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REVIEW

Pathology and genetics of phaeochromocytoma and paraganglioma

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Phaeochromocytoma and paraganglioma (PHEO/PGL) are rare tumours with an estimated annual incidence of 3 per million. Advances in molecular understanding have led to the recognition that at least 30–40% arise in the setting of hereditary disease. Germline mutations in the succinate dehydrogenase genes *SDHA*, *SDHB*, *SDHC*, *SDHD* and *SDHAF2* are the most prevalent of the more than 19 hereditary genetic abnormalities which have been reported. It is therefore recommended that, depending on local resources and availability, at least some degree of genetic testing should be offered to all PHEO/PGL patients, including those with clinically sporadic disease. It is now accepted that that all PHEO/PGL have some metastatic potential; therefore, concepts of benign and malignant PHEO/PGL have no meaning and have been replaced by a risk stratification approach. Although there is broad acceptance that certain features, including high proliferative activity, invasive growth, increased cellularity, large tumour nests and comedonecrosis, are associated with an increased risk of metastasis, it remains difficult to predict the clinical behaviour of individual tumours and no single risk stratification scheme is endorsed or in widespread use. In this review, we provide an update on advances in the pathology and genetics of PHEO/PGL with an emphasis on the changes introduced in the WHO 2017 classification of endocrine neoplasia relevant to practising surgical pathologists.

Keywords: multiple endocrine neoplasia type 2, paraganglioma, phaeochromocytoma, succinate dehydrogenase, von Hippel-Lindau syndrome

Introduction

The accurate pathological diagnosis of phaeochromocytoma and paraganglioma (PHEO/PGL) has never been more important, not only because correct diagnosis underpins both clinical management and translational research, but particularly because of a new understanding of the strongly hereditary nature of these tumours. It is now accepted that at least 30–40% of PHEO/PGL arise in the context of hereditary disease, and cascade testing of index patients facilitates risk reduction strategies across entire kindreds.[1,2] In this review we provide an update on the pathology and genetics of PHEO/PGL based on

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current concepts in the fourth edition 2017 World Health Organisation (WHO) classification of tumours of endocrine organs.[1]

Terminology

By convention, tumours arising in the adrenal medulla are referred to as phaeochromocytomas, whereas morphologically indistinguishable tumours arising from the chromaffin cells of the autonomic nervous system outside the adrenal medulla are termed paraganglioma.[1] That is, the distinction between phaeochromocytoma and paraganglioma is somewhat arbitrary – particularly because the adrenal medulla is considered the largest paraganglion in the body. Paragangliomas can be subdivided further into sympathetic and parasympathetic subtypes on the basis of function and location. Sympathetic paragangliomas typically arise along the sympathetic chains in the thorax and abdomen. Parasympathetic paragangliomas originate from the parasympathetic autonomic nervous system, usually in the head and neck, and are associated with the cranial nerves.[1,3,4]

As a group, germline mutations in the autosomal genes which encode the succinate dehydrogenase (SDH) enzymes [succinate dehydrogenase complex subunit A (*SDHA*), succinate dehydrogenase complex subunit B (*SDHB*), succinate dehydrogenase complex subunit C (*SDHC*), succinate dehydrogenase complex subunit D (*SDHD*) and succinate dehydrogenase complex assembly factor 2 (*SDHAF2*)] are now recognised to be the most frequent cause of hereditary PHEO/PGL, perhaps accounting for up to half of germline mutations in phaeochromocytomas and paragangliomas (Figure 1).[5–8] As succinate dehydrogenase deficient neoplasia is the topic of a separate review in this journal,[8] the *SDH* genes and associated neoplasms as well as the utility of SDHB and SDHA immunohistochemistry as a screening test for these mutations are not discussed further in this paper. The next most common germline mutations are those associated with von Hippel-Lindau syndrome (*VHL*), multiple endocrine neoplasia type 2 (*RET*) and neurofibromatosis type 1 (*NF1*).[1] However, it is now known that germline mutations in many other genes, most of which are individually rare, can also lead to hereditary tumour syndromes which manifest with PHEO/PGL. At the time of writing these genes include *EPAS1*, *TMEM127*, *MAX*, *KIF1Bβ*, *PHD2*, *FH*, *MDH2* and *MEN1*.[1,2,4,6,9–11] The genetic mutations which may present with PHEO/PGL and associated syndromes as reported in the WHO 2017 classification are summarised in Table 1 and their relative incidences are presented in Figure 1.[1]

Incidence and location

It is important to recognise that PHEO/PGL are rare tumours with a reported estimated annual incidence of up to 3 per million, with paragangliomas

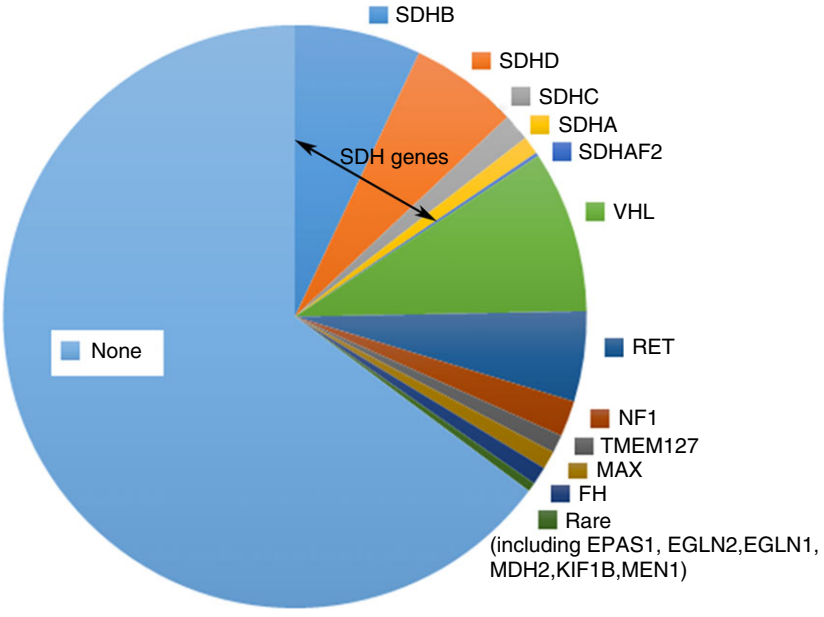

Figure 1. Frequency of different germline mutations in patients presenting with phaeochromcoytoma and paraganglioma.

probably outnumbering phaeochromocytoma by twofold.[1,7,8,12–16] Phaeochromocytomas may occur at any age; however, the median age at presentation is the 4th–5th decades with an equal gender distribution.[1,17] Phaeochromocytoma presenting in young patients are significantly more likely to be hereditary, particularly in children where germline mutations have been reported in at least 70% of patients.[18–20]

Parasympathetic paragangliomas occur predominantly in the head and neck, where they account for approximately 0.6% of all neoplasms.[1,21,22] The reported age range is wide, and the mean age is 44 years.[23,24] There is a strong female predominance, with female to male ratios reported to be as high as 8:1.[25,26] The tumours are frequently bilateral or multiple which, together with a younger age of onset, are clear clues to hereditary disease.[24,27–29] Head and neck paragangliomas, being parasympathetic, are very rarely functional.[1] Compared to other sites, metastasis from head and neck paragangliomas is relatively rare.[1,24,30]

Although 12% arise in the thorax (with 2% being associated with the heart), the majority of sympathetic paragangliomas occur below the diaphragm, particularly in close proximity to the adrenal gland (42%), organ of Zuckerkandl (28%) and bladder (10%).[1,31–40] Unlike their predominantly head and neck parasympathetic counterparts there is an equal gender distribution, with the most common age at presentation being the fifth decade but with a younger age of onset in hereditary disease.[1,41] The reported incidence of metastasis from sympathetic paragangliomas is highly variable, and ranges from 2.5% to 50% in some series.[42–44] However, it is generally recognised that intra-abdominal extra-adrenal paragangliomas have a higher rate of metastasis, perhaps because of a strong association with germline *SDHB* mutation.[7,8]

Clinical presentation and detection

Phaeochromocytomas and paragangliomas can be either functional, i.e. they secrete catecholamines, or non-functional, in which case they present usually as a mass and are found incidentally on imaging performed for other reasons. The catecholamines that are produced are either methylated (inactivated) or unmethylated.[1] Functional tumours that secrete unmethylated catecholamines produce symptoms related to catecholamine synthesis. In addition to the classic triad of sweating, palpitations and headache, which is found in only the minority of patients, symptoms associated with functional PHEO/PGL may include paroxysmal or persistent hypertension, pallor, anxiety, panic attacks, tremor or constipation.[1,15,19] Non-catecholamine-associated paraneoplastic syndromes have been reported, and include hypercalcaemia, cytokine secretion, human placental lactogen secretion, vasoactive intestinal peptide secretion and Cushing's syndrome due to ectopic adrenocorticotrophic hormone (ACTH) or, very rarely, corticotrophin-releasing hormone (CRH) production.[45,46] Unlike phaeochromocytomas, sympathetic paragangliomas secrete adrenaline very rarely, as the elevated levels of glucocorticoid needed for the enzymatic conversion of noradrenaline to adrenaline are absent.[1,47–49] Thus, the little over half of all sympathetic paragangliomas which are functional secrete noradrenaline or dopamine.[47–49] The biochemical profile can be used to suggest the location of PHEO/PGL, which can be confirmed by anatomical imaging [(ultrasound, computerised tomography (CT), magnetic resonance imaging (MRI)] and functional imaging [123I-MIBG scintigraphy and DOTATATE positron emission tomography (PET)/CT].[1,50–52] The biochemical profile can also be a clue to hereditary disease, as multiple endocrine neoplasia type 2 (MEN2) or neurofibromatosis type 1-associated tumours are more likely to produce adrenaline, whereas noradrenaline-producing tumours are associated more frequently with von Hippel-Lindau syndrome, while elevated levels of 3-methoxytyramine may suggest germline succinate dehydrogenase mutation.[49,53,54]

It is important to remember that clinically non-functional tumours may or may not be biochemically functional. Biochemical function, i.e. the ability to produce catecholamines or their metabolites, requires the expression of tyrosine hydroxylase (TH), the initial enzyme in catecholamine biosynthesis. Immunohistochemical stains for TH are positive in most sympathetic paragangliomas, but in only a minority of parasympathetic paragangliomas.[55] A TH stain of a paraganglioma, particularly in the head or neck, can be useful because recurrence or persistence of catecholamine metabolites in a patient whose tumour is TH-negative most probably indicates a second primary rather than recurrence or metastasis.

Morphology

PHEO/PGL may show a variety of architectural patterns (Figures 2–4), but generally these have little

Table 1. Genes and tumour associations of hereditary phaeochromocytoma (PCC), paranganglioma (PGL) of head and neck (H&N) and of abdomen or thorax (A/T)[1]

Gene	Chromosome location	Syndrome	Distribution	Tumour associations
SDHD	11q23	PGL1/CSS	PGL > PCC	SDH-deficient GIST, pituitary adenoma, ?SDH-deficient RCC
SDHAF2	11q12.2	PGL2/CSS	PGL H&N	Unknown/not reported
SDHC	1q23.3	PGL3/CSS	PGL H&N	SDH-deficient RCC and GIST
SDHB	1p36.13	PGL4/CSS	PGL A/T ≫ PGL H&N > PCC	SDH-deficient RCC and GIST, pituitary adenoma
SDHA	5p15.33	PGL5/CSS	PGL > PCC	Pituitary adenoma, SDH-deficient RCC and GIST
VHL	3p25.5	VHL	PCC >>> PGL	Clear cell RCC, haemangioblastoma; NETs, pancreatic serous cystadenoma
RET	10q11.2	MEN2	PCC >>> PGL	Medullary thyroid carcinoma, parathyroid hyperplasia/ adenoma, mucocutaneous manifestations
NF1	17q11.2	NF1	PCC >>> PGL	Neurofibroma and MPNST, oculocutaneous manifestations, duodenal NET
TMEM127	2q11.2		PCC > PGL	RCC?
EPAS1	2p21	PZS	PCC ~ PGL A/T	Duodenal NET, polycythaemia, ocular manifestations
EGLN2	19q13.2		PCC ~ PGL A/T	Polycythaemia
EGLN1	1q42.1		PCC ~ PGL A/T	Polycythaemia
MAX	14q23.3		PCC ~ PGL	Unknown/not reported
FH	1q42.1	HLRCC	PCC ~ PGL	Cutaneous and uterine fumarate hydratase deficient leiomyoma, HLRCC-associated RCC
MDH2	7q11.23		PGL A/T	Unknown/not reported
KIF1B	1p36.22			Ganglioneuroma, leiomyosarcoma, lung adenocarcinoma, neuroblastoma, ganglioneuroma
MEN1	11q13.1		PCC ~ PGL H&N	Pancreatic NET, bronchopulmonary and thymic NET, parathyroid adenoma/hyperplasia, pituitary adenoma

CSS, Carney–Stratakis syndrome; GIST, Gastrointesintal stromal tumour; HLRCC, Hereditary leiomyomatosis and renal cell carcinoma; MEN2, Multiple endocrine neoplasia type 2; MPNST, Malignant peripheral nerve sheath tumour; NET, Neuroendocrine tumour; NF1, Neurofibromatosis type 1; PA, Pituitary adenoma; PGL1-5, Paraganglioma syndrome types 1–5; PZS, Pacak–Zhuang syndrome; RCC, Renal cell carcinoma; SDH, Succinate dehydrogenase; VHL, von Hippel-Lindau syndrome.

clinical significance.[56–59] The classic pattern shows nests of cells ('Zellballen') with prominent surrounding capillaries. Trabecular or solid architecture may also be present, and different patterns may be intermixed in the same tumour. Composite tumours, usually consisting of PHEO/PGL combined with ganglioneuroblastoma or ganglioneuroma, are seen occasionally. The presence of a few isolated ganglion cells may be a clue to the presence of composite features, but on its own are insufficient to warrant the diagnosis of a composite phaeochromocytoma which requires the presence of a well-developed second component.[1,46]

Previously, small areas of expansion of the adrenal medulla less than 10 mm in diameter were considered hyperplastic medullary nodules. These small lesions, usually recognised only in the setting of hereditary disease, have been proved to be clonal and are now considered true pheochromocytomas.[1,56] Although a formal nomenclature change was not made in WHO 2017, the term 'microphaeochromocytoma' would not be inappropriate.

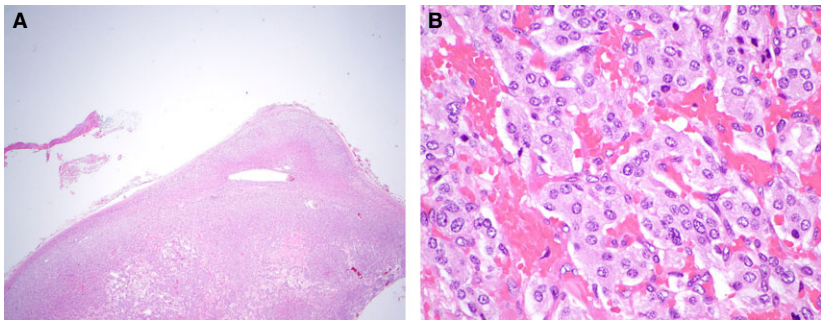

Figure 2. Phaeochromocytoma arising in an adrenal gland. **A**, Low-power view showing surrounding residual cortex [haematoxylin and eosin (H&E)]; **B**, high-power view showing typical nuclear morphology (H&E).

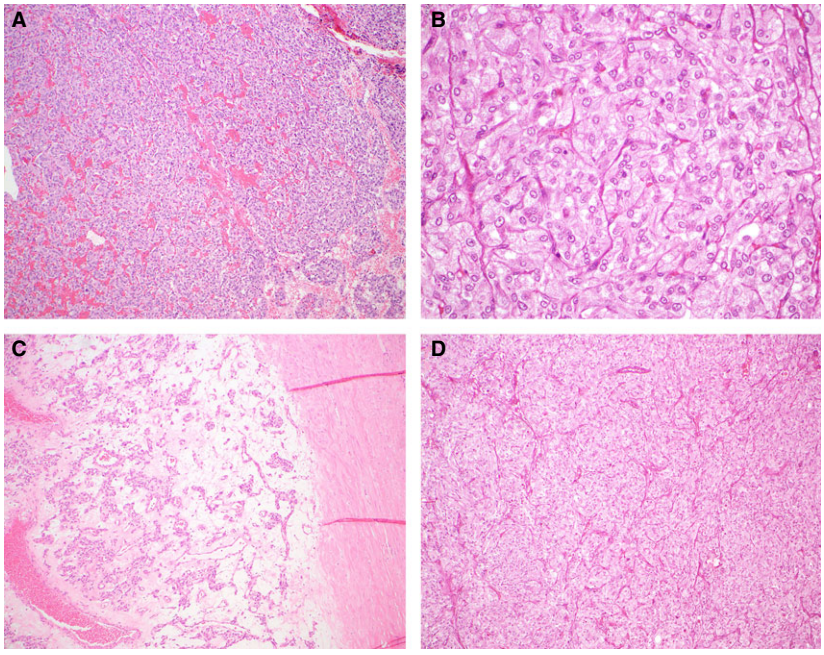

Figure 3. The variable morphology of phaeochromocytoma and paraganglioma. **A**, Prominent vascular spaces [haematoxylin and eosin (H&E)]; **B**, typical nested growth pattern with sustentacular cells (H&E); **C**, early fibrosis in an area of ischaemia and atrophy (H&E); **D**, diffuse and nodular growth (H&E).

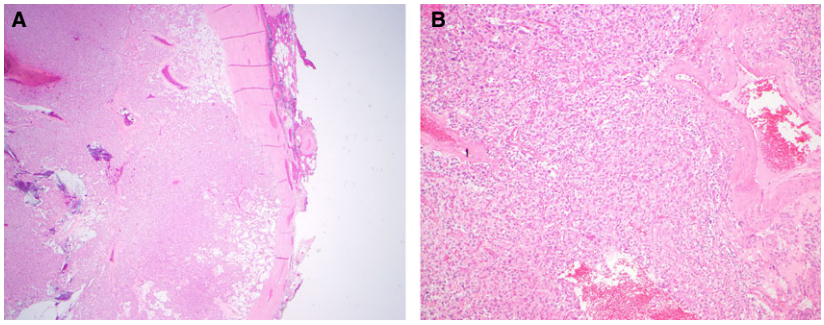

Figure 4. Paraganglioma arising in association with a large vein [**A**, haematoxylin and eosin (H&E); **B**, H&E].

Risk stratification and pathological parameters

In the third edition of the WHO classification from 2004, PHEO/PGLs were classified as malignant or benign on the basis of unequivocal metastatic disease, defined by the confirmation of metastatic tumour in a site that does not normally have a chromaffin cell population. Generally speaking, sites that qualify for metastasis are bone, lung, liver and histologically confirmed lymph node. Modern understanding, as reflected in the fourth edition WHO classification from 2017, is that all PHEO/PGL have some metastatic potential.[1] Although the risk of metastasis may be very low in a completely resected, adrenal-confined phaeochromocytoma the risk is not zero, and it is

therefore inappropriate to consider such a tumour as 'benign'. Therefore, the qualifiers of 'benign' or 'malignant' have no meaning in the context of PHEO/PGL and have been replaced by a concept of risk stratification with the implicit understanding that all PHEO/PGL have the potential to metastasise, but some possess higher risk than others. In general, risk is higher for sympathetic paraganglioma than phaeochromocytoma or parasympathetic paraganglioma. Tumours larger than 5 cm are also associated with increased risk.[60]

Various histological features in a primary PHEO/PGL have been reported to be associated with an increased risk of subsequent metastasis. These include invasion of soft tissue and blood vessels; particular architectural patterns including hypercellularity and large confluent nests; comedo-type necrosis; and a high mitotic count or Ki-67 proliferative index.[60–63] Less well-accepted factors which may connote an increased risk of metastasis include coarse nodularity, decreased numbers of sustentacular cells or the absence of hyaline globules.[60,64–66]

While there is widespread acceptance that some factors are associated with an increased risk of metastasis, it is difficult to quantify this risk in individual patients. Several grading schemes based on weighted composite scores of combinations of these factors have been proposed, with the most well-known being the Phaeochromocytoma of the Adrenal Scaled (PASS) score[62] and the Grading system for Adrenal Phaeochromocytoma and Paraganglioma (GAPP) score.[61,67] The PASS score seeks to give a threshold whereby all tumours over and above a set score are 'at risk' of metastasis (and, by implication, all tumours below this score at very low risk), whereas the GAPP score gives a scale of risk of metastasis and a likelihood of survival.[61,67] However, at the time of writing, both systems are underexamined and require validation in large independent cohorts before they can be endorsed for routine clinical use.

One interesting aspect of the histological examination is the potential role to suggest patients with hereditary disease and specific mutations. Small tumour cells, the presence of a myxoid component and a vascular pseudocapsule are suggestive of von-Hippel Lindau (VHL) disease,[1,68] whereas medullary hyperplasia with multiple tumours is more in keeping with MEN2,[1,69] and rounded epithelioid cells sometimes with relatively clear cytoplasm, in tightly nested balls surrounded by a well-developed capillary vasculature, may be associated with succinate dehydrogenase mutation.[8] The presence or absence of these features is prone to interobserver variability, and in no way replaces molecular testing.[1,70]

The pathological differential diagnosis of PHEO/PGL includes adrenal cortical oncocytic tumours, renal cell carcinomas and low-grade neuroendocrine tumours (NETs, known previously as carcinoids).[71] Our experience has been that oncocytic adrenal cortical tumours are the most common mimicker of adrenal phaeochromocytomas and NETs are the most common mimicker of paragangliomas. Knowledge that virtually all PHEO/PGL express chromogranin A can be particularly useful to resolve certain differential diagnoses.[46,72] However, pitfalls in the interpretation of immunohistochemistry include the fact that oncocytic phaeochromocytomas are more likely to express chromogranin A only weakly, and that PHEO/PGLs may rarely show immunoreactivity for MelanA, inhibin or cytokeratin.[71,73] S100 may be useful to highlight sustentacular cells; however, they are not infrequently absent[74] and our experience has been that neoplastic cells in many PHEO/PGL also express S100. The use of keratins may distinguish NETs from PHEO/PGL, as the latter have only focal and/or weak expression, whereas NETs usually show diffuse and strong expression. However, keratins are not very useful for the distinction of PHEO/PGL and adrenocortical tumours. The latter, however, can be stained reliably with the relatively new specific marker steroidogenic factor-1 (SF1).[75]

Genetics

As patients with phaeochromocytoma have at least a 30–40% chance of hereditary disease, it is now recommended that all patients undergo at least some degree of genetic screening.[1,49] With the rise of a panel approach to molecular testing, to a large extent the degree of genetic testing undertaken may depend more upon local availability and resources than the pretest probability of hereditary disease on the basis of age of onset, multifocality and family history. It is emphasised that in some studies up to 24% of patients with clinically sporadic PHEO/PGL have been shown to have hereditary disease, and therefore the absence of a family history or other syndromic manifestations in no way excludes the need for genetic testing.[1,76–79] The mode of inheritance is most commonly autosomal-dominant and associated with inactivating mutations or deletions in tumour suppressor genes. However, *RET*, *EPAS1* and *HIF2A* genes carry gain-of-function mutations.[79] Some mutations, including *MAX*, *SDHAF2* and *SDHD*, show a parent-

of-origin effect requiring paternal transmission for clinical disease, but not for the carrier state.[1]

Recurrent somatic mutations in the same genes which cause hereditary disease are being recognised increasingly, and somatic mutations can be detected in up to 20% of patients in one of the genes associated with hereditary susceptibility, most frequently NF1.[1,80,81] Recurrent somatic mutations in *BRAF* and *HRAS* are reported in up to 8.9%.[1,79–81] While mutations are a requirement for tumorigenesis, additional genetic abnormalities need to be present. The frequent loss of particular chromosomal regions, including 1p, 3q, 11p, 11q, 6q, 17p, 9q, 17q, 19p13.3 and 20q, has suggested the presence of tumour suppressor genes within these loci; however, to date no recurrent specific gene mutations have been identified at these sites.[1,81]

Conclusion

In conclusion, PHEO/PGL*s* are rare tumours which are important to recognise. Recent conceptual changes include the replacement of the qualifiers 'benign' and 'malignant' with the recognition that all PHEO/PGL have a metastatic risk and an approach based on risk stratification. Additionally, the very strong hereditary basis of this tumour is now emphasised, and there is an accompanying recommendation that at least some degree of genetic testing should be offered to all PHEO/PGL patients.

Conflict of Interests

The authors declare no conflicts of interest.

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