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Supplementary information

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

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Supplementary Material

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

Supplementary Table 1: Statements of the section "General Remarks"

Section: General Remarks	**Likert Scale (%)**						**Gr.**
Statements	**1**	**2**	**3**	**4**	**5**	**Abstain**	**A/B**
S1.The management of paediatric patients with PPGL requires specialist multidisciplinary input and should ideally be performed in a centre with expertise in managing PPGL.	94.6	2.7	2.7	0.0	0.0	0.0	A

1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree; A: degree of agreement of ≥ 85%; B: degree of agreement between 75-84%

Supplementary Table 2: Statements of the section "Diagnosis"

Section: Diagnosis	**Likert Scale (%)**						**Gr.**
Statements	**1**	**2**	**3**	**4**	**5**	**Abstain**	**A/B**
S2. Clinical suspicion of PPGL should be raised in paediatric patients with a) signs and symptoms of catecholamine excess, b) pathogenic variants in tumour susceptibility genes, c) previous history of PPGL, d) incidentally discovered adrenal or extra adrenal mass consistent with PPGL on imaging.	92.5	5.0	0.0	2.5	0.0	0.0	A
S3a. Biochemical testing for patients with suspicion of PPGL should include plasma urine (24 hour or spot) free normetanephrine and metanephrine.	68.4	23.7	2.6	0.0	2.6	2.6	A
S3b. Liquid chromatography is the gold standard method for the assessment of normetanephrine and metanephrine.	68.4	18.4	2.6	2.6	2.6	5.3	A
S4. Blood sampling for measurements of plasma metanephrines and methoxytyramine should be carried out with appropriate consideration of preanalytics.	42.7	44	4	5.4	0.0	4	A
S5. In situations of acute physical illness or intense emotional stress, biochemical test results should be interpreted with caution.	60.5	31.6	0.0	2.6	2.6	2.6	A

S6. For plasma or urine normetanephrine and metanephrine testing, laboratories should employ appropriate reference intervals.	68.4	23.7	0.0	2.6	0.0	5,3	A
S7. In case of borderline elevations (< 2 fold increase above the upper cut off) of only one metabolite in a paediatric patient with low degree of suspicion for PPGL (e.g. tested due signs and symptoms), biochemical testing should be repeated.	65.8	28.9	2.6	0.0	0.0	2.6	A
S8. In paediatric patients with biochemically confirmed PPGL, either MRI or CT can be performed to localize a tumour.	25.7	51.4	8.6	11.4	2.9	0.0	B
S9. Functional imaging should be considered preoperatively if multiple tumours or metastatic disease is suspected.	64.9	29.7	2.7	2.7	0.0	0.0	A
S10. Germline genetic testing is recommended for all children presenting with PPGL as well as all children with first degree relatives in whom germline pathogenic variants have been detected.	100	0.0	0.0	0.0	0.0	0.0	A
S11. If routine testing does not identify a pathogenic or likely pathogenic germline genetic variant, consider referral to a specialist genetic centre for genetic analyses on tumoral DNA for detection of somatic (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.	52.8	38.9	5.6	2.8	0.0	0.0	A

1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree; A: degree of agreement of ≥ 85%; B: degree of agreement between 75-84%

Supplementary Table 3: Statements of the section "Management"

Section: Management	**Likert Scale (%)**						**Gr.**
Statements	**1**	**2**	**3**	**4**	**5**	**Abstain**	**A/B**
S12. The decision for surgery and the surgical approach should be discussed at a specialist MDT and surgery should be performed by a surgeon experienced in PPGL surgery.	81.6	15.8	0.0	0.0	2.6	0.0	A
S13. A minimally invasive approach should be favoured when feasible for children with PPGL.	61.1	30.6	8.3	0.0	0.0	0.0	A

S14. Cortical sparing partial adrenalectomies should be considered for children with bilateral phaeochromocytoma or in whom presence of a pathogenic germline variant carries a high risk of recurrence but with a low malignant potential (e.g. patients with *RET* and *VHL* gene pathogenic variants).	57.9	31.6	7.9	2.6	0.0	0.0	A
S15.Pre-operative optimization with alpha-adrenoceptor blockers and/or calcium channel blockers, together with maintenance fluid intake of one to two times a weight-appropriate fluid intake should be considered in all children with PPGL ahead of a planned surgery or intervention. Beta-adrenoceptor blockers can be reserved for patients with persistent tachycardia despite optimal fluid intake and not being caused by alpha-adrenoreceptor blockers.	57.9	26.3	5.3	5.3	0.0	5.3	B
S16. Plasma or urine normetanephrine and metanephrine and plasma 3-methoxytyramine (if available) should be repeated between 2-8 weeks after surgery. For paediatric patients for whom pre-operative staging was not performed, post-operative imaging (at 3-6 months) should be considered to determine surgical remission.	52.6	39.5	0.0	7.9	0.0	0.0	A
S17. Children with PPGL should ideally have post-operative follow-up in a dedicated specialist clinic and surveillance strategies should be tailored based on individual clinical factors including presence of metastases, germline variant status, family history, tumour size, location, as well as tumour biochemical phenotype.	81.1	16.2	2.7	0.0	0.0	0.0	A
S18. Children with a germline pathogenic or likely pathogenic variant in a PPGL predisposition gene should be offered life-long clinical follow-up.	63.9	30.6	2.8	2.8	0.0	0.0	A
S19. For children with a history of PPGL, but without a pathogenic germline variant in a PPGL predisposition gene or evidence of a pathogenic germline mosaic or somatic variant, the duration of follow up should be a minimum of ten years.	40.5	48.6	8.1	2.7	0.0	0.0	A
S20. Children with a somatic or mosaic pathogenic or likely pathogenic variants in *EPAS1* or *VHL* or *SDHB* should be offered life-long clinical surveillance.	59.5	29.7	2.7	0.0	2.7	5.4	A

1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree; A: degree of agreement of ≥ 85%; B: degree of agreement between 75-84%

Supplementary Table 4: Statements of the section "Surveillance"

Section: Surveillance	**Likert Scale (%)**						**Gr.**
Statements	**1**	**2**	**3**	**4**	**5**	**Abstain**	**A/B**
S21. Surveillance in children with a pathogenic germline variant in the *SDHx* genes (*SDHA*, *SDHB*, *SDHC*, *SDHD*) should ideally include: i) Annual clinical symptoms review from the time of presentation or from age 5 years for asymptomatic *SDHB* carriers and age 10 for *SDHA/C/D* carriers. ii) Annual blood pressure check, biannual measurements of either plasma or urinary metanephrines and plasma methoxytyramine and interval MRI imaging of neck, thorax, abdomen and pelvis every 2-5 years.	45.9	32.4	10.8	8.1	2.7	0.0	B
S22. Surveillance for new or recurrent PPGL (as part of systemic *VHL* surveillance) in children with a pathogenic germline variant in *VHL* should ideally include: i) Annual clinical symptoms review from the time of presentation or from age 5 years for asymptomatic *VHL* carriers. ii) Annual blood pressure check, annual measurements of either plasma or urinary metanephrines and annual MRI imaging from the age of 16 years.	54.1	32.8	2.7	2.7	2.7	0.0	A
S23. Surveillance for new or recurrent PPGL (as part of systemic *RET* surveillance) in children with a pathogenic germline variant in *RET* should ideally include: i) Annual clinical symptoms review from the time of presentation or from age 11 years for high to moderate risk *RET* gene mutation carriers and 16 years for low-risk *RET* gene mutation carriers. ii) Annual blood pressure check, annual measurements of either plasma or urinary metanephrines. MRI imaging is not required routinely and can be reserved for patients with clinical symptoms or elevated or rising plasma or urinary metanephrines in order to inform early partial adrenalectomy and to reduce morbidity.	45.7	42.9	2.9	5.7	2.9	0.0	A
S24. Surveillance in children with a pathogenic germline mosaic *VHL* variant should ideally be carried out as per the guidelines for patients with germline *VHL* gene mutations.	52.8	36.1	2.8	5.6	0.0	2.8	A

S25. Surveillance for PPGL in children with a pathogenic or likely pathogenic mosaic or somatic variant in *EPAS1* should ideally include: i) Annual clinical symptoms review from the age of presentation. ii) Annual blood pressure check, annual measurement of plasma or urinary normetanephrine and metanephrines. Interval MRI imaging of the abdomen and pelvis can be considered at 2-3-year intervals.	27.8	50.0	8.3	0.0	2.8	11.1	B
S26. Children with a pathogenic or likely pathogenic mosaic variant in *VHL* should be offered life-long clinical surveillance.	52.8	36.1	2.8	2.8	2.8	2.8	A
S27. Surveillance in children and adolescents with pathogenic germline variants in *TMEM127* and children and adolescents with paternally inherited pathogenic variants in *SDHAF2* should ideally include: i) Annual or biannual clinical symptoms review from the age at presentation or from age 10-15 years for asymptomatic carriers. ii) Annual or biannual blood pressure check, measurement of either plasma or urinary metanephrines.	32.4	45.9	5.4	8.1	2.7	5.4	B
S28. MRI imaging of neck, thorax, abdomen and pelvis should be performed at the first screening visit and if negative interval MRI imaging of neck, thorax, abdomen and pelvis should be performed every 3-5 years for *TMEM127* variant carriers.	24.3	45.9	2.7	8.1	5.4	13.5	B
S29. MRI imaging of the neck should be performed at intervals of 3-5 years for *SDHAF2* carriers.	30.6	44.4	5.6	2.8	5.6	11.1	B
S30. Surveillance in children without a pathogenic germline variant in a PPGL predisposition gene or evidence of a germline mosaic variant in *EPAS1* or *VHL* should be tailored to the individual case and more frequent surveillance may be required for patients with extra adrenal tumours, a history of a large tumour (> 5cm), synchronous or recurrent tumours or a family history.	29.7	48.6	5.4	8.1	2.7	5.4	B

S31. Surveillance in children with a pathogenic germline variant in *MAX* should ideally include: i) Annual clinical symptoms review from the age of presentation or from age 10 years. ii) Annual blood pressure check, annual or two-yearly plasma or urinary normetanephrine and metanephrine and interval MRI imaging of neck, thorax abdomen and pelvis every 2-3 years from presentation or from age 15 years.	25.7	57.1	0.0	8.6	2.9	5.7	B

1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree; A: degree of agreement of ≥ 85%; B: degree of agreement between 75-84%

Supplementary Table 5: Statements of the section "Metastatic disease"

Section: Metastatic disease	**Likert Scale (%)**						**Gr.**
Statements	**1**	**2**	**3**	**4**	**5**	**Abstain**	**A/B**
S32. Treatment of metastatic PPGL in paediatric patients should be considered on an individualized 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.	55	37.8	3.6	0.9	0.9	1.8	A
S33. In paediatric patients with oligometastases or metastasis-related pain, ablation treatment including radiotherapy can be considered.	48.6	48.6	2.9	0.0	0.0	0.0	A
S34a. Pre-ablation treatment with an alpha-adrenoreceptor blocking agent should be initiated to reduce haemodynamic variability in case of catecholamine release during the procedure.	51.4	35.1	5.4	0.0	0.0	8.1	A
S34b. Post-ablation cardiovascular monitoring should be initiated in all paediatric patients for at least 24 hours.	56.8	35.1	5.4	0.0	0.0	2.7	A
S35. For paediatric patients with newly diagnosed metastatic disease, radiological follow-up should be initiated within 3-6 months, depending on clinical judgment, tumour burden and location of lesion(s).	62.2	32.4	2.7	2.7	0.0	0.0	A
S36. The option of fertile preservation should be discussed with teenage patients with advanced metastatic disease before cytotoxic treatment or radiotherapy of the pelvic area.	66.7	25.0	2.8	2.8	0.0	2.8	A

1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree; A: degree of agreement of ≥ 85%; B: degree of agreement between 75-84%

Supplementary Table 6: Statements of the section "Transition"

Section: Transition	**Likert Scale (%)**						**Gr.**
Statements	**1**	**2**	**3**	**4**	**5**	**Abstain**	**A/B**
S37a. Transition from paediatric to adult care is essential.	81.1	13.5	2.7	2.7	0.0	0.0	A
S37b. Transition should be initiated sometime after the 16th year of age.	64.9	27.0	5.4	2.7	0.0	0.0	A
S38.Psychological support should be offered to the children and their relatives at the time of initial PPGL diagnosis and genetic counselling, any PPGL-related procedures, as well as during follow-up.	73.0	24.3	0.0	2.7	0.0	0.0	A
S39. 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.	78.4	21.6	0.0	0.0	0.0	0.0	A

1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree; A: degree of agreement of ≥ 85%; B: degree of agreement between 75-84%

Supplementary Table 7: Statements that did not reach consensus

Statements that did not reach consensus
1. At initial diagnosis of PPGL in paediatric patients, an echocardiography should be considered pre-operatively.
2. The symptoms questionnaire should include the following: excessive sweating, hypertension, palpitations, tachycardia, headaches, pallor, constipation, tremor, visual disturbances, nausea, weight loss, vomiting, polyuria/polydipsia, abdominal pain, anxiety.
3. Because of the potential non-targeted uptake of ^{131}MIBG within the thyroid gland, paediatric patients should receive thyroid blockade (potassium iodine) beginning one day before the treatment administration and continuing for children older than 3 years. Neonates should receive thyroid blockade only one day before the treatment administration.
4. Tyrosine kinase inhibitors can be used to treat paediatric patients with advanced metastatic PPGL.
5. Check point inhibitors can be used to treat paediatric patients with advanced metastatic PPGL.

Supplementary Table 8: Definitions for grading the quality of evidence

Grade	Definition
High	High RCTs or exceptionally strong evidence from unbiased observational studies including meta-analysis and systematic reviews.
Moderate	Moderate Evidence from RCTs with important limitations (limited number of cases) or unusually strong evidence from unbiased observational studies (well-designed comparative studies or cohort studies).
Low	Low Evidence for at least one critical outcome from observational studies (case-control study), RCTs with serious flaws, or indirect evidence.
Very Low	Very low Evidence for at least one of the critical outcomes from unsystematic clinical observations (including consensus, expert opinion, retrospective studies, or case studies) or very indirect evidence.

Supplementary Table 9: Advantages and disadvantages of different anatomical imaging modalities.

Anatomical Imaging	Advantages	Disadvantages
Ultrasound	✓ Evaluate intra-regional vascularity ✓ Safe ✓ High availability including acute care management. ✓ No sedation required ✓ No radiation ✓ Useful in acute settings when contrast enhanced CT or MRI may not be readily available (e.g., to obtain imaging results quickly for patients presenting at urgent care clinics or at ICU setting) or when pregnancy is highly suspected	✓ Not sensitive enough to identify small lesions ✓ Cannot be used to stage or assess response
Magnetic resonance imaging (MRI) with intravenous contrast	✓ No radiation ✓ Better evaluation of the surrounding soft tissue ✓ Highly sensitive for HNPGLs and evaluation of metastatic disease (liver, soft tissues, bones)	✓ Longer examination time ✓ May require sedation ✓ Higher motion artefacts than CT ✓ Costly and less availability ✓ Unclear data regarding the long-term consequences of contrast deposit in brain, especially when used in children
Computer tomography (CT) with intravenous contrast	✓ Rapid acquisition ✓ Sedation seldom required. ✓ More easily interpreted by clinicians and surgeons ✓ Simultaneous imaging of chest and abdomen and pelvis ✓ Sensitive for most PPGLs ✓ Excellent for evaluation of bone extension (e.g., temporal bone) and metastatic disease including lungs	✓ May be less sensitive for small tumours in certain regions (liver, HNPGL) ✓ Radiation exposure

Supplementary Table 10. Support groups for patients with phaeochromocytoma/ paraganglioma

Support groups	Link
Pheochromocytoma Support Group	http://www.pheochromocytoma.org/
The Pheo-Para Alliance	https://pheopara.org/
The Pheochromocytoma Paraganglioma Patient Initiative	http://www.pheoparatroopers.org/
The VHL FamilyAlliance	http://www.pheoparatroopers.org/
The National Adrenal Diseases Foundation	http://www.nadf.us/index.htm
The Association for Multiple Endocrine Neoplasia Disorders (AMEND)	http://www.amend.org.uk/
The Paradifference Foundation	https://www.paradifference.org/

Supplementary Table 11. Ongoing clinical trials in paediatric patients with metastatic PPGL

PRRT	NCT Number	Clinical Trial
^{177}Lu-DOTATATE	NCT02236910	An open Label Registry Study of Lutetium-177 (DOTA0, TYR3) Octreotate (Lu-DOTA-TATE) Treatment in patients with Somatostatin Receptor Positive Tumors
^{177}Lu-DOTATATE	NCT01876771	A Trial to Assess the Safety and Effectiveness of Lutetium-177 Octreotate Therapy in Neuroendocrine Tumours
90Y-DOTA tyr3-Octreotide	NCT00049023	Radiolabeled Octreotide in Treating Children with Advanced or Refractory Solid Tumors
^{177}Lu-oxodotreotide/DOTATATE	NCT04711135	Study to Evaluate Safety and Dosimetry of Luthera in Adolescent Patients with GEP-NETs and PPGLs
^{177}Lu-Octreotate	NCT02743741	Lu-DOTATATE Treatment in Patients with ^{68}Ga-DOTATE Somatostatin Receptor Positive Neuroendocrine Tumors

Supplementary Table 12. Cancer treatment effect on gonadal function

Cancer Treatment	Complication	Risk factor
Chemotherapy	Hypogonadism (gonadotropin deficiency, delayed puberty, acute ovarian failure, premature menopause, infertility).	High dose of alkylating agents (e.g cyclophosphamide) Older age
Radiotherapy	Hypogonadism (gonadotropin deficiency, delayed puberty, acute ovarian failure, premature menopause, infertility).	Prepubertal gonadal irradiation >10 Gy Pubertal gonadal irradiation >5 Gy
	Uterine vascular insufficiency	Pelvic dose >18 Gy

Supplementary Box 1*:* Head and neck paragangliomas in childhood

Head and neck paragangliomas (HNPGL) are rarely reported in childhood and adolescence. In two large studies, HNPGL accounted for 9% and 22.5% of all PPGL cases in the paediatric cohorts[1,2] and account for less than 5% of reported cases of paediatric PPGL in the literature[1]. In the head and neck region a tumour is named by the location of origin; carotid body, jugulotympanic, vagal and laryngeal PGL. The majority of HNPGLs are biochemically silent and the associated metastatic risk is overall low to moderate[3,4]. However local compressive effects can cause significant symptoms and signs, particularly due to lower cranial nerve palsy e.g. including tinnitus, pain, and hearing impairment. Germline SDHB and SDHD pathogenic variants are most commonly implicated in children with HNPGL[1]. Due to their slow-growing pattern, an initial trial of observation is typically recommended for HNPGLs. Treatment options include surgery or radiotherapy (stereotactic or fractionated radiotherapy for localized tumours) and treatment should be individualized and discussed at the multidisciplinary team meeting. Surgery should be considered in patients with active symptoms and signs due to mass-related compressive effects or rare cases of catecholamine hypersecretion, tumours exhibiting sustained growth or progression after radiation[5]. Management decisions should carefully consider the risk avoidance of lower cranial nerve neuropathies in childhood or adolescence. HNPGL in children is rare and overall management should be guided by existing gene specific guidance for HNPGL in adults[5]. Given the rarity of HNPGL in childhood, this consensus statement has mainly focused on the management of phaeochromocytoma and abdominal and pelvic paraganglioma in childhood and adolescence.

Supplementary Box 2: Composite tumours

The combination of PPGL and other tumour types in a single tumour is rarely reported. This type of tumour is referred to as "composite" if the PPGL and non-PPGL components are of neural origin or "mixed," if both components have different embryologic origin. Composite paraganglioma are exceedingly rare and most reported literate focuses on composite phaeochromocytomas. A recent metanalysis demonstrated that composite tumours consisting of a combination of phaeochromocytoma and ganglioneuroma are most common followed by phaeochromocytoma and ganglioneuroblastoma and mixed tumours account for less than 10% of tumours[6]. The median age at diagnosis of composite tumours is the fourth decade but these tumours can occur in children. There is an overlap in the genetic drivers of PPGL and composite phaeochromocytoma. Careful histological characterisation of the tumoural components of a composite tumour is essential as management should be dictated by the highest-grade component. Composite phaeochromocytomas are rare tumours and diagnoses in childhood warrants specialist MDT discussion and consideration should be given to genetic testing as for PPGL.

Supplementary Box 3. Definition of metastatic disease

Metastatic disease is defined as the presence of metastases in tissues distant from the primary tumour where chromaffin cells are normally absent. Identification of metastases largely depends on the detection of organ lesions by conventional and functional imaging studies. The latter imaging studies in particular provide high specificity for correctly identifying PPGLs. Histopathological examination of resected tissue samples including lymph node or bone metastases is also informative though often not possible. According to the WHO classification,[7] primary tumours at unusual sites such as liver or lungs, although extremely rare, can be found, and thus lesions at these sites cannot definitively indicate metastatic spread. However, such primary tumours at unusual sites are extremely rare and mainly relevant for patients with lesions confined to the bronchus or where primary tumours in the mediastinum may be mistaken for metastatic lesions in the lungs.

Supplementary Box 4. Fertility preservation

The mean disease specific survival of patients with metastatic PPGL has progressively increased above 20 years[8] so that more and more long-term survivors consider the possibility of family planning. Cancer survivors have a 1.48-fold higher risk of infertility compared to their siblings[9] and this can be partially attributed to gonadotoxic treatment [10]. The American Society of Clinical Oncology recommends that counselling and fertility preservation should be offered to patients at risk of treatment related to gonadotoxicity and their parents, even if the risk of gonadal damage is low[11,12]. Known risk factors for gonadal damage among paediatric patients with PPGL include increasing doses of pelvic radiation and/or alkylating chemotherapy agents (e.g., cyclophosphamide)[9], which have a dose dependant effect on gonadal function[13,14] (Supplementary Table 12).

Supplementary Box 5. Transition from paediatric to adult care

Health care transition is the process of changing from the more "family-oriented" paediatric model to the more independent, "patient-specific" adult model of health care. It is well established that appropriate transition programs to adult care is essential as it improves treatment success rates and quality of life[15,16]. This is particularly relevant for paediatric patients with hereditary PPGL, as these patients typically require life-long follow-up with a significant risk of recurrent and metastatic disease[17]. The transition process should be aligned to the long-term follow up strategy[18-21] and it is generally recommended that transition occurs between the age of 16 to 19 years[22–25] with consideration of the patient's developmental stage, capacity, psychosocial issues, patient, and family needs.

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