotherapy by Pediatric Oncologists. *Current Oncology* **17**, 48–55 (2010).
202. Weaver, M. S. *et al.* Palliative Care as a Standard of Care in Pediatric Oncology. *Pediatr Blood Cancer* **62**, S829-33 (2015).
203. Rao, A. D. *et al.* Practice patterns of palliative radiation therapy in pediatric oncology patients in an international pediatric research consortium. *Pediatr Blood Cancer* **64**, e26589 (2017).
204. Hartsell, W. F. *et al.* Randomized Trial of Short- Versus Long-Course Radiotherapy for Palliation of Painful Bone Metastases. *JNCI: Journal of the National Cancer Institute* **97**, 798–804 (2005).
205. Chow, E., Harris, K., Fan, G., Tsao, M. & Sze, W. M. Palliative Radiotherapy Trials for Bone Metastases: A Systematic Review. *Journal of Clinical Oncology* **25**, 1423–1436 (2007).
206. Lutz, S. *et al.* Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol* **7**, 4–12 (2017).
207. Fishbein, L. *et al.* External beam radiation therapy (EBRT) for patients with malignant pheochromocytoma and non-head and -neck paraganglioma: combination with 131I-MIBG. *Horm Metab Res* **44**, 405–10 (2012).
208. Gu, Z. *et al.* Favorable outcome in advanced pheochromocytoma and paraganglioma after hypofractionated intensity modulated radiotherapy. *J Endocrinol Invest* **46**, 477–485 (2022).
209. Vogel, J. *et al.* External beam radiation therapy in treatment of malignant pheochromocytoma and paraganglioma. *Front Oncol* **4**, 166 (2014).
210. Breen, W. *et al.* External beam radiation therapy for advanced/unresectable malignant paraganglioma and pheochromocytoma. *Adv Radiat Oncol* **3**, 25–29 (2018).
211. Ayala-Ramirez, M. *et al.* Bone Metastases and Skeletal-Related Events in Patients With Malignant Pheochromocytoma and Sympathetic Paraganglioma. *J Clin Endocrinol Metab* **98**, 1492–1497 (2013).
212. OKUYAMA, C. *et al.* Utility of follow-up studies using meta-[123I]iodobenzylguanidine scintigraphy for detecting recurrent neuroblastoma. *Nucl Med Commun* **23**, 663–672 (2002).
213. Hadj-Djilani, N. L., Lebtahi, N.-E., Bischof Delaloye, A., Laurini, R. & Beck, D. Diagnosis and follow-up of neuroblastoma by means of iodine-123 metaiodobenzylguanidine scintigraphy and bone scan, and the influence of histology. *Eur J Nucl Med* **22**, 322–329 (1995).
214. Kushner, B. H., Kramer, K., Modak, S. & Cheung, N.-KongV. Sensitivity of Surveillance Studies for Detecting Asymptomatic and Unsuspected Relapse of High-Risk Neuroblastoma. *Journal of Clinical Oncology* **27**, 1041–1046 (2009).
215. Satharasinghe, K. *et al.* False-Positive MIBG Scans With Normal Computed Tomography Imaging in Patients With High-Risk Neuroblastoma. *Journal of Clinical Oncology* **27**, e233–e234 (2009).
216. Shah, M. H. *et al.* Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network* **19**, 839–868 (2021).

217. Berruti, A. *et al.* Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* **23**, vii131–vii138 (2012).
218. Coughtrey, A. *et al.* The Effectiveness of Psychosocial Interventions for Psychological Outcomes in Pediatric Oncology: A Systematic Review. *J Pain Symptom Manage* **55**, 1004–1017 (2018).
219. Liu, Y., Sundquist, J., Sundquist, K., Zheng, D. & Ji, J. Mental health outcomes in parents of children with a cancer diagnosis in Sweden: a nationwide cohort study. *EClinicalMedicine* **55**, 101734 (2023).
220. Malbasa, T., Kodish, E. & Santacroce, S. J. Adolescent Adherence to Oral Therapy for Leukemia: A Focus Group Study. *Journal of Pediatric Oncology Nursing* **24**, 139–151 (2007).
221. Wiener, L., Kazak, A. E., Noll, R. B., Patenaude, A. F. & Kupst, M. J. Standards for the Psychosocial Care of Children With Cancer and Their Families: An Introduction to the Special Issue. *Pediatr Blood Cancer* **62**, S419-S424 (2015).
222. SIOPE. European standards of care for children with cancer. *SIOP Europe*. https://siope.eu/european-research-and-standards/standards-of-care-in-paediatric-oncology/ (2009).
223. Seitz, D. C. M., Besier, T. & Goldbeck, L. Psychosocial interventions for adolescent cancer patients: a systematic review of the literature. *Psychooncology* **18**, 683–690 (2009).
224. Tejeda, H. A. *et al.* Representation of African-Americans, Hispanics, and Whites in National Cancer Institute Cancer Treatment Trials. *JNCI Journal of the National Cancer Institute* **88**, 812–816 (1996).
225. Bond, M. C. & Pritchard, S. Understanding clinical trials in childhood cancer. *Paediatr Child Health* **11**, 148–50 (2006).
226. Hunger, S. P. *et al.* Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol* **30**, 1663–9 (2012).
227. Bhakta, N. *et al.* Childhood cancer burden: a review of global estimates. *Lancet Oncol* **20**, e42–e53 (2019).
228. Unger, J. M., Cook, E., Tai, E. & Bleyer, A. The Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence, and Strategies. *American Society of Clinical Oncology Educational Book* 185–198 (2016).
229. Bleyer, W. A. Potential favorable impact of the affordable care act of 2010 on cancer in young adults in the United States. *Cancer J* **16**, 563–71 (2010).
230. Major, A., Cox, S. M. & Volchenboum, S. L. Using big data in pediatric oncology: Current applications and future directions. *Semin Oncol* **47**, 56–64 (2020).
231. Wells, S. A. *et al.* Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma. *Thyroid* **25**, 567–610 (2015).232. United States securities and exchange commission, Form 8-K, *investor.lantheus.com*. https://investor.lantheus.com/node/14836/html (2023)

Acknowledgements

R.T.C. was supported by the NIHR Cambridge Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of

Commented [OT7]: Au: The Acknowledgements section was rewritten according to our journal formatting, OK?

Commented [RC8R7]: YES

Health and Social Care. M. F., S. B., A. H., G. E. and C. P. were supported by the German Foundation (Deutsche Forschungsgemeinschaft) within the CRC/Transregio 205/2, Project Number 314061271-TRR 205 “Adrenal:Central Relay in Health and Disease”. N.N. and K.P. were supported by the National Institutes of Health. C.P. was supported by the P.R.I.S.-Programme and the “*Habilitationsforderung für Frauen*” Programme of the Medical Faculty, TU Dresden.

Author contributions

R.T.C., C.P., E.H., S.G.W., V.W., A.R., C.D., M.F., A.J.G., M.R., A.-P.G-R., A.B.G., D.T., E.R.M, J.L., G.E., C.J. and K.P. researched data for the article. R.T.C., C.P., E.H., S.G.W., V.W., A.R., M.F., A.J.G., M.R., A.-P.G.-R., A.B.G., D.T., E.R.M, J.L., G.E., C.J., K.P., S.A., R.P., R.J.C.-B., L.A., S.R.B., L.C., E.C., A.C., M.C.F., R.R.d.K., L.D.S., T.F., A.H., V.K., M.K., C.L., S.M., N.N., M.P.-C., H.T. and A.-L.Z. contributed substantially to discussion of the content. R.T.C. and C.P. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

R.T.C. has received a Novartis speaker honorarium and is in an editorial position in *Clinical Endocrinology*. C. J. has received funding to their institution from Lantheus, Progenics, Exelixis, Merck Sharpe and Dohme and is a clinical advisor for Lantheus and Merck Sharpe and Dohme. S. M. is the Director of the NIHR Clinical Research Facility at Great Ormond Street Hospital, London. D. T. has received speaker and attendance honoraria from AAA/NOVARTIS. M.F. is an unpaid member of the ExCo of the European Society of Endocrinology and J. W. M. L. is an unpaid member of the advisory board of the Phaeochromocytoma and Paraganglioma Alliance.

Peer review information

Nature Reviews Endocrinology thanks Daniel Orbach, Jonathan Wasserman and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Supplementary information

Supplementary information is available for this paper at https://doi.org/10.1038/s415XX-XXX-XXXX-X

Table 1. Upper cut-offs of reference intervals for plasma levels of normetanephrine, metanephrine and methoxytyramine (pmol/l) in two paediatric groups and according to sex where appropriate

Group	Age range	Normetanephrine	Metanephrine	Methoxytyramine
Girls, 97.5th percentile	3 to <13 years	600	430	74
Girls, 99th percentile		672	495	86
Boys, 97.5th percentile		740	537	109
Boys, 99th percentile		931	601	131
Girls and boys, 97.5th percentile	13 to <19 years	694	332	75
Girls and boys, 99th percentile		753	375	105

Upper cut-offs are displayed as both 97.5th and 99th percentiles. As phaeochromocytomas and paragangliomas are predominantly characterised by increases in normetanephrine, the 97.5th percentiles minimise false-negative results and are the appropriate cut-offs for normetanephrine. To minimise false-positive results for the combination of all three metabolites, the 99th percentiles are usually more appropriate for metanephrine and methoxytyramine. Data for nometanephrine and metanephrine are derived from populations of 154 girls and 150 boys for the 3–13-year-old group and 266 girls and boys for the 13–19-year-old group, for which there were negligible differences between sexes compared with the younger age group. Lower respective numbers of patients were available for methoxytyramine (n = 117, 126 and 187), for which 99th percentiles are less reliable than the 97.5th percentiles. Data are derived from several publications[44,70,79].

Table 2: Outline of a suggestion for selecting the most appropriate molecular imaging test based on genotype and the specific clinical indication.

Indication	Sporadic PPGL and/or no or unknown genetic diagnosis	Cluster 1 PPGL	Cluster 2 PPGL
Staging or restaging pre-operation or in metastatic disease	[^{68}Ga]-DOTATATE PET–CT Alternative: [^{18}F]-FDOPA PET–CT[a] or [^{123}I]-MIBG scintigraphy	[^{68}Ga]-DOTATATE PET–CT Alternative: [^{18}F]-FDG PET–CT	[^{68}Ga]-DOTATATE PET–CT Alternative: [^{18}F]-FDOPA PET–CT[a] or [^{123}I]-MIBG scintigraphy
Confirming a suspected diagnosis of a PPGL in chest abdomen or pelvis	[^{18}F]-FDOPA PET–CT Alternative: [^{68}Ga]-DOTATATE PET–CT or [^{123}I]-MIBG scintigraphy	[^{68}Ga]-DOTATATE PET–CT Alternative: [^{18}F]-FDOPA PET–CT[a] or [^{123}I]-MIBG scintigraphy	[^{18}F] -FDOPA PET–CT Alternative: [^{68}Ga]-DOTATATE PET–CT or [^{123}I]-MIBG scintigraphy
Confirming a suspected diagnosis of a head and neck paraganglioma	[^{68}Ga]-DOTATATE PET–CT Alternative: [^{18}F]-FDOPA PET–CT[a]	[^{68}Ga]-DOTATATE PET–CT Alternative: [^{18}F]-FDOPA PET–CT[a]	[^{68}Ga]-DOTATATE PET–CT Alternative: [^{18}F]-FDOPA PET–CT[a]
Selecting a targeted radionuclide therapy	[^{123}I]-MIBG scintigraphy[b] Alternative: [^{68}Ga]-DOTATATE PET–CT	[^{123}I]-MIBG scintigraphy[b] Alternative: [^{68}Ga]-DOTATATE PET–CT	[^{123}I]-MIBG scintigraphy[b] Alternative: [^{68}Ga]-DOTATATE PET–CT

[a]Note limited availability of [^{18}F]-FDOPA PET–CT. [b]The choice of targeted radionuclide therapy might be influenced by local availability and licensing

[^{18}F]-FDG, [^{18}F]-fluorodeoxyglucose; [^{18}F]-FDOPA, [^{18}F]-fluorodopa; MIBG, metaiodobenzylguanidine; PPGL, phaeochromocytoma and paraganglioma.

Table 3: A suggested approach to pre-operative and pre-procedure α-adrenoceptor blockade and β-adrenoceptor blockade, as well as suitable alternatives and suggestions for the starting dose and drug titrations.

Medication	Starting dose	Adverse effects	Suggested titration
Phenoxybenzamine (non-selective α-adrenoceptor blocker)	0.2 mg/kg per day, in two divided doses (maximum 10 mg/dose)	Nasal congestion, postural hypotension, tachycardia, dizziness and fatigue	Titrate by 0.2 mg/kg per day every 3–5 days as tolerated (maximum 2–4 mg/kg per day)
Doxazosin (selective α1 adrenoceptor blocker)	Age 6–11 years: 0.5 mg once daily Age >12 years: 1 mg once daily	Postural hypotension, tachycardia, dizziness and fatigue	Titrate by 1–2 mg per day every 5–7 days as tolerated (maximum 4 mg per day, rarely doses up to 16 mg per day can be required)
Metyrosine (tyrosine hydroxylase inhibitor)	20 mg/kg per day, in four divided doses (maximum 125 mg daily)	Diarrhoea, tachycardia, sedation, extra-pyramidal adverse effects and crystalluria	Titrate by 20 mg/kg per day (maximum 125 mg per day) every 5 days (max 60 mg/kg per day or 2.5 g per day)
Amlodipine (calcium channel blocker)	Age <12 years: 100–200 mg/kg once daily (maximum 5 mg per day) Age >12 years: 5 mg once daily	Dizziness, flushing, tachycardia, headaches and abdominal pain	Titrate by 200 mg/kg or 5 mg every 5–7 days (max 10 mg per day)
Propranolol (non-selective β-adrenoceptor blocker)	1–2 mg/kg per day, in 2–4 divided doses[a] (maximum 160 mg per day)	Fatigue, dizziness, exacerbation of bronchospasm	Titrate by 1–2 mg/kg per day every 3–5 days to 4 mg/kg per day (maximum 640 mg per day)
Atenolol (selective β1-adrenoceptor blocker)	0.5–2.0 mg/kg per day, once daily or in 2 divided doses[a] (maximum 50 mg per day)	Fatigue, dizziness, oedema and exacerbation of bronchospasm	Titrate by 1–2 mg/kg per day every 3–5 days (maximum 100 mg per day)

[a]β-Adrenoceptor blockers should only be initiated after a patient is stabilised on α-adrenoceptor blockade therapy. β-Adrenoceptor blockers are typically reserved for patients with persistent tachycardia despite adequate fluid resuscitation or patients with primarily adrenaline secreting tumours.

1940 **Table 4:** A guide for long-term follow-up after curative surgery for children and adolescents
1941 with PPGL.

Genetic Diagnosis	Duration of follow-up	Clinical review	Biochemistry	Radiological surveillance	Non-PPGL surveillance
No genetic diagnosis	10 years minimum	Annual clinical symptoms and signs review and 1–2 yearly blood pressure check	1–2 yearly plasma or urinary levels of metanephrines	MRI of thorax, abdomen and pelvis if symptoms and/or signs are present or biochemistry is abnormal, or interval imaging of thorax, abdomen and pelvis 1–2 yearly if PPGL was non-secretory. Longer intervals might be considered after several years of uneventful follow-up.	N/A
No genetic diagnosis with risk factors [a]	Life-long	Annual clinical symptoms review and 1–2 yearly blood pressure check	1–2 yearly plasma or urinary levels of metanephrines	Interval MRI of neck, thorax, abdomen and pelvis every 1–2 years. Longer intervals might be considered after several years of uneventful follow-up.	N/A
SDHx genes *(SDHA, SDHB*[b]*, SDHC* and paternally inherited *SDHD)*	Life-long	Annual clinical symptoms review and yearly blood pressure check	Annual plasma or urinary levels of metanephrines and plasma levels of 3-methoxytyramine	Interval MRI of neck, thorax, abdomen and pelvis every 1–2 years.	At present, surveillance focuses on PPGL, although imaging might identify other related tumours e.g., RCC, GIST. No clinical surveillance is recommended for children with maternally inherited SDHD variants.
VHL[b]	Life-long	Annual clinical symptoms review and yearly blood pressure check	Annual plasma or urinary levels of metanephrines	MRI of the abdomen and pelvis as indicated for RCC or pNET surveillance, or sooner if symptoms and/or signs are present or biochemistry is abnormal	Retinal examination, audiology evaluation and MRI studies for renal, spine, pancreatic and central nervous system surveillance[148]
RET	Life-long	Annual clinical symptoms review and yearly blood pressure check	Annual plasma or urinary levels of metanephrines	MRI of the abdomen or adrenals if symptoms and/or signs are present or biochemistry is abnormal and consider whole-body imaging if no abnormality is detected on adrenal MRI	Screening for medullary thyroid cancer, cutaneous lesions and primary hyperparathyroidism[231]
EPAS1	Life-long	Annual clinical symptoms review and 1–2 yearly blood pressure check	Annual plasma or urinary levels of metanephrines	Interval MRI of the neck, thorax, abdomen and pelvis every 2–3 years[c]. Longer intervals might be considered after several years of uneventful follow-up.	At present, surveillance focuses on PPGL and duodenal somatostatinoma
TMEM127	Life-long	Annual clinical symptoms review and 1–2 yearly blood pressure check	1–2 yearly plasma or urinary levels of metanephrines	Interval MRI of the neck, thorax, abdomen and pelvis every 2–3 years[c]. Longer intervals might be considered after several years of uneventful follow-up.	At present surveillance focuses on PPGL

SDHAF2 (paternally inherited)	Life-long	Annual clinical symptoms review and 1–2 yearly blood pressure check	1–2 yearly plasma or urinary levels of metanephrines	Interval MRI of the neck every 3–5 years. Consider MRI of the thorax, abdomen, and pelvis if symptoms and/or signs are present, or biochemistry is abnormal[c]. Longer intervals might be considered after several years of uneventful follow-up.	At present, surveillance focuses on PPGL, particularly head and neck PPGL
MAX	Life-long	Annual clinical symptoms review and 1–2 yearly blood pressure check	1–2 yearly plasma or urinary levels of metanephrines	Interval MRI of neck, thorax, abdomen, and pelvis every 2–3 years[c]. Longer intervals might be considered after several years of uneventful follow-up.	At present, surveillance focuses on PPGL

[a]Risk factors for metastatic recurrence include: tumour size >5 cm in diameter, extra-adrenal location, multifocal or invasive tumour and family history of PPGL. [b]Somatic and somatic mosaic variants in this gene should follow the same guidance as for germline variants for long-term PPGL surveillance. [c]Limited evidence base. GIST, gastrointestinal stromal tumour; N/A, not applicable; pNET, pancreatic neuroendocrine tumour; PPGL, phaeochromocytoma and paraganglioma; RCC, renal cell carcinoma.

1948 **Table 5**: Surveillance strategies for asymptomatic carriers of PPGL predisposition genes in
1949 childhood

Gene	Age to commence screening	Clinical review	Biochemistry	Radiological surveillance
SDHx (SDHA, SDHB, SDHC and paternally inherited *SDHD)*	5 years for *SDHB* carriers; 10 years for *SDHA, SDHC* and paternally-inherited *SDHD* carriers	Annual clinical symptoms and/or signs review and blood pressure check from the time of presentation or from age 5–10 years	Annual plasma or urinary levels of metanephrines and plasma levels of 3-methoxytyramine[a]	MRI of neck, thorax, abdomen and pelvis every 2–3 years
RET	11 years for 'highest' and 'high' risk *RET* pathogenic variants; 16 years for 'moderate' risk *RET* pathogenic variants [c]	Annual clinical symptoms and/or signs review and blood pressure check from the time of presentation or from age 11–16 years	Annual plasma or urinary levels of metanephrines	Not routinely performed in the absence of clinical symptoms and/or signs or abnormal biochemistry to suggest PPGL, but interval abdominal imaging using MRI can be considered in select instances (e.g., serial increases in plasma or urinary levels of metanephrines, patient or family anxiety or ahead of planned pregnancies)
VHL	5 years	Annual clinical symptoms and/or signs review and blood pressure check from the time of presentation or from age 5 years.	Annual plasma or urinary levels of metanephrines	MRI of the abdomen should start from the age of 15 years.
TMEM127	10–15 years	Annual clinical symptoms and/or signs review and blood pressure check from the time of presentation or from age 10–15 years.	1–2 yearly plasma or urinary levels of metanephrines[b]	MRI of the neck, thorax, abdomen and pelvis from age 15–18 years. If negative, interval imaging of the abdomen and pelvis can be considered at 2–3-year intervals and imaging of the neck and thorax at 3–5-year intervals. Longer intervals might be considered after several years of uneventful follow-up.
MAX	10 years	Annual clinical symptoms and/or signs review and blood pressure check from the time of presentation or from age 10 years.	1–2 yearly plasma or urinary levels of metanephrines[b]	MRI of neck, thorax, abdomen, and pelvis every 2–3 years from presentation or from age 15 years. Longer intervals might be considered after several years of uneventful follow-up.
SDHAF2 (paternally inherited)	18 years	Annual clinical symptoms and/or signs review and blood pressure check from the time of presentation or from age 18 years	1–2 yearly plasma or urinary levels of metanephrines[b]	MRI of the neck should be performed at 3–5-year intervals from presentation or from the age of 18 years. Longer intervals might be considered after several years of uneventful follow-up. Imaging of the thorax abdomen, and pelvis is not

				routinely required but can be considered if biochemistry or clinical symptoms suggest a sympathetic PPGL

[a]If available. [b]Limited evidence. [c]Highest risk RET variants affected codon: p. Met918Thr; high risk RET variants affected codons: p. Cys634, p. Ala883Pheo; moderate risk RET variants affected codons: p. Val804Met, p. Val804Leu, p. Leu790, p. Cys634, p. Cys630, p. Cys620, p. Cys618, p. Cys611, p. Cys609. PPGL, phaeochromocytoma and paraganglioma.

Figure 1: Overview of treatments options for paediatric patients with metastatic phaeochromocytoma and paraganglioma (PPGL) considering the rate of disease progression and burden of metastatic disease. Treatment options in children with PPGL should be individualised and directed by a multidisciplinary specialist team. If complete tumour resection is not possible, debulking surgery or metastasectomy can be considered in children with metastatic PPGL. Local treatment approaches can also be considered as general treatment options to reduce symptoms and/or signs of catecholamine excess, palliate metastasis-related pain, treat oligometastases and improve prognosis. Systemic treatment options are typically considered for paediatric patients with high tumour burden usually associated with rapid tumour progression rate or as an adjunct to debulking surgery. *Tumour burden and rate of tumour progression should be assessed on a case-by-case basis based on multidisciplinary team review and expert clinical opinion. **No longer commissioned in the USA. HIF, hypoxia inducible factor; MIBG, metaiodobenzylguanidine.

Box 1: Strengths and limitations of the Consensus Statement

This article is the first international Consensus Statement addressing the diagnosis, management and long-term surveillance of children and adolescents with or at risk of PPGL. 40 experts from 11 different countries participated, providing multidisciplinary expertise from specialties including paediatric oncology, paediatric endocrinology, adult endocrinology, adult oncology, radiation oncology, nuclear medicine, surgery, medical genetics, clinical chemistry, paediatric psychology and pathology. A Delphi process was applied to reach consensus and the participant expertise was crucial for adoption of this methodology. After adoption of the Delphi process, 39 statements reached consensus and five statements did not reach consensus and were removed (**Supplementary Table 7**). 30 of 39 statements had a level of agreement of >85% amongst participants (Grade A), with most experts voting 'strongly agree' or 'agree' for all statements (**Supplementary Tables 1-6**). Nine statements reached consensus but with a grade of consensus of <85% (75–84%, Grade B).

A limitation of this Consensus Statement is the quality of evidence available to support statements. The grade of evidence for statements provided was predominately 'low' or 'very low', and only seven statements were supported by a moderate grade of evidence. The quality of evidence did correlate with the level of agreement, with most of the statements with agreement <85% having a 'very low quality' of evidence available. However, a consensus was reached for 39 statements including those with a 'low' or 'very low' quality of evidence. Although those statements with 'low' or 'very low quality' of evidence were provided based predominately on individual opinion and expertise, it should be appreciated that the statements represent the unbiased and consensus opinion of 40 multidisciplinary experts in a subspecialty field for which no consensus statement currently exists and the evidence base is limited.

Phaeochromocytomas and paragangliomas (PPGL) are rare endocrine tumours that can affect paediatric patients as well as adults. In this first international Consensus Statement on PPGL in paediatric patients, the authors discuss the diagnosis, management and long-term surveillance of these tumours in children and adolescents.