nature reviews endocrinology

https://doi.org/10.1038/s41574-024-01024-5

Consensus statement

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

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Abstract

Phaeochromocytomas and paragangliomas (PPGL) are rare neuroendocrine tumours that arise not only in adulthood but also in childhood and adolescence. Up to 70–80% of childhood PPGL are hereditary, accounting for a higher incidence of metastatic and/or multifocal PPGL in paediatric patients than in 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.

Sections

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Introduction

Phaeochromocytomas and paragangliomas (PPGL) are rare neuroendocrine tumours arising from the adrenal medulla or extra-adrenal sympathetic and parasympathetic paraganglia. PPGL are more frequently diagnosed in adult than in 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 PPGL in childhood is likely to be much higher than currently estimated. The median age at presentation is 11–15 years[5,6], and PPGL are exceedingly rare in children under 5 years of age.

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 PPGL 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 personalized diagnostic, management, therapeutic and surveillance strategies in children and adolescents with PPGL.

As in adults, paediatric PPGL susceptibility genes can be divided into two main clinically relevant clusters defined by specific transcriptomic profiles, and a third cluster encompassing predominantly somatic gene variants[10]. Cluster 1 tumours include those caused by pathogenic variants in the von Hippel–Lindau suppressor gene (*VHL*), 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 (HIF) 2α gene (*HIF2A* or *EPAS1*). Cluster 2 tumours include those driven by pathogenic variants in neurofibromatosis type 1 tumour suppressor gene (*NF1*), the rearranged during transfection proto-oncogene (*RET*) and the genes encoding transmembrane protein 127 (*TMEM127*) and MYC-associated factor X (*MAX*)[10,11].

PPGL 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 in 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 lifelong follow-up, with surveillance tailored to the specific gene variant or clinical phenotype. Paediatric patients with metastatic PPGL have disease-related 5-year and 10-year survival rates 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 minimize, 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 1 provides a brief overview of head and neck paragangliomas (HNPGL) in children).

Methods

Participants

Participants were identified by their expertise in the field of PPGL management, through membership of the European Network for the Study of Adrenal Tumors and/or the Pheochromocytoma and Paraganglioma Research Support Organization. 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 11 different countries across three continents (Europe, North America (USA) and Oceana (Australia)). Survey participation was voluntary with no financial incentive.

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 in accordance with the Delphi recommendations. Consensus was defined prior to the study as ≥75% for agreement (Likert scale 1 or 2) or disagreement (Likert scale 4 or 5). Statements with >75% agreement in one round were removed from the next round as consensus was considered to have been 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 respondents, respectively.

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 comprised 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 1 July 2022 until 1 August 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 October 2022 until 26 November 2022) and commented on by each participant independently using the five-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 for which consensus was not reached were reviewed at a virtual subcommittee meeting, adjusted, and reformulated for the next round of rating. Consensus was not reached for five statements after three consecutive rounds, and these statements were removed (Supplementary Table 7). The responses and comments remained anonymous, except to moderators. The aim of this methodology was to facilitate an unbiased consensus.

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 for which consensus was reached based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach[16,17]. For each recommendation, the quality of evidence was rated as very low, low, moderate or high (Supplementary Table 8).

General remarks

- **Statement 1.** 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 advocates for 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 is associated with improved patient outcomes compared with outcomes in 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 2). 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 specialized centres can also provide the opportunity for patients and their families to participate in clinical trials.

Diagnosis

- **Statement 2.** Clinical suspicion of PPGL should be raised in paediatric patients with (a) signs and symptoms of catecholamine excess and (b) an 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 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 those of other disorders often encountered among paediatric patients, such as attention deficit hyperactivity disorder (ADHD)[29]. Finally, polyuria and visual disturbances have also been 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 children 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 tumour[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 an incidental adrenal or extra-adrenal mass 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.

Biochemical

- **Statement 3.** Biochemical testing for patients with suspicion of PPGL should include plasma-free or urine (spot or 24-h) 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-h urinary levels of deconjugated metanephrines should be the screening test of choice in 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 for 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-h urine collections.

It has been previously reported that both first morning and random spot urine levels of metanephrines show a similar diagnostic accuracy to 24-h 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 in paediatric patients[43,44]. Considering that 24-h urine collections can be troublesome in children, and blood sampling procedures followed in paediatric settings are stressful for children (see Statement 4), 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-h urinary levels of metanephrines. First morning spot urine could be an alternative option for the exclusion of PPGL among young children with a 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.

In older children, 24-h urine collections provide an alternative to blood samples. Due to a lack of evidence to indicate whether plasma or 24-h 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 4). 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 cut-off values 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].

- **Statement 4.** Blood sampling for measurements of plasma levels of metanephrines and methoxytyramine should be carried out with appropriate consideration of pre-analytical conditions. (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 in 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 min 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 a paediatric intravenous cannula by a provider experienced in paediatric phlebotomy[57,58], and the use of various distractions for children during this procedure[59], can help to minimize 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 acclimatization of the sympathetic nervous system to warmer inside temperatures over a long time period (such as overnight) is associated with a statistically significant reduction in 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 the treatment of ADHD) can elevate blood levels of normetanephrine and so affect the diagnostic test results[48]. Discontinuation of the interfering medication could be considered if biochemical test results are positive. The time interval for discontinuation of interfering drugs should be calculated according to the drug's half-life, the concept of exponential decay, and the patient's renal and hepatic function in accordance with the local hospital protocol.

- **Statement 5.** 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 in patients hospitalized due to severe illness, in whom levels of metanephrines can even be indistinguishable from those in patients with PPGL[68,69]. Thus, and despite the lack of studies in 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. In children at high risk of PPGL, however, clinicians could proceed directly to imaging studies if a biochemical test is positive.

- **Statement 6.** 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 1 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-off values for plasma levels of free metanephrines in children and adolescents is presented in Table 1.

24-h urinary outputs of normetanephrine and metanephrine are up to four times higher in older adolescents than in 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-h 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-h 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-h urine levels of metanephrines, show decreases throughout childhood[81]. Due to the practical difficulties of laboratories in establishing appropriate reference intervals, the use of spot urine levels of metanephrines is currently limited in paediatric settings.

- **Statement 7.** In case of borderline elevations (increase less than twofold above the upper cut-off value) of only one catecholamine metabolite in a paediatric patient with a low degree of suspicion of 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 Tumour Study (PMT Study), based mainly on adult patients, shows that 21% of patients diagnosed with PPGL present with borderline elevations of a single metabolite (less than twofold above the upper cut-off value)[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 in each metabolite and on the pretest clinical suspicion of PPGL. Although there is a lack of evidence in paediatric patients, elevations of one or more metabolites more than twofold above the upper cut-off values should prompt consideration for imaging studies regardless of the pre-test clinical suspicion of PPGL[36,82]. By contrast, for elevations of a single metabolite less than twofold above the upper cut-off value, the nature of follow-up should be decided based on the pretest clinical suspicion of the disease. In patients with a low risk of PPGL (for example, tested due to signs and symptoms of catecholamine excess) and borderline elevations in 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].

Radiology

- **Statement 8.** In paediatric patients with biochemically confirmed PPGL, either MRI or CT can be performed to localize 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 tumour 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, cross-sectional imaging must be interpreted 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).

Table 1 | Upper cut-off values of reference intervals for plasma levels of normetanephrine, metanephrine and methoxytyramine in two paediatric groups and according to sex where appropriate

Group	Age range	Normetanephrine (pmol/l)	Metanephrine (pmol/l)	Methoxytyramine (pmol/l)
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-off values are displayed as both 97.5th and 99th percentiles. As phaeochromocytomas and paragangliomas are predominantly characterized by increases in normetanephrine, the 97.5th percentiles minimize false-negative results and are the appropriate cut-off values for normetanephrine. To minimize false-positive results for the combination of all three metabolites, the 99th percentiles are usually more appropriate for metanephrine and methoxytyramine. Data for normetanephrine and metanephrine were derived from populations of 154 girls and 150 boys for the 3–13 years age group and 266 girls and boys for the 13–19 years age 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 the 99th percentiles are less reliable than the 97.5th percentiles. Data were derived from several publications[44,70,79].

Overall, MRI shows 95% sensitivity and 70% specificity for phaeochromocytomas and abdominal or pelvic paragangliomas, and it is the preferred imaging modality for 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 ionizing 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 ionizing 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 of patients with PPGL, although it can be used for surveillance in carriers of PPGL pathogenic variants[15,88]. Nevertheless, MRI is more time-intensive (and costly) than 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 ionizing irradiation[89–93]. Estimating the actual radiation risk is challenging, as children are not, in fact, more radiosensitive than adults in the radiological imaging dose range, rendering

dose reduction in children potentially unjustifiable[94]. Nevertheless, care 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, ultrasonography is considered the safest imaging modality in children as no ionizing radiation, contrast medium or sedation is involved. However, abdominal or pelvic ultrasonography 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).

- **Statement 9.** 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 preoperatively, detection of occult metastases or recurrent and/or multiple tumours, characterization 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 (SSTR) type 2 expression, 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 in 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 PPGL, particularly in patients harbouring germline pathogenic variants in cluster 1 genes[101], and in 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 activation of brown adipose tissue 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 uptake in adult patients, which might affect the detection of small tumours in these locations. [^{123}I]MIBG has lower sensitivity as a staging test in 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].

Genetic testing

- **Statement 10.** Germline genetic testing is recommended in 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) genes include *VHL*, *SDHx*, *MDH2*, *FH* and *EPAS1* and is characterized by transcriptional upregulation of genes implicated in angiogenesis, and cellular proliferation secondary to HIF complex stabilization[10,106]. Cluster 2 genes include *RET*, *NF1*, *TMEM127*,

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 before surgery 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 the 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

[^{18}F]FDG, [^{18}F]fluorodeoxyglucose; [^{18}F]FDOPA, [^{18}F]fluorodopa; [^{123}I]MIBG, [^{123}I]metaiodobenzylguanidine; PPGL, phaeochromocytoma and paraganglioma. [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.

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 populations (~80%) than in 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 selected 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 PPGL show a high degree of heterogeneity in clinical presentation, and the genotype cannot always be reliably predicted by the phenotype. Furthermore, the *NF1* gene is not always included in 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.

- **Statement 11.** If routine testing does not identify a germline pathogenic or probable pathogenic variant, consider referral to a specialist genetic centre for genetic analyses on tumoural 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: In 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 in tumours are more common in children than in adults[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].

Management

Surgical management and preoperative and perioperative optimization

- **Statement 12.** The decision to undertake 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 minimize the risk of tumour recurrence and/or metastasis by prioritizing 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 about this disease. In some centres, this might require close collaboration between paediatric and adult surgeons of different subspecialties with expertise in PPGL surgery.

- **Statement 13.** A minimally invasive approach should be favoured, when feasible, in 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, minimally invasive surgery is usually safe and can be preferable to open surgery, due to the shorter recovery time[116–120]. A minimally invasive surgical approach should be selected based on the expertise of the surgical team. There are no prospective clinical trials directly comparing laparoscopic and open adrenalectomy approaches for PPGL in adult or paediatric patients. An open approach should be considered in 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 preoperative 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, debulking surgery can be considered on an individualized basis, especially in children with localized tumours who are affected by symptoms due to compression or catecholamine secretion. Surveillance versus adjuvant treatment in patients with R1 resection status requires careful consideration and should be guided by patient symptoms and multidisciplinary team discussion.

- **Statement 14.** Cortical-sparing partial adrenalectomies should be considered in children with bilateral phaeochromocytomas, or in 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 PPGL 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 of <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 resection. There is a higher potential risk of parenchymal spillage and local seeding during a cortical-sparing adrenalectomy than 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 of bilateral phaeochromocytomas and, therefore, adrenal insufficiency is very low.

A large multicentre cohort study comparing 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 adrenalectomy. Most patients in this study had germline pathogenic variants in either the *RET* or the *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 in 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* pathogenic variants than in those with *SDHB* pathogenic variants, but due to a lack of longitudinal data to inform the risks and benefits of total versus cortical-sparing adrenalectomy, an individualized approach is advised after careful counselling and multidisciplinary discussion.

- **Statement 15.** Preoperative optimization with α-adrenoceptor blockers and/or calcium channel blockers, together with maintenance fluid intake of one or two times a weight-appropriate fluid intake, should be considered in all children with PPGL ahead of a planned surgical procedure 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 in adult patients with catecholamine-producing PPGL[20]. α-Adrenoceptor blockers (including non-selective ones such as phenoxybenzamine and selective α_1-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 hypovolaemia-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 optimized, to minimize the risk of a hypertensive crisis[20,123–125]. The cardioselective β_1-adrenoceptor blockers atenolol and metoprolol are preferred to non-selective β-adrenoceptor blockers (such as propranolol), due to a 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 a planned surgical intervention in a patient with PPGL[20] (Table 3), but it should be noted that it can take longer (2–3 weeks) to preoperatively optimize 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 below the 90th percentile using age and height-based reference charts; heart rate between the 10th and 90th percentile using age-based reference charts, and minimal or asymptomatic postural hypotension[31,127]. We also acknowledge that a minority of our panel was not in favour of administering α-adrenoceptor blockers preoperatively to all patients with PPGL.

Symptomatic patients with catecholamine-secreting metastatic PPGL should be treated with adrenergic blockade long-term to minimize complications related to catecholamine release.

Table 3 | A suggested approach to preoperative and preprocedure 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 α_1-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, extrapyramidal adverse effects and crystalluria	Titrate by 20 mg/kg per day (maximum 125 mg per day) every 5 days (maximum 60 mg/kg per day or 2.5 g per day)
Amlodipine (calcium channel blocker)	Age <12 years: 100–200 µg/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 µg/kg or 5 mg every 5–7 days (maximum 10 mg per day)
Propranolol (non-selective β-adrenoceptor blocker)	1–2 mg/kg per day, in two to four 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 β_1-adrenoceptor blocker)	0.5–2.0 mg/kg per day, once daily or in two 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 stabilized 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.

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 medications that are associated with the risk of precipitating a catecholamine crisis (such as steroids, ephedrine and metoclopramide)[91].

Postoperative follow-up

- **Statement 16.** Plasma or urinary levels of normetanephrine and metanephrine and plasma levels of 3-methoxytyramine (if available) should be repeated between 2 and 8 weeks after surgery. In patients in whom preoperative staging was not performed, postoperative imaging (at 3–6 months) should be considered to determine surgical remission. (Agreement A; Evidence, low)

Evidence: In children with localized, biochemically positive PPGL and adequate preoperative staging, postoperative remission can be determined by normalization of plasma or urinary levels of normetanephrine and metanephrine, and plasma levels of methoxytyramine (if available) on repeat measurement 2–8 weeks after surgery. These measurements should be timed in line with the child's postoperative 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 preoperatively (see Statement 9). In patients with non-secretory tumours, interval whole-body imaging using MRI should be considered at 12 weeks after surgery and at intervals of 1–2 years thereafter if stable (Table 4).

Long-term follow-up

- **Statement 17.** Children with PPGL should ideally have postoperative 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 varies between studies (2.4–85.7%) owing to potential referral bias and lack of long-term follow-up[1,6,122,131,132]. Importantly, studies have demonstrated that paediatric patients are more likely than adult patients to develop metachronous metastatic tumours rather than initially presenting with metastatic disease, highlighting the need for very close postoperative follow-up[6]. In a 2020 study in paediatric patients with *SDHB* pathogenic variants, the median time from surgery to local recurrence was 2 years (range 0–26 years) and the median time from diagnosis of the primary tumour to diagnosis of metastatic disease was 4 years (range 0–26 years)[122]. There is a recognized risk of late relapse or metastatic recurrence in paediatric patients with PPGL and a notable rate of metastatic recurrence later than 5 years after initial surgery has been reported[8,131].

In a 2011 study in 32 patients who presented with PPGL in childhood or adolescence and subsequently developed metastatic recurrence, extra-adrenal tumours in the abdomen or pelvis, a noradrenergic biochemical phenotype and germline pathogenic variants in *SDHB* were the most statistically significant risk factors for metastatic recurrence[131]. A primary tumour diameter of >5 cm in paediatric patients has also been associated with an increased risk of early metastatic recurrence and reduced overall survival compared with tumours of <5 cm in diameter[122]. The need for consensus on long-term follow-up was highlighted in a French study in paediatric patients with PPGL spanning two decades[8], in which 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 modality. Imaging should be reviewed by an experienced radiologist or reviewed at a specialist multidisciplinary team meeting (Table 4).

- **Statement 18.** Children with a germline pathogenic or probable pathogenic variant in a PPGL predisposition gene should be offered lifelong 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 in paediatric patients with PPGL, 38% of the 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 a less-penetrant tumour type (Tables 4, 5).

- **Statement 19.** In 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 than in patients with pathogenic variants in the cluster 1 genes (such as *SDHx*), but in one large multicentre study, the rate of recurrence in adult patients with sporadic PPGL was 14.7%[133]. In this same study, of the patients with recurrence of sporadic PPGL, just over half presented with recurrence within 10 years of initial surgery and in the remainder 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 10 years in patients with sporadic PPGL[133]. In 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 in those patients in whom initial genetic testing was negative but who develop recurrent PPGL or synchronous tumours, or in patients in whom discharge from clinical follow-up is being considered. Lifelong surveillance should be considered in selected patients including those with risk factors[131] (Table 4).

- **Statement 20.** Children with a somatic or somatic mosaic pathogenic or probable pathogenic variants in *EPAS1*, *VHL* or *SDHB* should be offered lifelong 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 than in adult patients. Furthermore, postzygotic somatic pathogenic variants in cluster 1 genes, including *EPAS1*, have been reported at a frequency of

Table 4 | A guide for long-term follow-up after curative surgery in children and adolescents 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 annual or biannual blood pressure check	Annual or biannual plasma or urinary levels of metanephrines	MRI of the thorax, abdomen and pelvis if symptoms and/or signs are present or biochemistry is abnormal, or interval imaging of thorax, abdomen and pelvis annually or biannually if PPGL was non-secretory; longer intervals might be considered after several years of uneventful follow-up	NA
No genetic diagnosis with risk factors[a]	Lifelong	Annual clinical symptoms review and annual or biannual blood pressure check	Annual or biannual plasma or urinary levels of metanephrines	Interval MRI of the neck, thorax, abdomen and pelvis every 1–2 years; longer intervals might be considered after several years of uneventful follow-up	NA
SDHx genes (*SDHA*, *SDHB*[b], *SDHC* and paternally inherited *SDHD*)	Lifelong	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 the 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]	Lifelong	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	Lifelong	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[232]
EPAS1	Lifelong	Annual clinical symptoms review and annual or biannual 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	Lifelong	Annual clinical symptoms review and annual or biannual blood pressure check	Annual or biannual 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)	Lifelong	Annual clinical symptoms review and annual or biannual blood pressure check	Annual or biannual 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	Lifelong	Annual clinical symptoms review and annual or biannual blood pressure check	Annual or biannual 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

GIST, gastrointestinal stromal tumour; NA, not applicable; pNET, pancreatic neuroendocrine tumour; PPGL, phaeochromocytoma and paraganglioma; RCC, renal cell carcinoma. [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.

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].

Identification and surveillance of asymptomatic PPGL predisposition gene carriers

- **Statement 21.** Surveillance in children with a pathogenic germline variant in the *SDHx* genes (*SDHA*, *SDHB*, *SDHC* and *SDHD*) should ideally include: (1) annual clinical symptoms review from the time of presentation or from age 5 years in asymptomatic *SDHB* carriers and from age 10 years in *SDHA*, *SDHC* or *SDHD* carriers; and (2) annual blood pressure check, biannual measurements of either plasma or urinary levels of metanephrines and plasma levels of methoxytyramine and interval MRI of the neck, thorax, abdomen and pelvis every 2–5 years. (Agreement A; Evidence, low)
- **Statement 22.** Surveillance for new or recurrent PPGL (as part of systemic *VHL* surveillance) in children with a pathogenic germline variant in *VHL* should ideally include: (1) annual clinical symptoms review from the time of presentation or from age 5 years in

asymptomatic *VHL* carriers; and (2) 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)

- **Statement 23.** Surveillance for new or recurrent PPGL (as part of systemic *RET* surveillance) in children with a pathogenic germline variant in *RET* should ideally include: (1) annual clinical symptoms review from the time of presentation or from age 11 years in high-to-moderate-risk *RET* gene mutation carriers and 16 years in low-risk *RET* gene mutation carriers; and (2) 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)
- **Statement 24.** Surveillance in children with a pathogenic germline mosaic *VHL* variant should ideally be carried out in accordance with the guidelines for patients with germline *VHL* gene pathogenic variants. (Agreement A; Evidence, very low)
- **Statement 25.** Surveillance for PPGL in children with a pathogenic or probably pathogenic mosaic or somatic variant in *EPAS1* should ideally include: (1) annual clinical symptoms review from the age at presentation; and (2) 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 intervals of 2–3 years. (Agreement B; Evidence, very low)
- **Statement 26.** Children with a pathogenic or probable pathogenic mosaic variant in *VHL* should be offered lifelong clinical surveillance. (Agreement A; Evidence, very low)
- **Statement 27.** 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: (1) annual or biannual clinical symptoms review from the age at presentation or from age 10–15 years

Table 5 | Surveillance strategies for asymptomatic carriers of PPGL predisposition genes in childhood

Gene	Age to commence screening	Clinical review	Biochemistry	Radiological surveillance
SDHx (*SDHA*, *SDHB*, *SDHC* and paternally inherited *SDHD*)	5 years in *SDHB* carriers; 10 years in *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-risk and high-risk *RET* pathogenic variants; 16 years for moderate-risk *RET* pathogenic variants[b]	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 selected 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	Annual or biannual plasma or urinary levels of metanephrines[c]	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 intervals of 2–3 years and imaging of the neck and thorax at intervals of 3–5 years; 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	Annual or biannual plasma or urinary levels of metanephrines[c]	MRI of the 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	Annual or biannual plasma or urinary levels of metanephrines[c]	MRI of the neck should be performed at intervals of 3–5 years 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

PPGL, phaeochromocytoma and paraganglioma. [a]If available. [b]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 and p.Cys609. [c]Limited evidence.

in asymptomatic carriers; and (2) annual or biannual blood pressure check and measurement of either plasma or urinary levels of metanephrines. (Agreement B; Evidence, very low)

- **Statement 28.** 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 in *TMEM127* variant carriers. (Agreement B; Evidence, very low)
- **Statement 29.** MRI of the neck should be performed at intervals of 3–5 years in *SDHAF2* carriers. (Agreement B; Evidence, very low)
- **Statement 30.** 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 child and more frequent surveillance might be required in 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)
- **Statement 31.** Surveillance in children with a pathogenic germline variant in *MAX* should ideally include: (1) annual clinical symptoms review from the age at presentation or from age 10 years; and (2) annual blood pressure check, annual or biannual 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 in all patients[20]. In 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 of PPGL within a family, allowing them to enter timely surveillance programmes 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 digitized 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 programmes. Such programmes are already in place in many centres with expertise on PPGL[145,146]. Finally, the success of these programmes is likely to be enhanced through the support of advocacy support groups (Supplementary Table 10) which 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 minimizing radiation exposure of a genetically vulnerable population, as well as aiming to minimize anxiety in and inconvenience to patients and families (Table 5). We advise that asymptomatic children identified as carriers of PPGL predisposition genes are monitored, in accordance with already existing guidelines or 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 multicentre prospective studies are required to determine the clinical, psychological and economic impacts of asymptomatic screening and long-term surveillance in and from childhood.

Management of metastatic PPGL

- **Statement 32.** Treatment of metastatic PPGL in paediatric patients should be considered on an individual 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 in paediatric patients should be individualized, directed by a multidisciplinary specialist team and discussed with the patient's family. The definition of metastatic disease is provided in Supplementary Box 3 (ref. 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 the patient's family (Fig. 1).

Findings from retrospective adult cohorts have shown that approximately 50% of all treatment-naive patients with metastatic PPGL have stable disease at 1 year[149]. These findings indicate that active surveillance with regular radiological monitoring could be considered in asymptomatic or minimally symptomatic patients with a 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 a low tumour burden showed longer disease-specific survival than those with a 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 and 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 in patients with a high tumour burden that is usually associated with rapid tumour progression rate, to prolong survival or as an adjunct to debulking surgery (Fig. 1). Targeted molecular radiotherapies are a treatment option in 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]

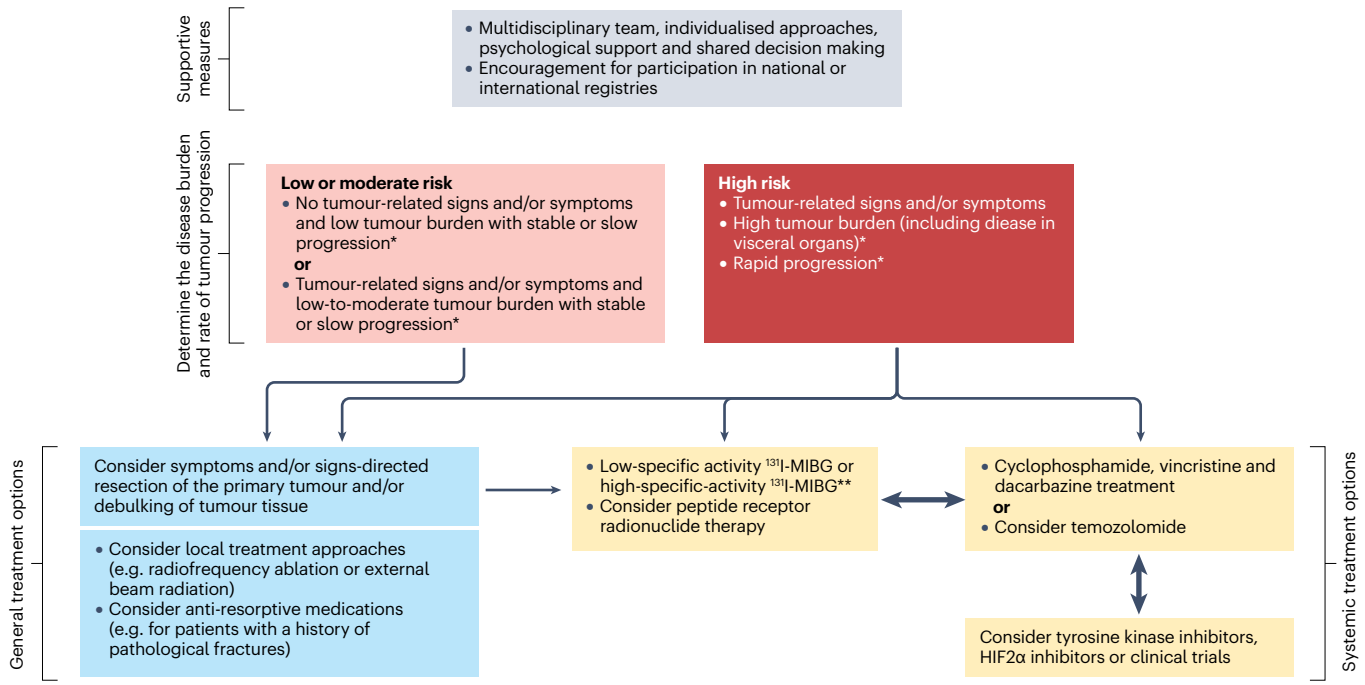

Fig. 1 | Overview of treatment options for paediatric patients with metastatic phaeochromocytoma and paraganglioma considering the rate of disease progression and burden of metastatic disease. Treatment options in children with phaeochromocytoma and paraganglioma (PPGL) should be individualized and directed 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 a high tumour burden usually associated with rapid tumour progression 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.

MIBG could be achieved in 82% of patients[161]. In two studies from the past 5 years, the use of high specific activity [^{131}I]MIBG molecules (that deliver lower mass doses) was associated with 92% partial response or stable disease[162,163] and this treatment was approved in 2018 by the FDA for use in children with metastatic PPGL older than 12 years[164]. However, the production of high specific activity [^{131}I]MIBG was terminated in the US in early 2024 due to high costs and lack of commercial demand[165]. Finally, clinicians should not discount the possibility that some children with metastatic PPGL may lack avidity for MIBG[163,166].

The use of peptide receptor radionuclide therapy (PRRT) targeting SSTR2 and SSTR5 (usually expressed on PPGL cells) has shown promising results in adult patients with metastatic PPGL, especially in those with *SDHx* pathogenic variants[167,168]. In addition, treatment with PRRT has been shown to be effective with minimal adverse effects in paediatric patients with metastatic neuroendocrine tumours[169]. PRRT has not yet been approved for use in children with metastatic PPGL and SSTR-expressing lesions[170]. However, several clinical trials (Supplementary Table 11) are currently evaluating PRRT in 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[169,171,172] 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[173–175], or in patients who have progressive disease despite previous treatment using targeted radionuclide therapies (Fig. 1). Although there are no prospective clinical trials to establish the effectiveness of CVD in children, and retrospective studies included mainly small cohorts of adults without systematic follow-up, cumulative findings indicate that CVD can delay tumour growth, and improve symptoms and signs of catecholamine excess[156,173,176]. Estimated disease control rates with CVD chemotherapy are approximately 40%, but a notable number of patients experience therapeutic failure after a short period of remission[173,174,176–178]. CVD chemotherapy is associated with adverse effects including myelosuppression, peripheral neuropathy and gastrointestinal toxicity[174,179].

As with other paediatric cancers[180], preliminary studies have shown promising results with temozolomide for the treatment of metastatic PPGL, especially among patients with *SDHB* pathogenic variants[181–184]. Notably, temozolomide is an oral analogue of dacarbazine and therefore is not advised in patients following failure of treatment with CVD[181]. Anti-angiogenic agents such as tyrosine kinase inhibitors are currently studied for the treatment of metastatic PPGL[185]. Despite their increasing use in other paediatric cancers[186–188], tyrosine kinase inhibitors have not yet been approved for use in the treatment of paediatric patients with metastatic PPGL. Similarly, HIF2α inhibitors are currently under evaluation as a potential treatment of paediatric PPGL[189,190]. Prospective clinical trials, however, are needed to validate the efficiency and long-term safety of targeted therapies[191].

- **Statement 33.** 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 localized 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 in adult cohorts[192–197]. In particular, thermal ablation in metastatic bone lesions can delay severe skeletal events[192–195]. Similarly, radiofrequency ablation (RFA) of hepatic lesions can lead to radiological disease response[192,196–198]. In a 2019 study in patients with metastatic PPGL, local therapies, such as RFA, cryoablation and percutaneous ethanol injections, were associated with 86% radiological and 92% biochemical control[199]. Although children older than 8 years were included in this latest study[199], 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[200,201].

Data on the use of local radiotherapy in paediatric cohorts with metastatic PPGL are sparse[202–204]. It is traditionally used for the management of pain and compressive symptoms and signs from localized disease not amenable to other therapies[205–207]. Nevertheless, apart from palliative purposes, targeted radiotherapies, such as external beam radiation or stereotactic body radiation therapy, are increasingly used to improve prognosis in patients with oligometastases, with promising results for long-term local tumour[208,209] and tumour-related control of symptoms and/or signs[210,211] in adults and children older than 11 years. Finally, antiresorptive treatments including zoledronic acid and denosumab can be considered for use in children with symptomatic bone metastases or skeletal-related events such as hypercalcaemia, a high burden of skeletal disease or a history of pathological fractures[212].

- **Statement 34.** Pre-ablation treatment with an 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 h. (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 3, to minimize the risks of a catecholamine crisis[192,193,196]. 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[193]. Children who undergo ablative procedures should be monitored after the procedure for at least 24 h[193]. In symptomatic paediatric patients with catecholamine-secreting metastatic PPGL, adrenoreceptor blockade should be continued at doses prior to pre-ablation titration interval for as long as tolerated to minimize complications related to catecholamine release. 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.

- **Statement 35.** In 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[213–216], a time interval of approximately 3 months for establishing the rate of disease progression after the initial diagnosis of metastatic disease is usually suggested[123,217,218]. This interval, however, can vary according to clinical judgement, the patient's clinical presentation, the size and location of the lesion(s) (for example, organs versus bones), and planning of specific treatment strategies.

- **Statement 36.** 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)

Evidence: 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 (Supplementary Box 4; Supplementary Table 12).

Transition to adult services

- **Statement 37.** Transition from paediatric to adult care is essential and should be initiated some time after the patient turns 16 years of age. (Agreement: A; Evidence, very low)

Evidence: 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 (Supplementary Box 5).

- **Statement 38.** Psychological support should be offered to the children and their relatives at the time of initial PPGL diagnosis, genetic counselling and 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[219]. The PPGL diagnosis influences not only the child but the entire family unit[220]. 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[221]. 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 to all family members[222]. 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

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. The 40 experts from 11 different countries who participated provided 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 participants' expertise was crucial for adoption of this methodology. After adoption of the Delphi process, consensus was reached for 39 statements and was not reached for five statements, and the latter were removed (Supplementary Table 7). Of the 39 statements, 30 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). Consensus was reached for nine statements but with a level of agreement of <85% (75–84%, grade B).

A limitation of this Consensus Statement is the quality of evidence available to support the statements. The grade of evidence for statements provided was predominantly 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 85% agreement 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 a low or very low quality of evidence were based predominantly 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.

child with cancer and their family 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[222,223]. 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[219,224].

- **Statement 39.** Children and their families should be offered participation in national and international registries with pseudonymized databases and tissue biobanks to promote research on disease diagnosis, management and treatment. (Agreement A; Evidence, very low)

Evidence: Historically, enrolment in research protocols has been higher among children (<15 years old) than among adults[225–227]. This higher 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[228]. 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 that in paediatric patients not enrolled in clinical trials[229,230]. 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 randomized controlled clinical trials with the power of large cohort data[231].

Conclusions

A Delphi process was applied to establish consensus among 40 experts from 11 countries, and we have provided 39 statements of recommendations for the diagnosis, management and long-term surveillance of children with or at risk of PPGL. Of note, not all 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 highlights the strong hereditary basis of PPGL and the requirement for surveillance of asymptomatic genetic carriers from childhood or early adulthood and the need for lifelong 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 intraoperative management of catecholamine-producing tumours.

Finally, this international and collaborative work emphasizes 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.

Published online: 15 August 2024

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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 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.

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R.T.C., C.P., E.H., S.G.W., V.W., A.R., C.D., M.F., A.J.G., M.Robledo, A.-P.G.-R., A.B.G., D.T., E.R.M, J.W.M.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.Raffaelli, A.-P.G.-R., A.B.G., D.T., E.R.M, J.W.M.L., G.E., C.J., K.P., S.A., R.P., R.C.-B., L.A., S.B., L.C., E.C., A.C., M.C.F., R.d.K., L.d.S., A.F., A.H., V.K., M.K., C.L.-L., S.D.M., N.N., M.P.-C., H.H.J.L.M.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 his institution from Lantheus, Progenics, Exelixis, Merck Sharpe and Dohme and is a clinical adviser for Lantheus and Merck Sharpe and Dohme. S.D.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. J.W.M.L. is an unpaid member of the advisory board of the Phaeochromocytoma and Paraganglioma Alliance.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41574-024-01024-5.

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.

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