

## REVIEW

# Congenital hepatoblastoma: Expanding knowledge, improving outcomes

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**Abstract**

Hepatoblastoma (HB) is a rare liver tumour, and its congenital counterpart (CHB) is even less frequent. CHB has a clinically challenging management and a generally perceived worse outcome. This study aims to review the literature on CHB to better define presentation, diagnosis, available treatments and management options. The analysis of outcomes suggests that a significant portion of mortality is unrelated to the malignant nature of the tumour. Key factors influencing overall outcomes were identified: mortality linked to the 'mass effect' during both the prenatal (22%) and perinatal (32%) stages, as well as 'oncological' mortality encompassing tumour and/or treatment-related factors (46%). Overall, after birth, CHB does not seem to confer a worse oncological prognosis per se, and should be managed similarly to older children, if patients are stable enough to undergo proper staging and treatment. A deeper knowledge and better outcomes would come from a large, homogeneous, collection of data possibly allowing a global protocol, focusing on a comprehensive management of CHB.

**KEYWORDS**

children, hepatic tumour, liver, newborn, prenatal tumour

## 1 | INTRODUCTION

Hepatoblastoma (HB) is a tumour affecting the liver, with an incidence of 1–1.5/1,000,000 children per year.<sup>1,2</sup> Despite its rarity, knowledge on HB has greatly improved in recent years, because of the collaborative studies like the Children's Hepatic Tumours International Collaboration (CHIC) consortium and the Paediatric Hepatic International Tumour Trial (PHITT).<sup>3–6</sup> Efforts in improving data collection, sharing and pooling, as well as surgical, medical and diagnostic advances, together with the development of a systematic approach, granted significant improvements in the overall outcomes of patients with HB.<sup>2,6–10</sup> Despite this general trend, there is no current consen-

sus on the management of congenital HB (CHB).<sup>11–13</sup> There is not even a univocal definition: some authors define HB as congenital when diagnosed within 4 weeks of life, while others within the first 3 months of life. We agree that very peculiar features typically characterise those tumours detected in the first 4 weeks of life. Hence, for the aim of this review, a CHB is defined as an HB diagnosed either prenatally or postnatally within the first month of life.

Despite a steadily increasing detection rate due to the routine use of ultrasound during pregnancy, congenital tumours remain very rare, accounting for 1.5%–2% of all paediatric tumours.<sup>9</sup> Among them, hepatic lesions are even rarer, representing only 5% of all congenital tumours.<sup>9,14,15</sup> Moreover, prenatally diagnosed liver masses are usually metastases, primarily from neuroblastoma and leukaemia, while the most frequent primary lesions are haemangiomas (60%) and mesenchymal hamartomas (23%), followed by HB.<sup>12,16–19</sup>

**Abbreviations:** CHB, congenital hepatoblastoma; HB, hepatoblastoma; IQR, interquartile range.

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As compared to HB in older children, CHB has distinct features and specific issues: a different clinical presentation, a challenging management due to the toxicity of chemotherapy and the risks of liver surgery in newborns, a high risk for metastases and a generally perceived worse outcome.<sup>20,21</sup> These insights derive from the analysis of the literature, which, unfortunately, lacks high-level evidence as data are reported as small case series or case reports. No structured protocols have ever been arranged to enrol these patients in homogeneous datasets.

Aim of this study is to gather the available English literature on CHBs to better define the most common presentation and tumour characteristics, the preferred diagnostic methods and, mostly, to focus on the state-of-the-art management and to highlight new potential therapeutic options.

## 2 | MATERIALS AND METHODS

PubMed and EMBASE were searched, including studies up to November 2023 using specific keywords: hepatoblastoma, new-born, neonate, neonatal, prenatal, and congenital. Initial screening of papers involved reviewing titles and abstracts, with further evaluation of eligible studies by reading them in their entirety. Additionally, reference lists of the included articles were examined. This study encompassed cases of HB diagnosed during pregnancy or within the first month of life. Only articles published in English within peer-reviewed journals were considered for inclusion.

Data collection focused on various aspects, including prenatal findings and examinations, the presence of associated anomalies or syndromes, clinical indications, and symptoms of both the mother and foetus, prenatal treatments, the clinical condition of the newborn at birth, medical and surgical interventions, and overall outcomes. To facilitate analysis, patients were categorized into two distinct groups based on the timing of CHB diagnosis: prenatal or postnatal. The chi-square test was employed to gauge statistical significance in mortality rates, and data were presented as median and interquartile range (IQR). The results of the literature search are summarized as a narrative review.

## 3 | RESULTS

The search identified 884 studies after removal of duplicates: 50 were included after screening from title, abstract and full text. The main characteristics of the included studies are summarized in Table S1. Overall, 132 patients who received a diagnosis of CHB were identified: 39 diagnosed during pregnancy (Group A) and 93 at birth or during the first month of life (Group B).

A summary of patients' demographics, details on delivery, imaging findings, clinical presentation (both during pregnancy and at birth) and associated anomalies can be found in Table 1. For patients in Group A, median gestational age at diagnosis was 35 weeks (32–37 weeks) and median age at birth was 37 weeks (34–39 weeks). Birth weight was 3230 g (2640–3400 g). For Group B patients, median gestational age at birth was 37 weeks (36–39 weeks), birth weight was 3200 g (2646–3759 g). Median age at diagnosis was 3 days (0–19 days).

Regardless of the timing of diagnosis, symptoms in neonates were mainly abdominal (distension, hepatomegaly or abdominal mass;  $N = 22$ ), followed by respiratory distress ( $N = 15$ ) and jaundice ( $N = 5$ ). Tumour rupture was observed in five cases, all delivered vaginally: one patient died immediately after birth, one after an emergency laparotomy and three patients survived (two patients underwent emergency laparotomy and surgical resection on Day 4 and 7 of life, respectively; one underwent radiological embolization of the left hepatic artery on Day 2 of life).

In Group A, a palpable abdominal mass or hepatomegaly or abdominal distension were the most frequent clinical finding at diagnosis. Ten patients presented with two or more clinical manifestations. Postnatal management is detailed in 11 patients: six needed mechanical ventilation, two needed haemodynamic support and transfusion, one needed intensive support and two were in good conditions. In Group B, data on postnatal conditions and management were available in 24 cases. Usual presentations were a palpable abdominal mass, abdominal distension or hepatomegaly ( $N = 13$ ) associated with respiratory distress ( $N = 11$ ) or jaundice ( $N = 5$ ). Fourteen patients had a combination of symptoms. One patient had an incidental diagnosis while investigating a prenatal suspect of pulmonary sequestration.

### 3.1 | Tumour assessment

For patients in Group A, foetal magnetic resonance imaging (MRI) was conducted in seven out of 39 cases to confirm the ultrasound findings. All were diagnosed after 2011, and four out of seven in the last 5 years. None of the patients in Group B had prenatal MRI and none detected a prenatal liver mass.

At birth, presence of a liver mass was confirmed by ultrasound and further investigated with specific imaging, like TC scan and/or MRI for anatomical details and definition of the extrahepatic extension of the disease. Alpha-fetoprotein (AFP) at diagnosis was reported in 79 cases. Unfortunately, only few papers detailed the changes of AFP levels over time, despite the well-known difficulty of correctly interpreting AFP elevations in newborns, which hinders our ability to interpret these findings.

Data correlating PRE-Treatment EXTent of tumour (PRETEXT) and outcomes were available for a very small number of cases, most with a favourable outcome.<sup>21–26</sup> In the series from Dall'Igna et al.,<sup>22</sup> all patients but one ( $N = 13$ ) were standard-risk PRETEXT 3. And they were all alive at follow-up. Moreover, four patients died: one with PRETEXT IV HB, along with one patient with PRETEXT II disease and two cases with PRETEXT III HB.<sup>2,27</sup>

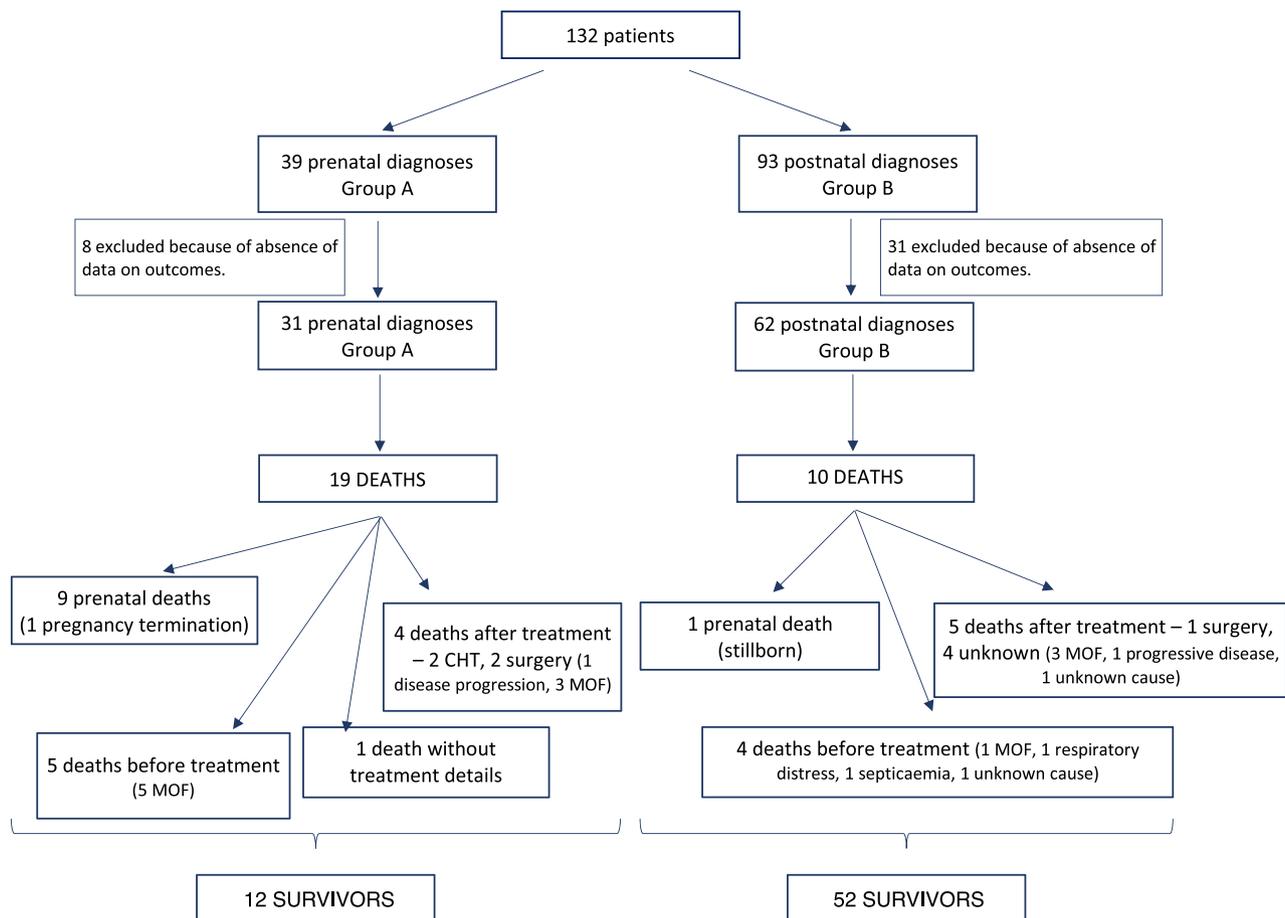
### 3.2 | Treatment

We found no reports on prenatal treatment. Overall, 91 patients received an oncological treatment (chemotherapy, surgery or both) after birth (details in Table S2). Preoperative chemotherapy was administered to 63 patients: the treatment was specified in 35 cases with 14 patients treated by SIOPEL-2 and SIOPEL-3 protocols, three

**TABLE 1** Patients' characteristics and symptoms.

	Group A	Group B
Age at diagnosis, median (IQR)	35 weeks of gestational age (32–37)	3 days of life (0–19)
Gestational age at birth, median (IQR)	37 weeks (34–39)	37 weeks (36–39)
Weight at birth, median (IQR)	3230 g (2640–3400)	3200 g (2646–3759)
Sex (n; %)		
Male	11; 8%	34; 26%
Female	11; 8%	25; 19%
Unknown	17; 13%	34; 26%
Mode of delivery (n; %)		
Vaginal delivery	11; 8%	10; 7%
C-section	11; 8%	2; 2%
Emergency/urgent C-section	4; 3%	5; 4%
Unknwon	13; 10%	76; 58%
Associated syndromes		
Yes	0; 0%	9; 7%
No	23; 17%	16; 12%
Unknown	16; 12%	68; 52%
Type	/	1 Tyrosinemia type 1 1 Trisomy 9p 1 Aicardi syndrome 6 Beckwith–Wiedemann syndrome
Presence of associated anomalies/manifestations during pregnancy (n; %)		
Maternal	6; 5%	3; 2%
Unknown	13; 10%	75; 57%
Fetal	9; 7%	12; 9%
Unknown	11; 8%	72; 55%
Symptoms	Symptoms at birth	Symptoms at diagnosis
Type	9 Abdominal mass/distension or hepatomegaly 4 Respiratory distress 2 Vomit 1 Paleness hypotonia 1 Hydropic placenta and petechiae 1 Anasarca e petechiae 1 Hypotension 1 Caput medusae	13 Abdominal mass/distension 11 Respiratory distress 5 Jaundice
Prenatal MRI		
Yes	8	
No	19	

Abbreviations: C-section, caesarean section; IQR, interquartile range; MRI, magnetic resonance imaging.



**FIGURE 1** Details of outcomes for patients with prenatal (Group A) and postnatal (Group B) congenital hepatoblastoma (CHB).

by Children's Oncology Group (COG) protocols, and the others with various combinations of drugs (carboplatin, cisplatin, doxorubicin, vincristine, 5-fluorouracil). In addition, 71 patients underwent surgery for tumour removal either after neoadjuvant treatment (44%) or followed by adjuvant treatment (14%). Surgery was the only treatment in seven patients.

### 3.3 | Outcomes

Data on outcomes are available for 118 out of 132 patients (Table S2 and Figure 1).

Regardless to the timing of diagnosis (Groups A + B), 46 patients died, with a calculated overall survival of 61% at the time of publication.

A more detailed evaluation of the causes of death showed that out of 46 deaths, 10 happened in utero. After birth, patients were split into two groups: those who died before any oncological treatment ( $N = 15$ ) and those who died after treatment (surgery and/or chemotherapy,  $N = 21$ ). Causes of death were reported in seven patients in the pre-treatment group (two respiratory distress, four multiorgan failure, one tumour haemorrhage) and six patients in the post-treatment group (two respiratory distress, one anaemia, two related to surgical complications, one multiorgan failure). Deaths in patients who did not receive

any oncological treatment mostly happened within the first 2 weeks of life (5/7).

Out of the patients for whom outcomes are available (118), 93 received an oncological treatment. In this specific group of patients, the survival rate increases up to 77% (72/93).

Among the 118 patients with available outcomes, 93 could be traced back to Group A or B. In Group A (31 patients with available data), 19 died (61%): nine in utero and 10 after birth (five before any treatment, four after oncological treatment, one without further details). In particular, in this group, 74% of deaths happened before any oncological treatment, either during pregnancy (47%) or after birth (27%). In Group B (62 patients with available data), 10 (16%) died (one stillbirth, four before any treatment and five after oncological treatment), and specifically, 50% of deaths in this groups were reported before any oncological treatment. The difference of mortality rates between the two groups appeared to be statistically significant ( $p$ -value  $< .00001$ ).

Data for long-term survivors were rarely reported: one child had hearing impairment, one developed symptoms related to Aicardi syndrome, one developed signs of schizencephaly.<sup>27–29</sup>

Follow-up was reported for 56 patients, with a median survival of 14.5 months (IQR: 11.5–48 months). Longest reported follow-up was 10 years.

## 4 | DISCUSSION

Approximately 130 congenital malignancies are diagnosed yearly in the United States, primarily through routine foetal ultrasound during pregnancy. Hepatic lesions cover about 5% of all congenital neoplasms, with CHB representing 20% of congenital hepatic lesions and 10% of all HB in children.<sup>12</sup>

Despite CHB cases dating back to the 1970s, specific management protocols have never been established due to their rarity.<sup>12,30,31</sup> Historically, a CHB diagnosis carried a poor prognosis. However, the findings from this analysis suggest that a significant portion of mortality is unrelated to the malignant nature of the tumour. Instead, various factors associated with potentially life-threatening complications of a large mass contribute to in utero and perinatal mortality, resembling other large, highly vascular, benign lesions, like haemangiomas.

A thorough examination of mortality causes among CHB-diagnosed patients aimed to pinpoint potential areas for intervention and alternative treatment strategies.

Overall, a 61% mortality rate was observed in prenatally diagnosed patients, with most deaths occurring in utero, compared to 16% in those diagnosed after birth. While this difference holds statistical significance ( $p$ -value < .00001), the limited patient sample and lack of long-term follow-up in many cases hinder drawing definitive conclusions.

Key factors influencing overall outcomes were identified: mortality linked to the 'mass effect' during both the prenatal (22%) and perinatal (32%) stages, as well as 'oncological' mortality encompassing tumour and/or treatment-related factors (46%). Analysis results suggest opportunities to enhance survival through aggressive pre- and postnatal support and tailored oncological approaches (medical, surgical or a combination thereof) for CHB patients.

Prenatal imaging plays a crucial role in assessing the impact of CHB on foetal health.<sup>32</sup> Foetal manifestations are primarily influenced by the tumour's mass effect and hyper-vascularization rather than oncological factors. Conditions like polyhydramnios, foetal hydrops, and later, respiratory distress, contribute significantly to intrauterine or postpartum mortality rates.<sup>33-36</sup> Regrettably, the high rate of in utero deaths remains unresolved, as no antenatal treatments have been successful so far. As most deaths in Group A occurred in utero related to polyhydramnios, foetal distress, foetal hydrops and placental hydrops, it is possible that patients with a prenatal diagnosis had larger tumours that on the one hand allowed their prenatal detection, but on the other hand caused foetal death through its mass effect. Therefore, efforts should be made to identify specific prenatal CHB characteristics associated with a poor prognosis and consider aggressive in utero interventions for selected cases, like in sacrococcygeal teratomas, such as embolization or laser/radiofrequency ablation.<sup>37-46</sup>

Prenatal imaging may also help early detection of complications, thereby determining optimal timing of delivery and postnatal care.<sup>13,15,47,48</sup> Unfortunately, the limitations of the data make it challenging to determine the optimal timing for birth in patients with CHB. Some authors propose early delivery due to the potential aggressive

**TABLE 2** Histology results.

Histology results	
Fetal HB	37
Mixed HB	32
Embryonal HB	11
Non-specified HB	5
Poorly differentiated HB	2
Epithelial HB	1
Well-differentiated HB	1
Macrotrabecular HB	1

Abbreviation: HB, hepatoblastoma.

intrauterine growth of CHB. However, any decision should carefully weigh the risks of prematurity, liver immaturity, and potential higher toxicity of chemotherapy and surgery in premature newborns.<sup>29,49,50</sup> Also, the type of delivery is controversial. Caesarean section might reduce the risk of tumour rupture, although evidence supporting this claim is limited.<sup>51</sup> In the present review, five patients had tumour rupture immediately after birth, all delivered vaginally. However, the small number of cases precludes drawing definitive conclusions.

In neonates with CHB, timely initiation of state-of-the-art life-support measures (mechanical ventilation, dialysis, pharmacological support, surgical approaches like abdominal silo) is essential. Although treatment may be ineffective when clinical instability stems from a long-standing, untreated prenatal condition, ongoing advancements in neonatal intensive care play a crucial role in mitigating this aspect of the mortality trend. Furthermore, emerging techniques and the adoption of non-invasive approaches offer new opportunities for stabilizing critically ill newborns. For instance, a few successful cases of endovascular treatment, such as arterial embolization for intraleisional bleeding, have been reported.<sup>24</sup> Hence, efforts should be done to maximize the patient's options to take advantage from the correct oncological treatment.

Patients who, regardless of when CHB was diagnosed, could receive oncological treatment ( $n = 91$ ) reflect the 'oncological' aspect of CHB, influenced by both tumour and patient-related factors. One noteworthy factor in these patients is the relatively high rate of non-pulmonary metastases in CHB, related to the persistence of a foetal circulation, which appears to have a negative impact on prognosis.<sup>2,13,33-35,52</sup> Additionally, a distinctive feature is the slight prevalence of a pure foetal histology, which unfortunately does not seem to correlate with a better prognosis (Table 2).<sup>20,33</sup> These inherent aspects of CHB can affect overall outcomes, including the potential for increased toxicity associated with oncological drugs in neonates. Customizing treatment is essential as conventional regimens may lead to over-treatment and increased toxicity in newborns.<sup>26,53</sup> A study conducted by the SIOPEL group suggests that newborns can tolerate chemotherapy well without significant acute toxicity.<sup>22</sup> Similar conclusions are drawn by Trobaugh-Lotrario et al.<sup>2</sup> Preoperative chemotherapy has a central role in the treatment of HB: in our review, most patients received neoadjuvant chemotherapy (63/91). Interestingly, seven patients were

treated by surgery only: in three cases, the indication was related to a life-threatening intra-abdominal compression, while in four cases reasons for upfront surgery were not detailed. Among these patients, outcomes are available for six with a 50% rate of survival. Overall, four patients who underwent upfront surgery received adjuvant chemotherapy with a 100% survival rate.

Surgery remains a cornerstone in the treatment for HB, with 71% of treated patients undergoing surgical procedures aiming to achieve complete resection through partial hepatectomy or total hepatectomy, followed by liver transplantation (LT). However, the role, timing and indication of surgery for CHB are not standardized. Older studies often use surgery as a life-saving intervention for complications such as bleeding and rupture, or silo implantation to address hepatomegaly and/or respiratory distress, while more recent series tend to integrate surgery into a comprehensive approach.<sup>22,54–62</sup> However, in neonates, liver surgery presents significant challenges, both from an anaesthesiologic and technical perspective. Presently, liver resections and even LT are reported as highly specialized and infrequent procedures within the first days of life.<sup>63</sup> From a technical point of view, major surgical challenges stem from the fragility and immaturity of the liver parenchyma, posing a considerable risk of bleeding and, in the case of large lesions, potential failure of the remaining liver. In such cases, LT may be considered despite a high rate of complications and mortality in neonates, exacerbated by the challenge of finding suitable donor.<sup>54,56,58,59,64–66</sup> Reports on alternative techniques are emerging. For instance, Hong et al.<sup>67</sup> reported a successful experience in a 54-day-old infant who underwent a modified associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure.

Despite the common assumption that survival rates for newborns with CHB are quite grim,<sup>34</sup> our observations reveal an overall survival rate of 61%, which rises to 77% for children who overcome the complications associated with the 'mass effect' and receive specialized HB treatment. It is increasingly clear that for those neonates stable enough to undergo a state-of-the-art oncological approach, outcomes are more favourable than previously described.<sup>68</sup> For CHB, the SIOPEL group reported no fatalities, and in Trobaugh-Lotrario et al.'s cohort, the overall 3-year survival rate stands at 86%.<sup>2,22</sup> The current, improved survival of these patients can be attributed to a multidisciplinary support in pursuit of optimizing the different (surgical, oncological, neonatal) therapies.

Limitations of this study include the small patient cohort and reliance on data primarily from case reports, case series and retrospective reviews spanning an extensive timeframe. This makes the data scattered and heterogeneous.

## 5 | CONCLUSIONS

Data on CHB are scant and heterogeneous. This strongly suggests the need for a well-designed, possibly multi-institutional, collection of data. A deeper understanding and potentially enhanced outcomes can be expected from large, homogeneous datasets and the establishment of globally shared treatment protocols.

Despite these limitations, once born, patients with CHB do not appear to have a more unfavourable oncological prognosis when compared to those with HB diagnosed beyond the neonatal period. Consequently, CHB should be approached with a management strategy akin to that applied to older patients, provided the patients exhibit sufficient stability to undergo thorough staging and treatment.

The management and treatment of CHB could greatly benefit from the development of a specific and comprehensive strategy. Patients with prenatally detected CHB should be referred to specialized centres to allow early identification of complications and potentially innovative in utero approaches. Postnatal team should be ready for aggressive measures aimed to stabilize patients, thereby granting them the opportunity to receive appropriate oncological treatments.

CHB presents a substantial challenge for neonatologists, oncologists and surgeons. However, the findings from this literature review underscore that a prompt diagnosis and a personalized combination therapy approach can lead to improved outcomes.

## CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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