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ORIGINAL ARTICLE – COLORECTAL CANCER

Colonoscopy-Assisted Laparoscopic Wedge Resection for the Treatment of Suspected T1 Colon Cancer

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ABSTRACT

Background. Local en bloc resection of pT1 colon cancer has been gaining acceptance during the last few years. In the absence of histological risk factors, the risk of lymph-node metastases (LNM) is negligible and does not outweigh the morbidity and mortality of an oncologic resection. Colonoscopy-assisted laparoscopic wedge resection (CAL-WR) has proved to be an effective and safe technique for removing complex benign polyps. The role of CAL-WR for the primary resection of suspected T1 colon cancer has to be established.

Methods. This retrospective study aimed to determine the radicality and safety of CAL-WR as a local en bloc resection technique for a suspected T1 colon cancer. Therefore, the study identified patients in whom high-grade dysplasia or a T1 colon carcinoma was suspected based on histology and/or macroscopic assessment, requiring an en bloc resection.

Results. The study analyzed 57 patients who underwent CAL-WR for a suspected macroscopic polyp or polyps with biopsy-proven high-grade dysplasia or T1 colon carcinoma. For 27 of these 57 patients, a pT1 colon carcinoma was diagnosed at pathologic examination after CAL-WR. Histological risk factors for LNM were present in three cases, and 70% showed deep submucosal invasion (Sm2/Sm3). For patients with pT1 colon carcinoma, an overall R0-resection rate of 88.9% was achieved. A minor complication was noted in one patient (1.8%).

Conclusions. The CAL-WR procedure is an effective and safe technique for suspected high-grade dysplasia or T1-colon carcinoma. It may fill the gap for tumors that are macroscopic suspected for deep submucosal invasion, providing more patients an organ-preserving treatment option.

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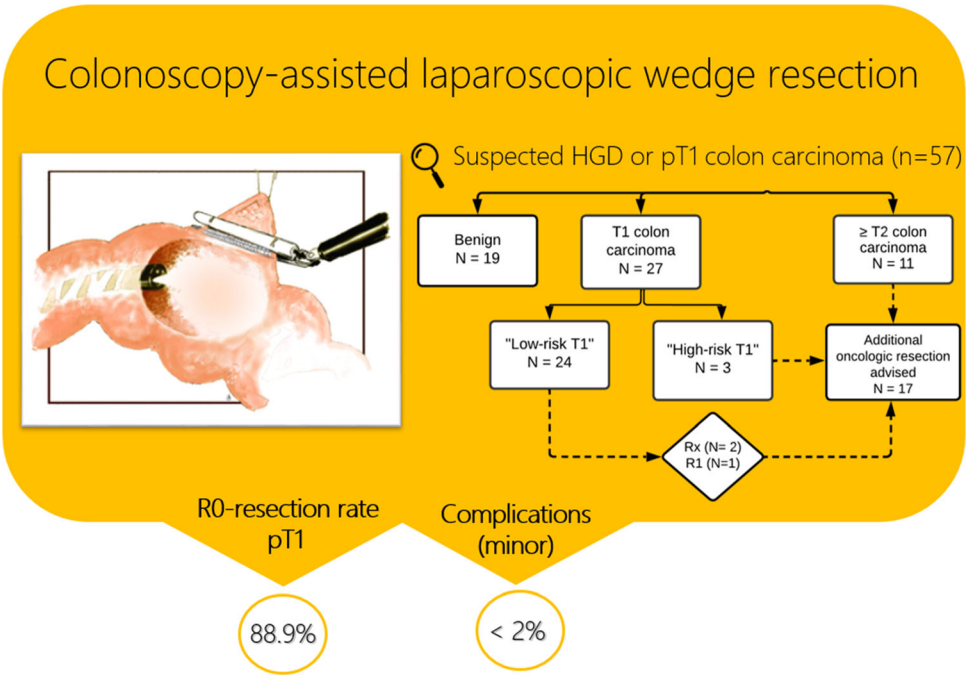


Patients with T1 colorectal cancer (CRC) lacking any histological risk factor for lymph-node metastases (LNM) (i.e., carcinomas with absence of [lympho-] vascular invasion [LVI], deep submucosal invasion [>1000 μm], poor [high-grade] tumor differentiation, or high-grade tumor budding) are considered as low-risk tumors.[1–6] Patients without these high-risk features might not benefit from major oncologic surgery because the risk of lymph node metastasis in this group is only 1%,[7–9] which does not outweigh the significant morbidity (24%) and mortality (2%) of an oncologic resection.[10]

In contrast to the previous insights, deep submucosal invasion (DSI) is not an independent risk factor for LNM in the absence of the other high-risk features.[11] The presence of DSI is associated with only a 2.6% risk of LNM.[11] Therefore, patients without LVI, Bd2-3 tumor budding, or G3 differentiation are currently suitable for a local resection regardless of the depth of invasion.

Deep invasive T1 CRCs need to be removed with full-thickness resection techniques as submucosal-based dissection techniques (endoscopic mucosal resection [EMR] or endoscopic submucosal dissection [ESD]) are known to obtain an inappropriate R0 resection rate.[12]

Currently, the only option for endoscopic local en bloc resection of deep invasive lesions in the colon is an endoscopic full-thickness resection (eFTR). The eFTR procedure offers the opportunity to perform a transmural resection with an R0 resection rate varying between 61 and 90%.[13–15] However, the size of a lesion suitable for eFTR is limited to 15 mm.[13,15]

Expert endoscopists are able to differentiate deep invasive T1 CRCs from non-invasive or superficially invasive T1 CRCs with high performance scores.[16] However, the problem remains that in case of suspected deep invasive lesions larger than 15 mm in the colon, no local endoscopic resection technique is currently available.

In recent years, several combined endoscopic laparoscopic surgical (CELS) approaches have been gaining acceptance for the removal of endoscopic irresectable benign lesions.[17] Previous studies have shown high R0-resection rates varying from 88 to 100%, short hospital stays, and low morbidity.[18–20]

Colonoscopy-assisted laparoscopic wedge resection (CAL-WR) is an effective and safe technique as an alternative to a segmental colon resection for complex benign polyps.[18] This study evaluated whether CAL-WR is an appropriate local en bloc technique as primary treatment for T1 colon cancer in terms of radicality and safety.

MATERIALS AND METHODS

This retrospective cohort study was performed in Isala, Zwolle, The Netherlands. All patients treated with CAL-WR between March 2015 and April 2022 were identified. The study enrolled all the patients who underwent CAL-WR because of a colonic lesion that was macroscopic and/or histologically suspected for high-grade dysplasia (HGD) or T1 carcinoma requiring en bloc resection. Patients who underwent an endoscopic resection (or an attempt) before CAL-WR, were excluded. The

primary outcomes of this study were the radical resection rate (R0) and the safety of CAL-WR in terms of the 30-day morbidity rate.

CAL-WR

As a minimally invasive technique, CAL-WR is a procedure for resecting lesions locally without making an anastomosis by using a linear stapler. This technique has been described in detail by Leicher et al.[19]

Before the procedure, all the patients underwent a split-dose bowel preparation. At first, the surgeon starts with a diagnostic laparoscopy to identify the marking spot of the colon and mobilize the affected part of the colon. If space is sufficient for placement of the stapler, the procedure is continued by the gastroenterologist with a colonoscopy to identify the tumor intraluminally. Under intraluminal endoscopic view, a suture is placed by the surgeon close to the tumor. After traction is applied to the suture, the stapler is placed. While the gastroenterologist checks the patency of the lumen endoscopically, the surgeon staples off the tumor.

Definitions and Data Analysis

Patient characteristics such as gender, age, and comorbities were collected from the electronic hospital records. Tumor characteristics were extracted from the original diagnostic colonoscopy report. Macroscopic signs of malignancy were assessed using the internationally applied scoring systems including Paris classification, Hiroshima classification, NBI International Colorectal Endoscopic (NICE) classification, and morphology (e.g., Paris 2c/3, Hiroshima C, depression/excavation, spontaneous bleeding, poor lifting).

The patients were classified as having suspected T1 if either macroscopic signs of malignancy were observed during colonoscopy or the preoperative biopsy had already confirmed the diagnosis of adenocarcinoma, indicated a suspicion of carcinoma, or showed at least HGD.

All the patients were discussed at our "complex polyp" team meeting before referral for surgery. The definite tumor location and size were determined based on the macroscopic pathology report. The right colon was defined as the cecum, ascending colon and hepatic flexure. The left colon was defined as the splenic flexure and descending colon. The operation time was calculated from the original operative report.

Postoperative complications were assessed and noted according to the Clavien-Dindo classification (grades 1–5).[21] Minor morbidity was defined as Clavien-Dindo grade 1 or 2 and major morbidity as Clavien-Dindo grade 3 or higher.

All the patients also were discussed in the colorectal multidisciplinary team meeting. Completion surgery was advised in case of high-risk pT1 colon cancer, irradical low-risk pT1 colon cancer, or ≥pT2 colon carcinomas. Incomplete resection was defined as a resection margin smaller than 0.1 mm (R1)[22] and/or when radicality could not be determined.

Subgroup Analysis of pT1 Colon Cancer Patients

Cases were categorized as high-risk T1 if either one or more of the following independent histological risk features for LNM were present: (lympho-) vascular invasion, poor (high-grade) differentiation, or high-grade tumor budding. In the absence of all these risk features, cases were defined as low-risk T1.

Data Analysis and Statistic

Data on demographic and baseline characteristics for continuous variables were summarized as mean ± standard deviation or as median and range. For discrete variables, data were summarized as proportions and percentages. The radical resection rate was described as the proportion of R0 resections in percentages. Postoperative morbidity also was summarized as percentages. Data analysis was performed using the Statistical Program for the Social Sciences (SPSS) version 26.0 (SPSS, Chicago, IL, USA).

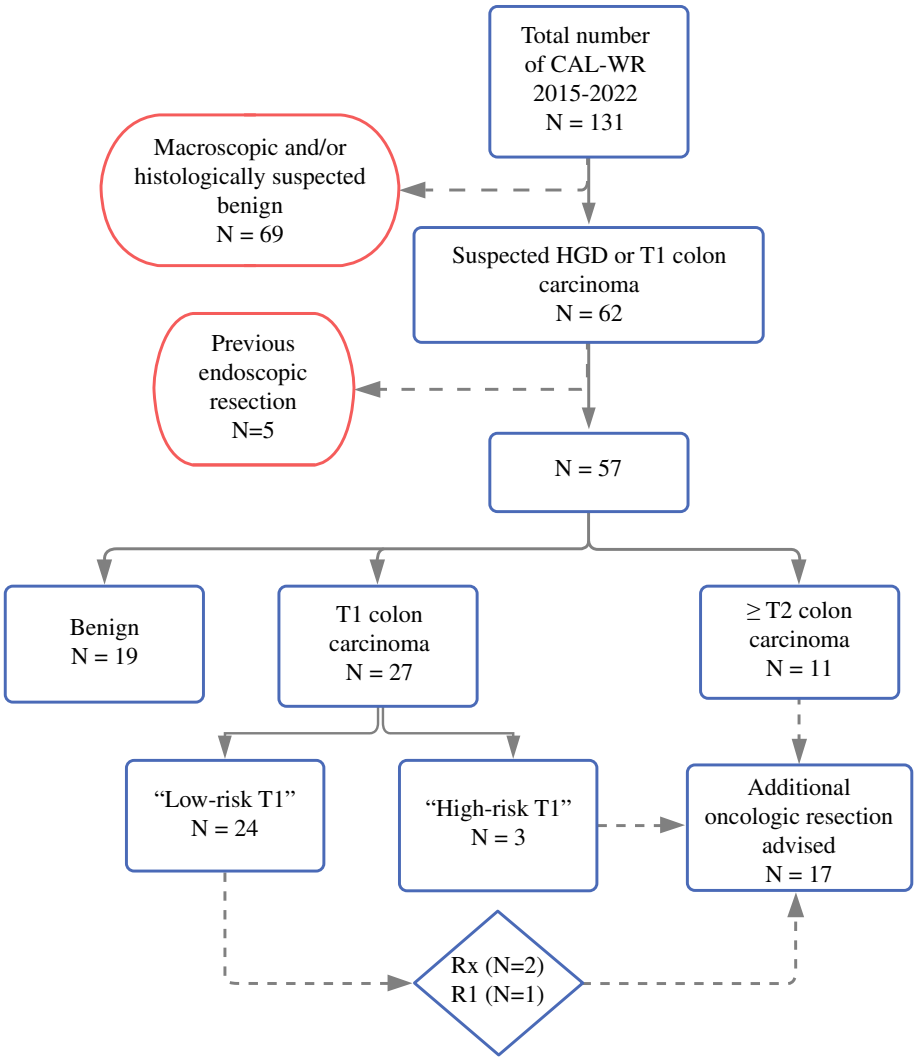
RESULTS

Patients

Of the 131 patients who underwent CAL-WR, 62 were initially suspected for HGD or a pT1 colon carcinoma requiring en bloc resection to allow precise pathologic assessment. Five of these patients had undergone an endoscopic resection (attempt) before CAL-WR and were therefore excluded (Fig. 1). The characteristics of the remaining 57 patients are presented in Table 1.

Histologic Outcome

In this study, 57 patients underwent CAL-WR as a primary resection for suspected HGD or T1 colon carcinoma. Postoperative pathology showed adenomas in 19 patients (33.3%), pT1 in 27 patients (47.4%), pT2 in 8 patients (14%), and pT3 in 3 patients (5.3%) (Table 1). Of the 27 patients with a diagnosis of pT1 colon carcinoma, 3 (11.1%) were defined as high risk pT1 based on the presence of high-grade tumor budding (Bd2-Bd3) or (lympho-) vascular invasion. One of the three patients had both



HGD—high grade dysplasia, Rx—margins unassessable, R1—microscopic incomplete resection

FIGURE 1 Flowchart summarizing the identification of eligible patients and patient inclusion with subsequent an overview of the postoperative outcomes

features (Table 2). The majority of all T1 carcinomas (74%) were deep submucosal invasive tumors (Sm2 or Sm3).

R0 Resection

An overall R0-resection rate of 86% was achieved (Table 3). The R0 resection rate of CAL-WR for benign adenomas was 94.7%. The R0 resection rates were significantly compromised in case of T2 or T3 colon carcinoma. For pT1 colon carcinomas, an R0 resection rate of 88.9% was achieved. Of the 25 cases without histologic risk features for lymph node metastases (i.e., low-risk pT1), 3 (11.1%) were defined as an incomplete resection because the resection margin was not free (1 patient) or not assessable due to manipulation of the staple line (2 patients) (Table 2).

Safety of CAL-WR

The median operation time for CAL-WR was 51 min (range, 20–98 min) (Table 3). The median hospital stay after CAL-WR was 1 day, with a maximum of 3 days. In fact, more than 70% of the patients could be discharged from the hospital on the same day as the procedure or the day after. Complications were noted in one patient (1.8%), which was minor according to the Clavien-Dindo classification (postoperative urinary retention). No re-interventions were performed.

TABLE 1 Baseline patient characteristics of all patients in which CAL-WR was performed because of suspected high-grade dysplasia or T1 colon carcinoma

	Cohort (n = 57) n (%)
Patient characteristics	
Mean age (years)	69.5 ± 7.0
Male gender	35 (61.4)
BMI (kg/m^2)	28.5 ± 5.4
ASA	
1	5 (8.8)
2	41 (71.9)
3	11 (19.3)
4	–
Comorbidity	
Hypertension	21 (36.8)
Cardiovascular comorbidity	22 (38.6)
Lung comorbidity	7 (12.3)
Renal comorbidity	4 (7.0)
Indication for CAL-WR	
Macroscopic malignant features	27 (47.4)
Preoperative pathology showing HGD or adenocarcinoma (macroscopic not suspected)	2 (3.5)
Macroscopic malignant features and corresponding pathology (HGD or ''suspicious for carcinoma'' or adenocarcinoma)	28 (49.1)
Tumor characteristics	
Primary tumor location	
Right colon	28 (49.1)
Transverse colon	12 (21.1)
Left colon	6 (10.5)
Sigmoid	11 (19.3)
Median tumor size: mm (range)	20 (6–40)
Postoperative pathology	
Benign	19 (33.3)
Tubular adenoma low-grade dysplasia	7 (36.8)
Tubulovillous adenoma low-grade dysplasia	2 (10.5)
Tubular adenoma high-grade dysplasia	7 (36.8)
Tubulovillous adenoma high-grade dysplasia	3 (15.8)
Malignant	38 (65.5)
pT1NxMx	27 (71.1)
pT2NxMx	8 (21.0)
pT3NxMx	3 (7.9)

BMI, body mass index; ASA, American society of Anesthesiologists; CAL-WR, colonoscopy-assisted laparoscopic wedge resection; HGD, high-grade dysplasia

Corresponding pathology: preoperative pathology showed high-grade dysplasia or adenocarcinoma

TABLE 2 Postoperative descriptive of all patients with pT1 colonic cancer

	Cohort (n = 27) n (%)
High-risk histologic features	
Yes	3 (11.1)
No	24 (88.9)
Tumor characteristics	
Poor (high-grade) differentiation (G3)	–
High-grade tumor budding (Bd2-Bd3)	2 (7.4)
(Lympho-)vascular invasion	2 (7.4)
Depth of submucosal invasion	
Sm1	8 (29.6)
Sm 2	7 (25.9)
Sm3	12 (44.4)
Resection status	
R0	24 (88.9)
R1	1 (3.7)
Rx	2 (7.4)
Additional oncologic resection advised	5 (18.5)
Additional oncologic resection performed	2 (7.4)
Type of additional oncologic resection	
Right hemicolectomy	2 (7.4)

R0, resection margin >1 mm; R1, microscopic incomplete resection; Rx, margins unassessable

TABLE 3 Overall procedure related characteristics and R0-resection rates

	Cohort (n = 57) n (%)
Median operation time: min (range)	51 (20–98)
Median hospital stay: days (range)	1 (0–3)
Postoperative complications	
Clavien-Dindo Classification	
1–2	1 (1.8)
≥3	–
R0- resection rate	49 (86.0)
Benign	18 (94.7)
Malign	
pT1NxMx	24 (88.9)
pT2NxMx	5 (62.5)
pT3NxMx	2 (66.7)

Values in parentheses are percentages

Completion Surgery

All the patients with ≥T2 CRC (n = 11), high-risk T1 CRC (n = 3), or low-risk T1 CRC with incomplete resection (n = 3) were advised to receive a completion oncologic resection with lymph-node dissection according to current national guidelines (Fig. 1). Overall, 17 (29.3%) of the 57 patients were advised to receive additional surgery, and 11 of the patients eventually underwent completion surgery. The remaining six patients were chosen for close surveillance after a shared decision, primarily because these patients experienced severe comorbidity.

Postoperative complications of the additional oncologic resections were reported for 3 (27.2%) of the 11 patients. Two of the three patients had minor complications, and the remaining patient had a major complication involving percutaneous abscess drainage.

Additional oncologic resections were not complicated due to the initially performed CAL-WRs. Lymph-node metastasis was found in the resection specimen of one patient with a pT2 colon carcinoma, whose pathologic examination showed high-grade tumor budding as well as lymph and vascular invasion.

Follow-up Endoscopy

Follow-up data were available for 17 (70.8%) of the 27 patients with pT1 CRC. For these patients, the median interval between CAL-WR and follow-up colonoscopy was 7 months (range, 2–16 months). No recurrences were detected during the follow-up colonoscopy. Furthermore, none of the patients experienced a symptomatic stenosis of the colon, and no significant luminal narrowing was observed during the follow-up colonoscopy.

DISCUSSION

This retrospective observational study showed that CAL-WR is an effective and safe local resection technique as primary treatment for suspected (deep invasive) pT1 colon cancer. The achieved R0 resection rate was 88.9%, with an overall (minor) complication rate of 1.8%.

We believe that CAL-WR is a valuable technique besides eFTR for the local treatment of deep invasive early colon cancer and has the potential to fill the gap between endoscopic therapeutic options and major surgery. For deep invasive lesions with a maximum size smaller than 15 mm, eFTR is an effective removal technique with a R0 resection rate of 90%.[15] However, in case of larger lesions, its radicality is significantly compromised, to 71.4% for lesions of 16–20 mm and to 11.1% for those larger than 20 mm.[15]

The CAL-WR procedure is the first full-thickness resection technique currently available to remove deep submucosal invasive lesions larger than 15 mm, showing high R0 resection rates. Moreover, it is a simple and fast technique for any surgeon with colorectal laparoscopic experience.

As demonstrated in this study, CAL-WR is a safe technique. The current results are in line with previous reports.[18,23] Compared with CAL-WR, complications are more frequent with eFTR (9.3%), 2.7% of which are serious adverse events such as a perforation.[13] In ESD, procedure-related perforations are also more frequently seen, with rates varying from 4.8% in Asia to as high as 8.2% in Europe.[24]

The choice of the most favorable local resection for suspected T1 colon cancer should be based on the location and size of the lesion, the macroscopic estimated depth of the invasion, and local expertise. Because deep submucosal invasion is no longer a strict indication for primary oncologic surgery, local resection with curative intent also is justified if there is a suspicion of deep invasion. The CAL-WR procedure is suited for suspicious colonic lesions with involvement of a luminal circumference smaller than 50%[18] and applicable for both superficial and deep invasive large colon carcinomas. In case of macroscopic superficial neoplastic lesions, an ESD also could be considered depending on the local expertise with ESDs of the colon. However, in case of deep invasive lesions, ESD should be avoided because its R0 resection rate is significantly reduced to 64.7%.[12,24]

The CAL-WR procedure could be an alternative to an oncologic resection for patients not eligible for eFTR due to the size of the tumor. By identifying histological risk features for LNM based on the local resection specimen, more patients will have the option to receive well-considered advice about completion surgery and its benefits compared with its risks.

Previous studies have shown that secondary surgery after initial local resection (or an attempt) is safe and has no negative effects on the development of LNM or the cancer recurrence rate.[24–29] Furthermore, secondary oncologic surgery has never been described as more complicated after the initial CAL-WR. This corresponds with our own experiences. These findings support the objective to treat suspected T1 colon carcinomas through a local resection (i.e., CAL-WR) as the first step to prevent unnecessary surgery for low-risk T1 CRC. However, this has to be proved in a multicenter prospective trial.

Unfortunately, discrimination between deep invasive T1 CRCs and T2 CRCs on macroscopic assessment can be challenging.[30] This also was reflected in our study as 11 patients with more advanced CRC (≥pT2) were treated by CAL-WR. Besides the irradical and high-risk T1 colon

carcinomas, this group of patients also was advised to receive an additional oncologic resection. In this analysis, CAL-WR was considered curative in 40 (70.2%) of 57 cases.

Depending on the degree of completion surgery, CAL-WR has the potential to lower hospital costs significantly. Almost half of the patients in our study were discharged the same day as the procedure, indicating that patients recover soon, with the potential to perform CAL-WR as outpatient treatment. Jayaram et al.[34] calculated the total costs of combined endo-laparoscopic surgery to be approximately €5213. Despite enhanced recovery after surgery (ERAS) programs, the median length of stay for an oncologic resection is 4 to 6 days,[31,32] and costs vary from €10.474 to €20.865.[33]

Jayaram et al.[34] directly compared the cost of CELS with that of traditional laparoscopic colectomy for benign colon polyps and found a cost saving of €6705 per patient.[34] Only a large prospective trial could provide actual insight into the overall cost-effectiveness of our approach, accounting for the number of patients that should undergo an oncologic resection afterward.

This study was limited by its small sample size and retrospective single-center design. The technical success rate and the number of cases in which the surgeon intended to perform a CAL-WR but converted to an oncologic resection was not addressed. Furthermore, accurate short- and long-term oncologic follow-up evaluation was lacking. Additionally, many patients in our study population underwent CAL-WR for a suspected polyp. This resulted in a relatively high proportion of benign pathology and a relatively low number of more advanced colon carcinomas (≥T2). A prospective multicenter trial focusing on the efficacy of CAL-WR as first-line local treatment for deep invasive T1 colon carcinomas has currently started in our country and should provide more insight into its efficacy and long-term oncologic outcomes.

CONCLUSION

CAL-WR is an effective and safe local resection technique with a high R0 resection rate for pT1 colon carcinoma. Implementation of CAL-WR as upfront local therapy for suspected (deep invasive) T1 colon carcinoma has the potential to reduce unnecessary oncologic surgery for patients with low-risk pT1. Before CAL-WR can be embedded as standard local therapy in international guidelines, larger prospective studies with appropriate oncologic follow-up evaluation are warranted.

DISCLOSURE There are no conflicts of interest.

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