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Meta-analysis: the safety and efficacy of dilation in eosinophilic oesophagitis

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SUMMARY

Background
Oesophageal dilation is one of the most effective options in the management of symptoms of eosinophilic oesophagitis (EoE). However, earlier reports described an increased rate of complications.

Aim
To perform a meta-analysis of population-based studies of the risks associated with dilation and the clinical efficacy and duration of response to dilation in EoE.

Methods
Using MEDLINE and EMBASE, a systematic search was performed for published articles since 1977 describing cohort or randomised controlled trials of dilation in EoE. Summary estimates, including 95% confidence interval (CI), were calculated for the occurrence of complications associated with dilations (perforations, haemorrhage, chest pain, lacerations) and percentage of patients with symptom improvement following dilation. Heterogeneity was calculated using the I^2 statistic.

Results
The search resulted in 232 references, of which 9 studies were included in the final analysis. The studies described 860 EoE patients, of whom 525 patients underwent at least one oesophageal dilation and a total of 992 dilations. There were three cases of perforation (95% CI 0–0.9%, I^2 0%) and one haemorrhage (95% CI 0–0.8%, I^2 0%). Six studies reported postprocedural chest pain in 2% of cases (95% CI 1–3, I^2 53%). Clinical improvement from dilation occurred in 75% of patients (95% CI 58–93%, I^2 86%).

Conclusions
Dilation in patients with eosinophilic oesophagitis is a safe procedure with a low rate of serious complications (<1%), and seems to result in at least a short-term improvement of symptoms in the majority of patients.

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INTRODUCTION

Eosinophilic oesophagitis (EoE) is a chronic inflammatory immune-mediated condition characterised by symptoms of oesophageal dysfunction and marked eosinophilic infiltration of the oesophageal mucosa.[1] Dysphagia and recurrent food impactions are the predominant symptoms seen in adults.[2] For many EoE patients, these symptoms may significantly affect their quality of life.[3] Several treatment options exist; however, symptom relapse remains high.[4–7] Oesophageal dilation is one of the most effective therapies for symptomatic relief of EoE, even though it does not alter the underlying disease process.[6, 8, 9] Earlier reports on performing dilation in patients with EoE described a higher than expected rate of complications, which included perforation, bleeding, postprocedural discomfort and hospitalisation, making this a less attractive approach in management.[10–16] More recent studies, however, have shown dilation to be an otherwise safe procedure.[8, 17–19] The aim of this study was to perform a systematic review of the literature and meta-analysis of the risks associated with oesophageal dilation in adult patients with biopsy-proven EoE, as well as the clinical efficacy and duration of response to dilation in these patients.

METHODS

Literature search

To identify EoE patients who have undergone dilation, we conducted a systematic search of EMBASE and MEDLINE using the MESH headings and Emtree search terms for 'eosinophilic esophagitis' combined with 'dilations' or 'perforations' or 'complications' or 'clinical outcomes' or 'outcome assessment (health care)'. The search included all articles from 1977, the year when the first case of EoE was described[20], until March 2013. The reference lists of every included and relevant article were cross-referenced to identify additional articles. The search was limited to studies published in English and performed on humans.

Inclusion criteria

Two authors (FM, JC) independently extracted data from each abstract and manuscript to determine if these reports met inclusion criteria. Reports were required to describe adult patients with confirmed EoE, dilations performed at the reporting institution(s) and the presence or absence of at least one complication (e.g. perforation). EoE was defined as a clinical-pathological entity in which patients had symptoms suggestive of EoE (dysphagia, food impaction, heartburn or chest discomfort) and at least 15 eosinophils per high-power field on oesophageal biopsies. Previous treatment with a proton pump inhibitor (PPI) was not a diagnostic criterion as several of the articles extracted were published prior to the 2007 and 2011 EoE consensus statements.[1, 21] In addition to the clinical inclusion characteristics, studies were required to be cohort or randomised controlled trials. To qualify as a cohort study, the article needed to describe all patients, either presenting with EoE or dilated for EoE, within a defined time frame in a defined clinic or clinics. Review articles, editorials, letters to the editor, abstracts, case series and case reports were excluded, as the goal of this study was to calculate complication rates, and these types of reports do not report original data or the number of patients who had uncomplicated procedures. Studies describing patients <18 years old were excluded, unless the mean age was similar to trials describing only adults. In cases of discrepancy between reviewers, consensus was made through discussion with the senior author (KD).

Data collection

When available, data regarding EoE for each study were recorded on a standardised data sheet for demographics (age and gender), number of patients enrolled and analysed, number of patients who underwent dilation, number of dilation sessions per patient, predominant symptoms, history of allergies, concurrent medication use and duration of treatment, clinical response and duration of response, percentage of patients lost to follow-up prior to assessing duration of response, method used to assess duration of response, type of dilator used, endoscopic findings and complications (perforations, bleeding, lacerations, chest pain and hospitalisation). As above, this step was performed independently and in duplicate, with discrepancies resolved by consensus. Quality of the studies was described by the type of cohort (retrospective vs. prospective), the percentage of patients who followed up after dilation, the duration of follow-up following dilation, the method used to determine a clinically successful treatment and the method used to assess clinical response. A high-quality follow-up method was any method that described a systematic technique to assess for clinical improvement that was seemingly applied to all patients; simple chart reviews were deemed low quality.

Statistical analysis

For continuous variables (age, dilations per patient), the mean and standard deviation (s.d.) were recorded from

each study when available. If the s.d. could not be calculated, the mean s.d. from the other studies was imputed. For dichotomous variables, the exact binomial method was used to calculate the standard error and 95% confidence intervals of the percentage of subjects with the outcome of interest (e.g. presenting with dysphagia, having a perforation, etc.). Summary estimates, including 95% CI, were calculated for the following variables using a random effects model: age, percentage of male patients, mean dilations per patient, percentage of patients with a particular presenting symptom (dysphagia, food impaction, heartburn and chest pain), percentage of patients with an allergic history (any allergy, allergic rhinitis, asthma, food allergy, eczema), percentage of patients with particular endoscopic findings (rings, furrows, strictures, white plaques, normal oesophagus), eosinophils in gastric biopsies, percentage of patients with dilation complications (perforations, chest pain (any), chest pain requiring hospitalisation, haemorrhage and mucosal tears) and percentage of patients with symptom improvement with dilation.[22] Heterogeneity was calculated using the I^2 statistic, which estimates the 'percentage of total variation across studies that is due to heterogeneity rather than chance.'[23] In other words, the higher the value, the more the variation in the summary estimate is due to differences among the studies. All analyses were carried out using STATA (version 11.2; Statcorp, College Station, TX, USA). No funding was received in support of this review.

RESULTS

The search strategy resulted in 232 references, 209 of which were excluded by the title and abstract (Figure 1). Of the remaining 23 articles, 14 articles were excluded for the following reasons: 5 did not report complications,[24–28] 3 had duplicate records,[6, 9, 29] 1 was not clear whether the complication was a result of dilation,[12] 1 was excluded because dilations were reported by patient history at an outside institution and not by the investigators,[30] 2 articles were systemic reviews,[17, 31] 1 did not have histology available for the diagnosis of EoE[32] and 1 was excluded due to inconsistencies in data.[33]

Nine studies were included in the final analysis. All but one were retrospective studies,[34] and all but one were single-centre studies.[8] When combined, the studies described 860 patients with EoE, of whom 525 patients underwent at least one oesophageal dilation. The mean age of patients in the studies was 40 years (95% CI 31–49 years, I^2 0%). The minimum reported age was 14 and the maximum reported age was 77. The percentage of male patients in the studies was 77% (95% CI 73–82%, I^2 43%). Details are presented in Table 1.

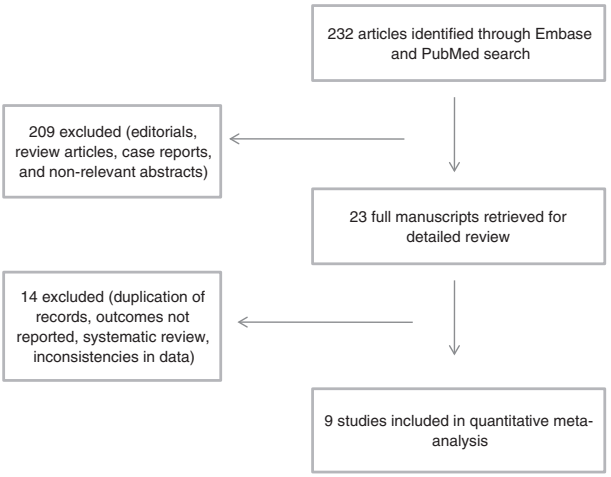

Figure 1 | Diagram of process for identifying studies that were included and excluded in the meta-analysis.

When combining all 9 studies, 525 patients underwent dilation to manage symptoms of EoE, with a mean of 1.5 (95% CI 1–2.5, I^2 0%) dilations per patient, resulting in a total of 992 total dilations. Two studies reported that at least one patient had 13 dilations, which was the maximum number reported.[8, 13] The method of dilation included 346 through-the-scope (TTS), 311 Savary and 31 Maloney. Some studies did not report the method of dilation in all patients. Four studies reported either stricture size or dilator size achieving a mean postdilation diameter of 13 mm.[8, 18, 35, 36] No study reported the length of stricture. Clinical improvement from dilation occurred in 75% of patients (95% CI 58–93%, I^2 86%) (Figure 2). However, the median duration of improvement was only reported in four studies, the durations of which were as follows: <3 months, 12 months, 15 months and 22 months.[8, 34, 35, 37] Follow-up rates exceeded 80% in only two studies.[13, 35] Furthermore, only two studies had a high-quality method of assessing for clinical outcomes.[8, 34]

Serious adverse events from oesophageal dilation were rare. Six studies reported postprocedure chest pain in the chart in a mean of 2% of cases (95% CI 1–3, I^2 53%).[8, 13, 18, 19, 34, 38] However, one study reported that 'most' patients experienced moderate chest pain after dilation.[35] Schoepfer *et al.* reported that 74% of patients had at least mild chest pain when asked directly, yet only 7% was recorded in the charts.[8] Of note, postprocedural chest pain requiring hospitalisation for pain management

Table 1 | Demographics, clinical outcomes and complications for each study included in the meta-analysis

Author	Year	EoE pts total	EoE pts dilated	Total # dilations	Mean age	Male (%)	Clinical improvement (%)	Duration of follow-up (mo)	Perforations	Haemorrhage	Chest pain (%)
Croese[13]	2003	31	17	58	34	77	94	NR	0	0	3.4
Potter[35]	2004	29	13	13	35	72	54	2.5	0	NR	NR
Pasha[36]	2007	42	13	13	44	74	85	NR	0	NR	NR
Bohm[34]	2010	16	9	11	41	75	89	22	0	NR	8.3
Dellon[18]	2010	124	36	70	26	76	83	NR	0	NR	4.2
Schoepfer[8]	2010	207	207	453	44	80	93	15	0	0	7.2
Enns[37]	2010	54	15	15	43	76	17	12	0	NR	NR
Jung[38]	2011	161	161	293	44	70	NR	NR	3	1	3
Ally[19]	2012	196	54	66	41	85	NR	NR	0	0	4

NR, not reported; mo, month.

occurred in 1% of patients in six studies (95% CI 0–2, I^2 0%).[13, 18, 19, 34, 35, 38] There was a single case of significant haemorrhage in four studies (95% CI 0–0.8%, I^2 0%).[8, 13, 19, 38] There were three perforations (95% CI 0–0.9%, I^2 0%, nine studies), all from one study.[38] Only one study explicitly commented on whether or not perforations occurred in follow-up dilations (18). One study commented on a perforation that occurred at an outside facility.[36] Finally, a summary estimate of lacerations could not be performed due to variation in the definition of lacerations. One study seemingly reported all mucosal disruptions (87% of patients),[13] whereas another study only reported 'deep mucosa rents or tears' in 3% of patients.[18]

The frequency of four symptoms (dysphagia, food impaction, heartburn and chest pain) was reported in enough studies to calculate a summary estimate (Figure 3). All studies reported a frequency of dysphagia, with three of these at 100% of patients.[8, 34, 37] The mean percentage of dysphagia in the remaining six studies was 83% (95% CI 75–91, I^2 76%).[13, 18, 19, 35, 36, 38] A history of food impaction was present in 45% (95% CI 26–63%, I^2 97%, nine studies). Heartburn was reported in all but one study (29% of patients, 95% CI 20–38%, I^2 82%)[19]; and chest pain (16% of patients, 95% CI 5–26%, I^2 80%) was noted in four studies.[13, 18, 36, 37] For the latter three symptoms, only food impaction was significantly different when excluding the three studies with every patient

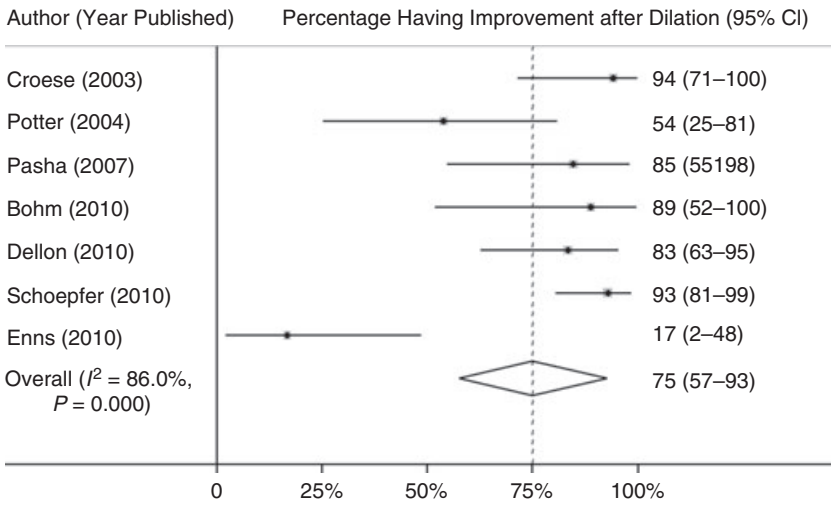

Figure 2 | Percentage of clinical improvement after dilation was abstracted from each article and 95% CI was calculated using the exact binomial method. A random effects model was used to calculate the overall effect size. The I^2 of 86% indicates that between-study differences (heterogeneity) account for 86% of variability in overall effect size.

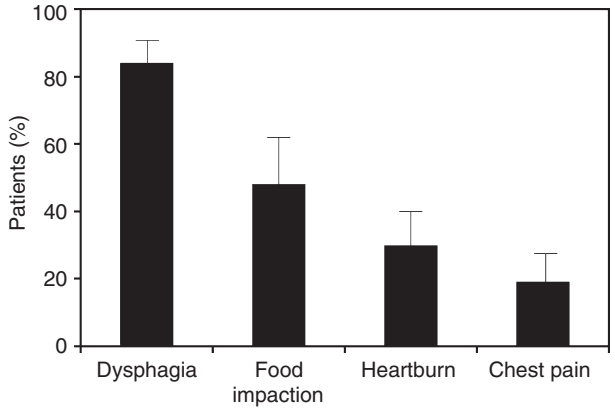

Figure 3 | Percentage shown is the overall estimate using all studies for each presenting symptom. Patients could have more than one symptom. Error bars show the upper limit of the 95% confidence interval.

having dysphagia (food impaction 32%, 95% CI 17–49, I^2 94%, six studies).

Most studies provided data on history of allergic diseases. Four studies provided a composite allergy history, typically defined as any history of asthma, environmental allergy, allergic rhinitis and/or atopy. Using this definition, 55% of patients (95% CI 46–64, I^2 44%) had a history of at least one of these diagnoses.[8, 34–37] In four studies, allergic rhinitis was present in 36% (95% CI 24–48, I^2 65%).[8, 13, 34, 38] Asthma was present in 37% (95% CI 28–45%, I^2 57%)[8, 13, 36–38] and a medical history of food allergy was present in 16% (95% CI 5–26, I^2 87%).[8, 13, 34, 36, 38] Only one study performed IgE testing for food allergens and found that six of eight patients were positive.[34] Lastly, two studies reported the frequency of atopic eczema (4%, 95% CI 1–6%).[8, 38]

Most studies provided data on the classic endoscopic findings in EoE, but there was considerable study variation. Oesophageal rings was the most common finding (61%, 95% CI 49–72%, I^2 89%),[8, 18, 19, 34–38] closely followed by furrows (49%, 95% CI 21–77%, I^2 98%).[13, 18, 19, 34, 36, 37] Strictures were found in 32% of patients in eight studies (95% CI 14–49%, I^2 98%).[8, 13, 18, 19, 35–38] White plaques were present in 10% (95% CI 3–17, I^2 83%) in five studies.[18, 19, 34, 37, 38] A normal appearing oesophagus was found in 13% (95% CI 7–19%, I^2 65%) in six studies.[18, 34–37] Lastly, three studies performed random gastric biopsies for eosinophils, with no positive results (95% CI 0–5%, I^2 0%).[13, 35, 36]

Concurrent medication use with oesophageal dilation varied widely. Six studies reported on PPI use,[8, 19, 34–37] ranging from 12 to 94% of patients, followed by topical fluticasone (6–98%) in five studies,[8, 19, 34, 36, 37] oral steroids (0–7%) in five studies[8, 19, 34, 36, 37] and montelukast (0–6%) in five studies.[8, 19, 34, 36, 37] One study reported two populations; 63 patients without any concurrent medication and 144 with concurrent medications.[8] No other study listed its results separately to permit comparison between success rates of dilation with and without concurrent medications.

DISCUSSION

This meta-analysis of nine published studies suggests that dilation in EoE patients is a safe procedure, which can result in short-term improvement of symptoms. In a total of 992 dilations performed on 525 patients, we determined that serious complications (perforations or haemorrhage) are extremely unlikely, occurring 0.4% of the time, which is consistent with previously reported complication rates.[39] We also found that clinical improvement in symptoms occurred in the majority of patients.

There were only three perforations and one case of haemorrhage as a result of dilations for EoE when performed at the reporting institution. Two systematic reviews, which included all case reports and case series, also found a low rate of perforations.[17, 31] Our study improves on this estimate by calculating a 95% CI, where the upper bound is <1%. Our estimate puts the case reports of perforation of EoE in perspective, which is to say that while it is true that perforations do occur as a result of dilation of EoE, they are quite rare. It is worth noting that these dilations were primarily performed at academic institutions with experience in managing EoE strictures and studies have demonstrated that perforation risks are influenced by endoscopists' experience.[39, 40] Lastly, there were no deaths reported in any of the studies included in our meta-analysis, nor were any deaths reported in the articles identified in the search strategy. With regard to the possibility of concurrent medical treatment reducing the risks of complications, only one study addressed this. Schoepfer *et al.* compared two cohorts, one treated with medications and dilation and the other exclusively with dilation.[8] Complication rates were similar between the two.

The most common complication described was post-procedural chest pain, which was reported in 2% of patients undergoing dilation, with only 1% requiring hospitalisation. Interestingly, in one study, chest discomfort noted on chart review was documented in only 7% of patients.[8] However, in a questionnaire mailed to patients following endoscopy, 74% (31/42) noted post-procedural chest pain, with 30% of patients describing

symptoms lasting 4 or more days. This suggests that most chest pain experienced by patients was either not reported by the patients to their physicians immediately following endoscopy, was deemed not significant enough by physicians to warrant documentation in the chart, or occurred once the patient left the clinic or hospital and sedation had waned. Six studies reported mucosal laceration, which occurred in 3–87% patients, as a complication of dilation. This wide range in complication rate may be related to the definition used for laceration. The one study reporting 3% of their patients developing tears described these as 'deep mucosal rents',[18] whereas others described these as 'mucosal tears'. It is unclear whether these two terms constitute the same finding. Generally, mucosal lacerations are superficial, whereas rents may involve deeper layers of the oesophageal wall. One would expect a less compliant and fibrotic mucosal layer to tear upon stretching; however, the majority of these tears are often limited to the superficial layers of the oesophageal wall. Indeed, mucosal friability or crepe-like mucosa is a well-described feature of EoE.[41] Even though mucosal tears are likely to be underreported, as oesophageal re-intubation is not commonly performed following bougie dilations (Savary or Maloney), we chose to report this finding as a 'complication' as the majority of studies used in this meta-analysis reported it as such. However, we contend that such tears should not be perceived as complications, but that they actually represent an intended outcome. For many EoE patients, dysphagia may not improve until the stricture is effectively disrupted. Lastly, these tears are probably the major source of postprocedural transient chest discomfort.

Our analysis also demonstrated that endoscopic dilation can result in short-term clinical improvement of dysphagia. One study following the natural history of EoE found that dysphagia improved in 91% (10/11) of patients undergoing dilation, with clinical response lasting a mean of 9 months.[6] Schoepfer *et al.* reported that 41% (17/42) of patients had symptom relief longer than 2 years as assessed by a questionnaire. Our analysis showed that 75% of patients had clinical improvement in symptoms; however, only four studies reported the duration of follow-up, ranging from 3 to 22 months. Only four studies reported either stricture size or dilator size, in which the mean diameter achieved following dilation was ≥13 mm, the threshold diameter in which most patients have improvement in dysphagia symptoms. It remains unclear whether concurrent use of antieosinophilic medications helps to maintain patients in remission following dilation. In the only study to compare cohorts of EoE patients undergoing dilation with and without concurrent medication, dysphagia scores and duration of response were similar before and after dilation.[8] It is noteworthy that all studies apparently used a historical control to determine effectiveness. This method is subject to numerous biases, which may inflate the results, as opposed to the method of comparing with an untreated group or sham dilations.

Based on our review, we suggest counselling patients to the following when performing dilation for EoE: 'Dilation has a good chance of providing short-term improvement in your symptoms. How long these improvements last is unclear. Many patients may need another dilation. Several patients will have some chest pain following the procedure. However, only about 1% will need to be admitted to the hospital to control their pain. The risks of significant bleeding or rupturing your oesophagus are extremely low (<1%). There have been no deaths reported as a result of this procedure.'

In our analysis, we also examined epidemiological data. Similar age and gender distribution was described in all nine studies. The majority of EoE patients were men with a mean age of 40 years. These demographics are consistent with patients seen at our institution.[42, 43] Dysphagia was present in 83% of patients, with three studies reporting this symptom universally present in their cohorts. This clinical presentation is also consistent with data in the literature.[1, 2] In addition, 55% of patients had coexisting allergy histories, most commonly reported as seasonal allergic rhinitis. This once again is similar to previously published reports.[44–47]

There are several limitations to our study. Most importantly, the quality of studies included in this meta-analysis was not optimal. Specifically, there were no controlled studies and nearly all of the studies were retrospective in design and probably had different methods of assessing and recording the data. This lack of standardisation may explain some of the heterogeneity among studies for subjective data such as presenting symptoms (e.g. dysphagia). It is somewhat reassuring that routine items, such as age and gender, had no statistical heterogeneity among studies, which suggests that these studies had a similar patient population. Our main results focus on the complications of dilation, three of which (perforation, haemorrhage and chest pain requiring hospitalisation) are dramatic and easily captured, so it is reasonable to assume that most, if not all, of these complications would have been correctly documented if they had occurred. On the other hand, the frequency of chest pain was noticeably different depending on the method of ascertainment of the symptom in the studies,

and more than likely represents underreporting of this symptom. After dilation of an EoE stricture, it is not uncommon for patients to develop transient chest discomfort. Other significant limitations include variations in determining what constituted a clinical success with dilation, the follow-up for the duration of improvement and particularly the lack of any untreated (or sham treated) comparison group. Therefore, just how effective dilations are for EoE cannot be determined. Lastly, while we used two databases and hand-searched reference lists, it is possible that we may have missed some articles with our search strategy, particularly as we limited our search for articles published in English.

In summary, dilation is a safe and seemingly effective (at least in the short-term) method of managing EoE, with major complications (perforation, haemorrhage and chest pain requiring hospitalisation) occurring in less than 1% of patients. The duration and intensity of this improvement, particularly when compared with medical therapy, have not been adequately described in the literature. Randomised controlled trials comparing dilation with sham dilation, with or without medical therapy, are needed to determine the role of dilation in the treatment of EoE.

AUTHORSHIP

Guarantor of the article: Fouad J. Moawad.

Author contributions: Fouad J. Moawad: study concept and design, article selection, article retrieval, data abstraction, analysis, and interpretation, quality rating, manuscript writing. Joseph G. Cheatham: article retrieval, article selection, data abstraction, quality rating, manuscript writing. Kent J. DeZee: article selection, analysis and interpretation of data, quality rating, statistical analysis, drafting of the manuscript, critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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