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REVIEW ARTICLE

Open and minimally invasive pancreatic neoplasms enucleation: a systematic review

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Abstract

Background Pancreatic enucleation (pEN) as parenchyma-sparing procedure for small pancreatic neoplasms is quickly becoming the most common surgical option in such setting. Nowadays, pEN is frequently carried out through a minimally invasive approach either laparoscopic or robotic. Its impact on overall perioperative complications and pancreatic fistula (POPF) is still under evaluation. The scope of our systematic review is to assess pEN's perioperative outcomes and to evaluate the effect of the minimally invasive techniques over POPF and other surgical complications.

Methods We performed a systematic literature search (time-frame January 1999–September 2018), considering exclusively those studies which included at least 5 cases of either open or minimally invasive pEN. Data regarding postoperative outcome and POPF were extracted and analyzed. We defined postoperative morbidities by the Clavien–Dindo classification while POPF according to the International Study Group of Pancreatic Fistula (ISGPF) definition.

Results Sixty-three studies met the criteria selected, accounting for a study population of 2485 patients. 27.7% had a minimally invasive pEN. The overall postoperative morbidity rate was 46.1% with 11.9% rated as severe (Clavien–Dindo ≥ 3). Mortality rate was 0.69%. The minimally invasive approach to pEN led to a statistically significant reduction of both the overall POPF rate (28.7% vs. 45.9%, $p < 0.001$), and clinically significant B-C POPF ($p < 0.027$). The postoperative overall morbidity rate was clearly in favor of the minimally invasive approach (27.6% vs. 55.2%, $p < 0.001$).

Conclusions Our review confirms that pEN is a safe and feasible technique for the treatment of small benign or low-grade pancreatic neoplasms and it can be implemented with an acceptable morbidity rate along with low mortality. The minimally invasive approach is gaining widespread acceptance due to its supposed non-inferiority compared with the traditional open approach. In our review, it showed to be even better in terms of POPF incidence rate and short-term postoperative outcome. Still, such data need to be corroborated by randomized clinical trials.

Keywords Pancreatic enucleation · Pancreatic fistula · Pancreatic neoplasms · Laparoscopic pancreatic surgery · Minimally invasive pancreatic surgery

Pancreatic enucleation (pEN) is rapidly becoming the preferred surgical option for a wide spectrum of small pancreatic neoplasms, such as pancreatic neuroendocrine tumors (pNETs), serous (SCN) and mucinous cystadenomas (MCN), solid pseudo-papillary neoplasms (SPN), and branch-duct intraductal papillary mucinous neoplasms (BD-IPMN) [1–9].

Standard pancreatic resections (SPR), although advisable for oncological reasons, may lead to an undesirable loss of healthy and functional parenchyma, increasing the risk of both exocrine and endocrine pancreatic failure [6, 10]. Such sequelae are particularly unwished in case of benign or pre-malignant pancreatic lesions, which are generally associated with favorable long-term outcomes. Besides, while POPF incidence rate and other complications related to SPR have been extensively analyzed, their true risk after pEN is yet to be defined with few experiences reporting even an higher morbidity rate comparing to SPR [11–14]. Again, pEN, like other pancreatic procedures, is increasingly performed

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laparoscopically and/or robotically in the effort to achieve pain control, reduce blood loss, and hasten patient recovery. So far, the impact of a minimally invasive approach on postoperative morbidities is still under evaluation.

The aim of this review was to assess pEN postoperative outcome and to appraise the role of minimally invasive surgery on POPF and pancreatic resection-related complications.

Materials and methods

Literature search strategy

A systematic literature search (Medline/PubMed and Cochrane Library between January 1991 and September 2018) was carried out looking for the key words ''pancreatic enucleation'' or ''parenchymal-sparing pancreatic surgery'' in combination with ''diagnosis,'' and ''surgical treatment.''

The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

The reference list of retrieved relevant articles was also cross-screened for additional studies. We considered papers in which open or minimally invasive pancreatic enucleation, diagnosis, postoperative complications, and outcome data were presented. Only studies including at least 5 cases were eligible for analysis. Articles published in languages other than English (except a spanish paper which included data from a national registry) and/or providing insufficient data were excluded from the review. Furthermore, to prevent reviewing repetitive cases, ''review articles'' or ''double publications'' were cross-checked and omitted. Finally, the reference list of these reviewed articles was also cross-checked to find other valuable articles.

Study selection and data extraction

Two of the authors (LL and EC) evaluated all titles identified as relevant articles, and data extraction from each study was carried out independently according to the inclusion criteria concerning type of neoplasm, surgical techniques, and early surgery-related postoperative complications. A total of 63 studies including 2485 patients were selected for the review. Data extraction on tumor size and location, both overall and severe perioperative morbidities, reoperation, in-hospital mortality, recurrence, readmission, and surgical technique were listed separately from each report by the authors. Early postoperative severe morbidities were defined by the Clavien–Dindo classification. In each publication, POPF incidence rate was reported, even if there was some discrepancy in definition, not being consistently classified according to the ISGPF. Most reports included data on readmission, but discharge-to-readmission time interval has been rarely specified.

Cystic neoplasms were compared with pNETs by selecting articles with an adequate number of cases qualitatively suitable for analysis. To verify the advantages of a minimally invasive approach for pEN, we evaluated papers where a specific surgical approach (open vs. minimally invasive either laparoscopic or robotic-assisted) was clearly specified, and correlated data were available.

Statistical analysis

All the analyses were performed using IBM-SPSS Statistic Version 22 and Microsoft Excel as statistical software. For continuous variables, the mean, median, and minimum and maximum range were reported. We reported qualitative data, namely, categorical variables, in frequency table and express as absolute, relative, and percentage frequencies. Categorical variables were compared using the Chi-squared test and the Fisher's exact test. A p value < 0.05 was considered statistically significant.

Institutional review board approval (IRB) was not required, research being limited to the analysis of data.

Results

A total of 63 studies met the criteria selected (January 1999 and September 2018). They all consisted in retrospective and uncontrolled reports. The PRISMA flow chart of literature studies for the purpose of the systematic review is illustrated in Fig. 1. A total of 2485 patients were included.

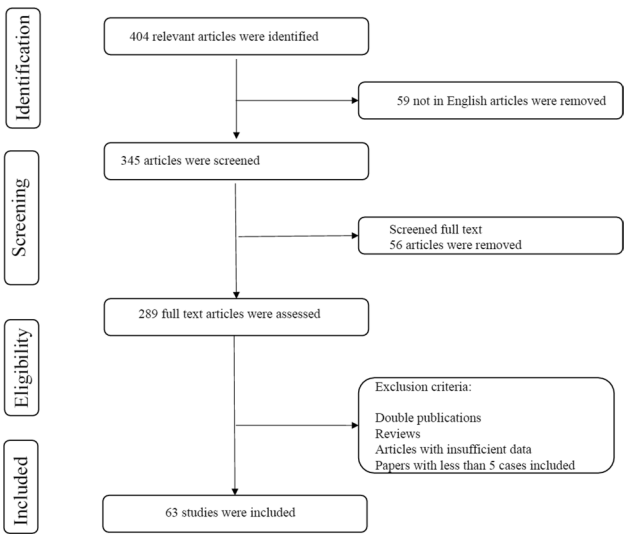

Fig. 1 PRISMA diagram illustrating the selection process

Details and early postoperative outcomes are given in Table 1.

pEN was performed predominantly for pNETs (66.4%). In 25 cases, multiple enucleations were performed. Mean size of the tumor was 21.7 mm (range 11–50 mm).

In 219 (8.8%) cases, the surgical approach (open/MI) was not specified. Of the remaining 2266 patients, 27.4% had a minimally invasive procedure. Neoplasms were located in the pancreatic head and neck (56.4%) and in the body and tail (43.2%).

The overall rate of postoperative morbidity was 46.1%, severe complications accounted for 12.1% of total morbidities (Clavien–Dindo ≥ 3).

According to ISGPF classification, POPF incidence rate after pEN was 38.9%. The rate of clinically significant POPF (B-C) was 21.5%. Besides, reintervention rate and in-hospital mortality were, respectively, 4.3% and 0.7%.

Table 2 describes the postoperative outcomes of the minimally invasive approach *vs* open in the population in which data were available in the original articles for comparison (343pts vs. 655pts). Overall postoperative morbidity rate was clearly in favor of the minimally invasive approach (27.6% vs. 55.2%, $p < 0.001$), as well as the overall POPF incidence rate (28.5% vs. 45.9%, $p < 0.001$) and the B-C POPF rate ($p < 0.027$).

Under the same principle in Table 3, we reported a comparison between pNETs and cystic tumors enucleation (571pts vs. 130pts). The overall complication rate was clearly in favor of pNETs ($p < 0.014$), whereas no impact on Clavien–Dindo ≥ 3 morbidities was registered ($p < 0.365$). Besides, B-C POPF incidence rate did not differ between pNETs and cystic tumors (19.2% vs. 16.9%, $p < 0.277$), while reintervention rate showed to be higher in the cystic tumors cohort (3.6% vs. 8.4%, $p < 0.009$).

The mean recurrence rate after pEN for any kind of tumor pathology (data reported only in 1223 patients) was 2.2% (27pts), with a follow-up ranging from 1 to 5 years.

Table 1 Included patients with details and outcomes

No. of studies	63
No. of patients	2485
Mean tumor size	21.7 mm (11–50 mm)
Pathology	Cystic 631/2399 (26.3%) pNET 1595/2399 (66.4%) Other 181/2399 (7.5%)
Location	Right pancreas (head/neck) 1204/2134 (56.4%) Left pancreas (body/tail) 924/2134 (43.2%)
Minimally invasive surgery	621/2266 (27.4%)
Morbidity	Total 1064/2308 (46.1%) Severe 243/2004 (12.1%)
Reintervention	88/2016 (4.3%)
Mortality	17/2456 (0.7%)
Readmission	68/1009 (6.7%)
Recurrence	27/1223 (2.2%)
POPF	Total 903/2318 (38.9%) Type A 431/2230 (19.3%) Type B + C 489/2275 (21.5%)

Discussion

Nowadays, a wide spectrum of pancreatic lesions are treated with parenchyma-sparing techniques. The main benefit of such approach is to spare as much pancreatic parenchyma as possible in the effort to achieve a substantial risk reduction of both exocrine and endocrine postoperative failure, especially in the long term.

In the setting of small pancreatic lesions, pEN is a reasonable option to preserve healthy pancreatic parenchyma.

Selection criteria for pEN include a size of the lesion ≤ 40 mm, a distance from the main pancreatic duct (MPD) of at least 2–3 mm, and no evidence of malignancy [50].

We deem intraoperative ultrasound (IOUS) mandatory to assess if a safe distance between the tumor and the MPD is preserved, otherwise pEN might be contraindicated. Still, IOUS was not consistently utilized in the analyzed case series.

The impact of such limited pancreatic resections on perioperative complications is still unclear, being apparently higher comparing to SPR, according to previous reports [11, 14].

Therefore, available data on pEN perioperative outcomes, in this minimally invasive era, should be pooled together and analyzed to provide evidence.

According to our review, pEN was performed in the vast majority of cases (66.4%) for pNETs, making such tumors probably the best indication for this approach, providing strict tumor selection criteria are respected.

Also a significant rate of cystic neoplasms (26.3%) was treated by pEN, usually by open surgery and mainly in high-volume pancreatic centers.

Sure enough, pEN in cystic tumors, mostly MCN and BD-IPMN, does require an extremely accurate dissection along with intraoperative sampling for frozen-section to rule out malignant lesions which, at that point, must be treated with SPR.

There is a general agreement that pEN should be considered with caution for neoplasms larger than 30–40 mm. Such principle is quite supported by the data analyzed in our review which showed a mean tumor size of 21.7 mm, with only very few studies reporting pEN for size ≥ 40 mm [20, 30, 51, 52].

pEN was associated with a very low in-hospital mortality (0.7%) along with a favorable rate of severe early

Table 2 Comparison of surgical outcomes and recurrence between open and minimally invasive pEN

Reference	No.	Morbidity	Reintervention	Mortality	Recurrence	POPF (A-B-C)	POPF (B + C)
Open							
Hackert 2011 [9]	53	15 (28.3%)	0 (0%)	0 (0%)	0 (0%)	11 (20.7%)	0 (0%)
Crippa 2012 [15]	106	50 (47%)	9 (8.5%)	0 (0%)	–	44 (41.5%)	22 (20.7%)
Heeger 2014 [16]	60	39 (65%)	8 (13.3%)	2 (3.3%)	2 (3.3%)	31 (51.6%)	28 (46.6%)
Faitot 2015 [17]	126	80 (63.5%)	4 (3.2%)	1 (0.8%)	5 (3.9%)	72 (57.1%)	52 (41.3%)
Strobel 2015 [18]	166	91 (54.8%)	9 (5.4%)	1 (0.6%)	–	68 (41%)	34 (20.5%)
Wolk 2015 [19]	17	14 (82,3%)	0 (0%)	0 (0%)	–	12 (70.6%)	6 (35.3%)
Xiao 2016 [20]	53	29 (54.7%)	–	0 (0%)	0 (0%)	29 (54.7%)	11 (20.7%)
Kaiser 2016 [21]	74	44 (59.4%)	10 (13.5%)	0 (0%)	2 (2.7%)	34 (46%)	20 (27%)
	655	362 (55.2%)	40/602 (6.6%)	4 (0.6%)	9/366 (2.4%)	301 (45.9%)	173 (26.4%)
Mini-invasive							
Ayav 2005 [22]	19	8 (42.1%)	–	–	–	–	–
Ardbuckle 2007 [23]	13	–	0 (0%)	0 (0%)	0 (0%)	1 (7.7%)	7.7%
Fernandez Cruz 2007 [24]	20	8 (40%)	–	0 (0%)	0 (0%)	7 (35%)	15%
Sa Cunha 2007 [25]	7	–	–	0 (0%)	–	–	–
Sweet 2007 [26]	7	–	0 (0%)	0 (0%)	–	5 (71.4%)	28.6%
Luo 2009 [27]	16	–	0 (0%)	0 (0%)	0 (0%)	4 (25%)	25%
Fernandez Cruz 2011 [28]	13	–	0 (0%)	0 (0%)	1 (7.7%)	5 (38.5%)	23.1%
Costi 2013 [29]	22	14 (63.6%)	3 (13.6%)	0 (0%)	–	8 (36.4%)	22.8%
Choi 2014 [30]	11	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	1 (9.1%)	0%
Haugvik 2014 [31]	14	8 (57.1%)	–	0 (0%)	–	7 (50%)	42.9%
Thomas 2015 [32]	12	–	0 (0%)	0 (0%)	–	4 (33.3%)	25%
Boggi 2016 [33]	12	1 (8.3%)	0 (0%)	0 (0%)	–	1 (8.3%)	8.3%
Sahakyan 2017 [34]	44	18 (40.9%)	–	2 (4.5%)	–	–	27.3%
Tian 2016 [35]	60	8 (13.3%)	1 (1.7%)	0 (0%)	–	6 (10%)	10%
Song 2015 [36]	30	3 (10%)	0 (0%)	0 (0%)	0 (0%)	3 (10%)	–
Jin 2016 [37]	31	6 (19.3%)	1 (3.2%)	0 (0%)	0 (0%)	23 (74.2%)	38.7%
Di Benedetto 2018 [38]	12	1 (8.3%)	0 (0%)	0 (0%)	0 (0%)	3 (25%)	1 (8.3%)
	343	76/275 (27.6%)	5/239 (2.1%)	2/324 (0.6%)	1/146 (0.7%)	78/273 (28.5%)	59/287 (20.5%)
p Value		< 0.001	0.004	0.495	0.096	< 0.001	0.027

postoperative complications (12.1%), which is slightly inferior to the 15.8% recently reported by the Verona group over a cohort of 775 SPR [51].

We found that pEN overall complication rate (46.1%) resembled what was reported for SPR in recent studies (30–50%) [53–55] and in the Chua meta-analysis (47%) [56].

The most important single variable affecting pEN safety seems to be the close anatomical relation between the tumor and the MPD. Surprisingly, such parameter is seldom reported in the papers reviewed, preventing an accurate assessment of its real impact on the overall complication rate. The risk of POPF seems to rise the closer the tumor to the MPD, as reported by Heeger et al. [16] B-C POPF rate was significantly higher after deep pEN (< 3 mm) compared to shallow pEN (> 3 mm). These data are not confirmed by the Heidelberg experience where the cystic pattern of the lesion was the sole independent variable associated with B-C POPF after pEN. The authors stressed that such results may have been biased by the nature of the surgical procedure (open surgeries/no coagulation or sealing near MPD) [18].

Lately, Duconseil et al. [57] described the posterior face of the pancreatic head as the highest risk zone for the development of severe POPF after surgery. He suggested that when a deep pEN of such anatomical zone is planned, the patients should be carefully evaluated to select who might benefit from auxiliary pre- or intraoperative procedures (MPD stenting, pancreaticojejunostomy, teres ligament patch) to prevent it.

pEN has the clear advantage to preserve functional pancreatic gland, but, in order to be validated as a safe and effective surgical technique, its POFP incidence rate should be lower or equivalent to SPR. Considering that the small pancreatic tumors generally treated by pEN do not induce fibrotic changes in the pancreatic gland, the risk of POPF could theoretically be increased. Comparing to SPR, pEN transection line may be wider, particularly for tumors

Table 3 Surgical outcome after pEN in pNETs and cystic neoplasms

Reference	No. of patients	Mini-invasive surgery	Morbidity		Reintervention	POPF (B + C)
pNETS			Total	Severe		
Balzano 2003 [39]	13	–	4 (30.8%)	–	1 (7.7%)	0 (0%)
Ayav 2004 [22]	19	19 (100%)	8 (42.1%)	–	–	–
Fernandez Cruz 2006 [40]	15	15 (100%)	6 (40%)	0 (0%)		–
Ardbuckle 2007 [23]	14	13 (92.8%)	–	–	0 (0%)	1 (7.1%)
Casanova 2007 [41]	9	–	5 (55.5%)	1 (11.1%)	1 (11.1%)	3 (33.3%)
Liu 2007 [42]	32	6 (18.7%)	7 (21.9%)	–	1 (3.1%)	1 (3.1%)
Sa Cunha 2007 [25]	11	7 (63.6%)	–	–	–	–
Sweet 2007 [26]	7	7 (100%)	–	0 (0%)	0 (0%)	2 (28.6%)
Luo 2009 [27]	18	16 (88.8%)	–	–	0 (0%)	4 (22.2%)
Fernandez Cruz 2011 [28]	13	13 (100%)	–	–	0 (0%)	3 (23.1%)
Hu 2011 [43]	65	21 (32.3%)	–	–	1 (1.5%)	–
Crippa 2012 [15]	106	6 (5.6%)	50 (47.2%)	–	9 (8.5%)	22 (20.7%)
Haugvik 2014 [31]	14	14 (100%)	8 (57.1%)	–	–	6 (42.9%)
Tsang 2014 [44]	18	6 (33.3%)	12 (66.7%)	1 (5.5%)	1 (5.5%)	5 (27.7%)
Anneke 2015 [45]	60	–	39 (65%)	18 (30%)	3 (5%)	–
Wei 2015 [46]	19	–	13 (68.4%)	1 (5.3%)	1 (5.3%)	4 (21%)
Tian 2016 [35]	120	60 (50%)	24 (20%)	8 (6.7%)	1 (0.8%)	16 (13.3%)
Uccelli 2016 [47]	18	3 (16.6%)	7 (38.9%)	1 (5.5%)	0 (0%)	1 (5.5%)
Total	571	206/470 (43.8%)	183/443 (41.3%)	30/236 (12.7%)	19/527 (3.6%)	68/401 (16.9%)
Cystic neoplasms						
Choi 2014 [30]	11	11 (100%)	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)
Thomas 2015 [32]	12	12 (100%)	–	1 (8.3%)	0 (0%)	3 (25%)
Turrini 2011 [48]	7	0 (0%)	3 (43%)	–	0 (0%)	1 (14%)
Blanc 2008 [49]	26	0 (0%)	14 (53%)	–	1 (4%)	1 (4%)
Kaiser 2016 [21]	74	1 (1.3%)	44 (59.4%)	10 (13.5%)	10 (13.5%)	20 (27%)
Total	130	24/130 (18.4%)	62/118 (52.5%)	11/97 (11.3%)	11/130 (8.4%)	25/130 (19.2%)
p Value			0.014	0.365	0.009	0.277

≥ 30 mm. Furthermore, the secondary branches of the MPD might be involved, increasing the risk of POPF.

A recent pooled analysis of a large number of studies showed a POPF incidence rate between 22% and 30% after SPR [58].

In our review, the overall rate of POPF after pEN was slightly superior (38.9%), but, as recently reported by the ISGPF, only grade B-C POPF must be considered to provide better comparison of the postoperative outcome between different series of pancreatic resections in literature [59].

Inchauste recently reported the incidence of clinically significant POPF in two groups of patients who underwent pEN or SPR for pNET [60]. POPF rate was, respectively, 27.4% and 20% in pEN and SPR group, without statistical significance.

In our review, the rate of B-C POPF after pEN was comparable (21.5%) and a similar rate (20.5%) was reported by Beger in a review of 811 patients published in 2015 [61]. Same rate (20.5%) was documented by the Heidelberg group [9].

In a recent meta-analysis which compared pEN versus SPR for small pancreatic lesions (total of 1100 cases), pEN was associated with a borderline higher rate of overall and B-C POPF [56].

A further meta-analysis by Huttner et al. showed 25.5% and 19.7% POPF rate in the pEN and SPR group, respectively, suggesting a certain superiority of SPR [62]. However, such difference was no longer significant when only high-volume studies (more than 20 pEN and at least 4 pEN/year) were took into consideration.

Generally, minimally invasive pancreatic surgery is considered to be associated with a higher rate of POPF when compared with the open approach. The well-known advantages of the laparoscopic approach (reduced postoperative pain, hospital stay, and recovery time) might consequently be negatively counteracted by the potential severity of POPF. Unfortunately, no RCTs comparing open versus laparoscopic pEN are available in the current literature. Nevertheless, in our review, both overall and clinically significant POPF incidence rates appear to be much higher with the

open approach ($p < 0.001$ and $p < 0.027$). The most interesting data emerging from our analysis are apparently superior of the minimally invasive pEN over the classical open approach in terms of incidence of POPF, complications, and reoperations.

Besides, once solid and cystic tumors were compared in the pEN setting, our data showed a significant difference in terms of overall morbidity and reintervention rate in favor of the solid tumors group (Table 3).

Lack of available data concerning the postoperative outcome between head/neck and body/tail lesions treated with pEN did not allow us to draw any definitive conclusion. Costi et al. [29] analyzed the different outcomes of the right-sided and left-sided laparoscopic pEN, concluding that laparoscopy did not provide any advantage over the open approach in case of right-sided lesions, due to the more technically demanding nature of the procedure. On the contrary, Zhang et al. [63] claim in their experience that laparoscopic pEN led to better perioperative outcomes comparing to open pEN, as long as neoplasms are located in the pancreatic head.

Tumor recurrence rate associated with pEN has not been clearly documented in literature, actually appearing quite variable (range 0–19%) [28, 30, 45]. Besides, published series are limited in numbers and tend to display variable follow-up intervals (range 1–5 years). Our pooled analysis conducted over 1223 patients who underwent pEN showed a 2.2% mean recurrence rate, which is by the way highly acceptable, considering that the vast majority of treated neoplasms were benign.

Conclusions

In summary, the data presented in literature suggest that pEN is a safe and feasible technique for the treatment of small pancreatic neoplasms, especially small-sized pNETs and cystic tumors.

Such technique is associated with both acceptable morbidity and low mortality rates and it seems comparable to SPR in terms of perioperative surgical outcomes.

A pEN minimally invasive approach is gaining more and more popularity due to the well-known benefits over the open technique, without any evidence of an higher perioperative complication rate.

Our systematic review is not flawless; the cumulative results are impaired by the suboptimal methodological quality of most studies. Selection bias could not be avoided, owing to lack of randomization, and scarcity of substantial data in some of the included papers.

Still, these results provide a good level of evidence supporting the findings of most single-center studies.

Compliance with ethical standards

Disclosures Raffaele Dalla Valle, Elena Cremaschi, Laura Lamecchi, Francesca Guerini, Edoardo Rosso, and Maurizio Iaria have no conflict of interest or financial ties to disclose.

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