

# Journal Pre-proofs

Full length article

Invasive cervical cancer following treatment of pre-invasive lesions: a potential theory based on a small case series

Evangelos Paraskevaïdis, Antonios Athanasiou, Ilkka Kalliala, Anna Batistatou, Maria Paraskevaïdi, Evripidis Bilirakis, Maria Nasioutziki, Minas Paschopoulos, Deirdre Lyons, Marc Arbyn, Margaret Cruickshank, Pierre Martin-Hirsch, Maria Kyrgiou

PII: S0301-2115(21)00334-1  
DOI: <https://doi.org/10.1016/j.ejogrb.2021.06.049>  
Reference: EURO 12107

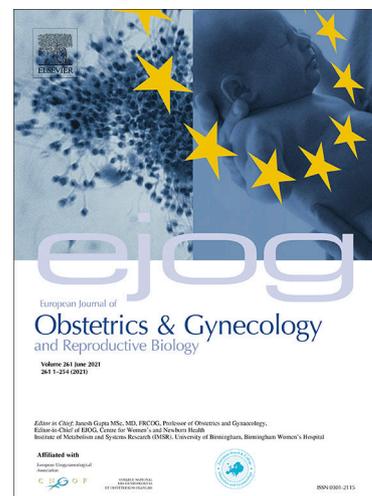
To appear in: *European Journal of Obstetrics & Gynecology and Reproductive Biology*

Received Date: 22 May 2021  
Revised Date: 23 June 2021  
Accepted Date: 30 June 2021

Please cite this article as: E. Paraskevaïdis, A. Athanasiou, I. Kalliala, A. Batistatou, M. Paraskevaïdi, E. Bilirakis, M. Nasioutziki, M. Paschopoulos, D. Lyons, M. Arbyn, M. Cruickshank, P. Martin-Hirsch, M. Kyrgiou, Invasive cervical cancer following treatment of pre-invasive lesions: a potential theory based on a small case series, *European Journal of Obstetrics & Gynecology and Reproductive Biology* (2021), doi: <https://doi.org/10.1016/j.ejogrb.2021.06.049>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier B.V.



**Invasive cervical cancer following treatment of pre-invasive lesions: a potential theory based on a small case series**

Evangelos Paraskevaïdis<sup>1</sup>, Antonios Athanasiou<sup>2</sup>, Ilkka Kalliala<sup>2,3</sup>, Anna Batistatou<sup>4</sup>, Maria Paraskevaïdi<sup>2,5</sup>, Evripidis Bilirakis<sup>6</sup>, Maria Nasioutziki<sup>7</sup>, Minas Paschopoulos<sup>1</sup>, Deirdre Lyons<sup>8</sup>, Marc Arbyn<sup>9</sup>, Margaret Cruickshank<sup>10</sup>, Pierre Martin-Hirsch<sup>11</sup>, Maria Kyrgiou<sup>2</sup>

<sup>1</sup>*Department of Obstetrics and Gynaecology, University Hospital of Ioannina, Ioannina, Greece*

<sup>2</sup>*Institute of Reproductive and Developmental Biology, Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK*

<sup>3</sup>*Department of Obstetrics and Gynaecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*

<sup>4</sup>*Department of Pathology, University Hospital of Ioannina, Ioannina, Greece*

<sup>5</sup>*Department of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, UK*

<sup>6</sup>*Department of Obstetrics & Gynaecology, IASO Hospital, Athens, Greece*

<sup>7</sup>*Second Department of Obstetrics & Gynaecology, University Hospital of Thessaloniki, Thessaloniki, Greece*

<sup>8</sup>*Department of Obstetrics and Gynaecology, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK*

<sup>9</sup>*Unit of Cancer Epidemiology, Belgian Cancer Centre, Sciensano, Brussels, Belgium*

<sup>10</sup>*Department of Obstetrics & Gynaecology, University of Aberdeen, Aberdeen, Scotland, UK*

<sup>11</sup>*Department of Obstetrics and Gynaecology, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK*

**Corresponding Author:**

Evangelos Paraskevaïdis, MD, PhD

Professor in Obstetrics & Gynaecology, University of Ioannina, Ioannina, Greece

President of the Hellenic Society of Colposcopy & Cervical Pathology (HSCCP)

Tel: +30 6944981000, email: vangelispar@hotmail.com

**ABSTRACT**

**Purpose:** The aim of this study is to present a single department's experience on cervical cancer cases following previous excision of cervical intraepithelial neoplasia (CIN) and to discuss potential pathogenesis.

**Methods:** Nine cervical cancer cases meeting the inclusion criteria, with available pathological and follow-up data, were considered eligible for this study.

**Results:** The majority (7/9) have had clear excisional margins. The interval between initial treatment and cancer diagnosis ranged from 7 to 17 years. In all cases cancer diagnosis was "unexpected", as the prior cytological and/or colposcopic evaluation was not suggestive of significant cervical pathology. All cancers were squamous, and 5/9 at stage I.

**Conclusion:** The long interval between initial CIN treatment and final diagnosis as well as the normal post-treatment follow-up may suggest a 'de novo' underlying but 'hidden' carcinogenesis process. It might be that dysplastic cells entrapped within crypts (or normal metaplastic affected by the same predisposing factors) continue undergoing their evolution, undetectable by cytology and colposcopy until they invade stroma and surfaces (endo- and/or ectocervical) approximately a decade later. Heavy cauterisation of cervical crater produced post excision might be a potential culprit of this entrapment.

**Keywords:** CIN; excision; carcinogenesis; cervical cancer; cervical crypts

## **INTRODUCTION**

After successful treatment of cervical intraepithelial neoplasia (CIN), it would be expected that the risk of future invasive cervical cancer would be the same compared to the general population. However, all available data shows that women with a history of treatment for cervical intraepithelial neoplasia remain at substantially increased risk of cervical cancer. Soutter et al[1] first published a large, robust population-based study in 1997 which illustrated this increased risk (4-5 greater than the general population); this finding was subsequently confirmed by many other studies[2-9]. A recent systematic review and meta-analysis from our group[10] estimated this risk at over three times, and another recent large population-based study[11] at over two times greater, respectively, than the general population. The increased risk of subsequent cancer persists over at least 20 years and this finding is often cited as the justification for recommendations to keep women during two decades under intensified surveillance (United States guidelines[12]). However, almost none of the available studies provides a history of post-treatment cytology, HPV status and/or colposcopic findings and therefore any possible explanation of this increased risk remains rather obscure or arbitrary.

The aim of this study was to present a 24-year experience with cases of invasive cervical cancer that were referred to or diagnosed in an academic hospital department having had previous treatment of cervical intraepithelial neoplasia, in whom the interval cytology and colposcopy data were available at large. To the best of our knowledge, this is the first study to provide individual history interval data, carefully collected over such a long period of time.

## **METHODS AND MATERIALS**

### **Setting**

Women who presented with cervical cancer from 1997 to 2020 in the University Hospital of Ioannina, Greece, with a history of local excisional treatment for high-grade CIN [cold knife conisation (CKC), laser conisation (LC), or large loop excision of the transformation zone (LLETZ)]. Initial CIN treatment could have been performed either regionally or elsewhere in Greece.

### **Eligibility criteria**

Women who did not comply with follow-up scheme after CIN treatment according to national guidelines, were excluded. To eliminate the possibility of underdiagnosed micro-invasive cervical cancer at the time of initial treatment, only women in whom the diagnosis of cervical cancer had

been made after the first two post-operative years were included. We chose a two-year 'lag period' because the majority of residual disease is identified during this interval[13, 14]. Finally, we excluded patients treated with ablation due to lack of cone specimen and subsequent histological examination of the whole transformation zone as in patients treated with excision.

### **Collection of data**

Clinical characteristics, histological type and stage of cervical cancer were prospectively recorded. Data on initial treatment of CIN (date, technique, CIN grade, margin status and crypt involvement) and post-treatment follow-up (intervals and results) were retrospectively collected. National guidelines for post-treatment surveillance recommend follow-up with cytology and colposcopy every six months for the first two years, and annually thereafter if this initial period is negative for residual/recurrent disease. In the last ten years, hrHPV (high-risk HPV) testing as test-of-cure is also recommended at 6 months after treatment, but since none of the cases had been treated for CIN after 2010, test-of-cure HPV status was not available.

### **RESULTS**

26 women with cervical cancer after previous treatment of high-grade CIN were identified. Of these, we excluded women with diagnosis of cervical cancer in less than two years after treatment (n=8), women without regular follow-up after treatment (n=5) and women with ablative treatment (n=4). Therefore, the women fulfilling the eligibility criteria were nine. None of these individuals had co-morbidities or immunodeficiency. Smoking history was reported in five cases.

Treatment for CIN, histological evaluation of excised cone and follow-up surveillance had been performed in four academic hospitals in seven cases (two in our own hospital, and five in three other academic hospitals), and in two private hospitals in two cases. Five women had been treated with LLETZ, three with CKC and one with LC. Final histopathological diagnosis was CIN2 in three and CIN3 in six cases. Endo- and ectocervical margins were clear in seven cases, but in one out of seven, a clear endocervical margin was achieved after a repeat excision; margin status was not available in two cases. Crypt involvement was present in three cases and absent in one case. The pathologist did not make any comments regarding crypts in the remaining five cases. We were able to contact with the clinician who had performed the conisation for seven patients and we were advised that endocervical curettage (ECC) at the time of treatment had not been performed and that the crater of the excision had been cauterised for control/prevention of bleeding in all seven cases.

The interval between CIN treatment and diagnosis of cervical cancer ranged from 7 to 17 years. Cytology within the last 2 years before cancer diagnosis was normal in all but one case where cytology showed atypical squamous cells of undetermined significance (ASC-US). In two cases with normal cytology, there was a lack of endocervical cells on the smear due to post-operative cervical stenosis. HPV testing within the last 2 years prior to cancer diagnosis was available in four cases, where it was positive in three of them despite a concomitant unimpressive cytology ( $\leq$ ASC-US). Cervical cancer was squamous in all cases (stage I: 5; stage II: 1; stage III: 3). Table 1 presents the main characteristics of the eligible patients, by chronological order of cervical cancer diagnosis.

*Table 1: Main characteristics of eligible patients diagnosed with cervical cancer after treatment for CIN*

Case	CIN treatment technique	Histological CIN grade	Margin status	Crypt involvement	Interval between CIN treatment and cancer diagnosis (in years)	Most recent cytology prior to cancer diagnosis	HPV testing prior to cancer diagnosis	Stage
1	CKC	CIN3	NA	NA	11	WNL	-	SCC IIB
2	LC	CIN2	Clear	NA	11	WNL	-	SCC IB1
3	LLETZ	CIN3	Clear	Yes	9	WNL (lacking endo-cervical cells)	-	SCC IA2
4	LLETZ	CIN2	NA	NA	8	WNL (lacking endo-cervical cells)	-	SCC IB2
5	CKC	CIN3	Clear	NA	17	WNL	Positive (16)	SCC IIIA
6	LLETZ	CIN3	Clear	Yes	13	WNL	Negative	SCC IA2
7	CKC	CIN3	clear	NA	7	ASC-US	Positive (16)	SCC IIIB
8	LLETZ (2)	CIN3	Clear (in second LLETZ)	Yes (in first LLETZ)	13	WNL	-	SCC IIIB

9	LLETZ	CIN2	Clear	No	7	WNL	Positive (45)	SCC IA1
---	-------	------	-------	----	---	-----	------------------	---------

**Abbreviations:**

ASC-US; atypical squamous cells of undetermined significance; CIN: cervical intraepithelial neoplasia; CKC: cold knife conisation; LC: laser conisation; LLETZ: large loop excision of the transformation zone; NA: not available; SCC: squamous cell carcinoma; WNL: within normal limits

**DISCUSSION****Main findings**

The aim of this study is to provide a potential explanation of cervical carcinogenesis after previous CIN treatment, based on a limited number of cervical cancer cases with a history of CIN treatment. In our cases, the facts that the interval from initial CIN treatment to diagnosis of invasion was almost a decade and that five out of nine cancers were early stages, may fit well with the established natural history of the *de novo* cervical carcinogenesis, according to which cervical cancer occurs from a persistent HPV infection/pre-invasive lesion over an interval of 10-20 years[15, 16]. It may be quite likely that cervical cancer arose from precursors which had not been completely removed during treatment and subsequently progressed to cancer. We suggest that cytology/colposcopy failed to detect these precursors on time because these might have been entrapped inside cervical crypts under a thick thermal plaque, caused by cauterisation of the crypts along with the rest of the crater's surface during treatment, and under subsequent extended metaplasia of the new transformation zone. As a result, they might have remained undetected until they progressed to cancer and reached the endo- and/or ectocervical surface. Another explanation for the emergence of cervical cancer after previous CIN treatment is a new HPV infection. However, we would expect that regular follow-up would have detected HPV-related pre-invasive lesions before progression to cancer, therefore a new HPV infection is less likely to account for the cervical cancer development in our case series.

The 'crypt theory' could explain why the risk is greater with more conservative treatment methods, since shallow excision/ablation is not deep enough to remove/destroy all crypts. Optimal excision dimensions to ensure minimum risk of cervical carcinogenesis and minimum risk of reproductive morbidity is yet to be determined, probably in an individualised fashion[17-19].

There are several practical implications ensuing from the 'crypt theory'. Firstly, cauterisation of the crypts as well as at the whole crater created after cone excision, should be limited to the bare minimum in order to minimise the risk of affected cells being buried inside the crypts. An

alternative to cauterisation would be the use of haemostatic solutions, such as Monsel's. Secondly, treated women with high-grade histology or other unfavourable characteristics such as crypt involvement, satellite lesions[20] or aggressive HPV types might benefit from a rigorous (longer and more frequent) follow-up after treatment even if initial excisional margins were clear. Nonetheless, this is not practised in most countries, and some guidelines, such as in the UK, even support discharge to general population screening as early as at 6 months[21]. Thirdly, clinicians should be aware of the possibility of cervical cancer after CIN treatment and be alert especially if a previously treated woman presents with otherwise unexplained vaginal bleeding. Fourthly, it might be plausible that HPV testing, due to its higher sensitivity than cytology and colposcopy[22, 23], would also feature better long-term sensitivity for the diagnosis of these hidden lesions inside the crypts, and indeed HPV testing has been included in the post-treatment follow-up guidelines of many countries such as the UK, USA and Finland[21, 24, 25]. Of course, this is only a hypothesis since entrapped lesions inside the crypts might not exfoliate cells and HPV genetic material, thus HPV DNA or mRNA testing might be negative as well.

### **Strengths and limitations**

Our explanation is unproven but is plausible and original. Also, review of the initial histology specimen and interval cytological smears, in order to rule out false negatives, was not feasible in half of the cases. However, treatment of CIN2+ and follow-up took place in academic hospitals in most cases (7/9), with experienced pathologists, cytologists and colposcopists involved. Additionally, post-treatment high-risk HPV testing as test of cure was not available since all cases had been treated before its introduction. Finally, we were not able to calculate the cervical cancer incidence rate after CIN treatment because some cases were referred to us by other clinicians, but our aim was not to calculate the prevalence but to suggest a potential explanation for the increased incidence as already shown in other studies.

### **CONCLUSION**

Until better evidence may sometime appear, the original data of this small series could probably allow someone to consider the endocervical crypts as the origin of these 'hidden' and suddenly appearing carcinomas after CIN treatment. Apart from awareness regarding intra-operative technicalities, clinicians should also have at least an average index of suspicion particularly in symptomatic cases with a history of treatment for CIN, performing endocervical dilation and curettage (E&C) or even repeat excision. After all, most of these women would have had already completed their families.

## REFERENCES

- (1) Soutter WP, de Barros Lopes A, Fletcher A, Monaghan JM, Duncan ID, Paraskevaidis E, et al. Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. *Lancet*. 1997;349:978-80.
- (2) Evans HS, Newnham A, Hodgson SV, Møller H. Second primary cancers after cervical intraepithelial neoplasia III and invasive cervical cancer in Southeast England. *Gynecol Oncol*. 2003;90:131-6.
- (3) Kalliala I, Anttila A, Pukkala E, Nieminen P. Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study. *BMJ*. 2005;331:1183-5.
- (4) Strander B, Andersson-Ellström A, Milsom I, Sparén P. Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population based cohort study. *Bmj*. 2007;335:1077.
- (5) Melnikow J, McGahan C, Sawaya GF, Ehlen T, Coldman A. Cervical intraepithelial neoplasia outcomes after treatment: long-term follow-up from the British Columbia Cohort Study. *J Natl Cancer Inst*. 2009;101:721-8.
- (6) McCredie MR, Paul C, Sharples KJ, Baranyai J, Medley G, Skegg DC, et al. Consequences in women of participating in a study of the natural history of cervical intraepithelial neoplasia 3. *Aust N Z J Obstet Gynaecol*. 2010;50:363-70.
- (7) Jakobsson M, Pukkala E, Paavonen J, Tapper AM, Gissler M. Cancer incidence among Finnish women with surgical treatment for cervical intraepithelial neoplasia, 1987-2006. *Int J Cancer*. 2011;128:1187-91.
- (8) Rapiti E, Usel M, Neyroud-Caspar I, Merglen A, Verkooijen HM, Vlastos AT, et al. Omission of excisional therapy is associated with an increased risk of invasive cervical cancer after cervical intraepithelial neoplasia III. *Eur J Cancer*. 2012;48:845-52.
- (9) Rebolj M, Helmerhorst T, Habbema D, Looman C, Boer R, van Rosmalen J, et al. Risk of cervical cancer after completed post-treatment follow-up of cervical intraepithelial neoplasia: population based cohort study. *BMJ*. 2012;345:e6855.
- (10) Kalliala I, Athanasiou A, Veroniki AA, Salanti G, Efthimiou O, Raftis N, et al. Incidence and mortality from cervical cancer and other malignancies after treatment of cervical intraepithelial neoplasia: a systematic review and meta-analysis of the literature. *Ann Oncol*. 2020;31:213-27.
- (11) Loopik DL, IntHout J, Ebisch RMF, Melchers WJG, Massuger LFAG, Siebers AG, et al. The risk of cervical cancer after cervical intraepithelial neoplasia grade 3: A population-based cohort study with 80,442 women. *Gynecol Oncol*. 2020:S0090-8258(20)30067-6.
- (12) Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis*. 2013;17:S1-S27.
- (13) Kocken M, Helmerhorst TJM, Berkhof J, Louwers JA, Nobbenhuis MAE, Bais AG, et al. Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: a long-term multi-cohort study. *The Lancet Oncology*. 2011;12:441-50.

- (14) Paraskevaïdis E, Jandial L, Mann EM, Fisher PM, Kitchener HC. Pattern of treatment failure following laser for cervical intraepithelial neoplasia: implications for follow-up protocol. *Obstet Gynecol.* 1991;78:80-3.
- (15) Ault KA. Epidemiology and natural history of human papillomavirus infections in the female genital tract. *Infect Dis Obstet Gynecol.* 2006;2006 Suppl:40470.
- (16) Gravitt PE. The known unknowns of HPV natural history. *J Clin Invest.* 2011;121:4593-9.
- (17) Athanasiou A, Veroniki AA, Efthimiou O, Kalliala I, Naci H, Bowden S, et al. Comparative efficacy and complication rates after local treatment for cervical intraepithelial neoplasia and stage 1a1 cervical cancer: protocol for a systematic review and network meta-analysis from the CIRCLE Group. *BMJ Open.* 2019;9:e028008.
- (18) Athanasiou A, Veroniki AA, Efthimiou O, Kalliala I, Naci H, Bowden S, et al. Comparative fertility and pregnancy outcomes after local treatment for cervical intraepithelial neoplasia and stage 1a1 cervical cancer: protocol for a systematic review and network meta-analysis from the CIRCLE group. *BMJ Open.* 2019;9:e028009.
- (19) Ang C, Mukhopadhyay A, Burnley C, Faulkner K, Cross P, Martin-Hirsch P, et al. Histological recurrence and depth of loop treatment of the cervix in women of reproductive age: incomplete excision versus adverse pregnancy outcome. *Bjog.* 2011;118:685-92.
- (20) Paraskevaïdis E, Lolis ED, Koliopoulos G, Alamanos Y, Fotiou S, Kitchener HC. Cervical intraepithelial neoplasia outcomes after large loop excision with clear margins. *Obstet Gynecol.* 2000;95:828-31.
- (21) Public\_Health\_England. Colposcopic diagnosis, treatment and follow up. 2020.
- (22) Paraskevaïdis E, Arbyn M, Sotiriadis A, Diakomanolis E, Martin-Hirsch P, Koliopoulos G, et al. The role of HPV DNA testing in the follow-up period after treatment for CIN: a systematic review of the literature. *Cancer Treatment Reviews.* 2004;30:205-11.
- (23) Heinonen A, Jakobsson M, Kiviharju M, Virtanen S, Aro K, Kyrgiou M, et al. Role of Colposcopy after Treatment for Cervical Intraepithelial Neoplasia. *Cancers (Basel).* 2020;12.
- (24) Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. *Journal of lower genital tract disease.* 2020;24:102-31.
- (25) Finnish\_Medical\_Society\_Duodecim. Current Care Guidelines. Cytological Changes in the Cervix, Vagina and Vulva. Current Care Guidelines. Working Group Set Up by the Finnish Medical Society Duodecim and the Finnish Cardiac Society. 2021.

**Author contributions:** This study was designed by E.P. Data were collected by E.P., and were interpreted by all authors. The manuscript was drafted by E.P. and A.A., and was revised by all authors. E.P. is the guarantor.

**Additional information:** The authors declare no conflicts of interest.

## ICMJE DISCLOSURE FORM

Date: 23/06/2021

Your Name: Evangelos Paraskevaïdis

Manuscript Title: Invasive cervical cancer following treatment of pre-invasive lesions: a potential theory based on a small case series

Manuscript number (if known): \_\_\_\_\_

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
<b>Time frame: Since the initial planning of the work</b>			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) <b>No time limit for this item.</b>	<input checked="" type="checkbox"/> None	
<b>Time frame: past 36 months</b>			
2	Grants or contracts from any entity (if not indicated in item #1 above).	<input checked="" type="checkbox"/> None	
3	Royalties or licenses	<input checked="" type="checkbox"/> None	

4	Consulting fees	<input checked="" type="checkbox"/> None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None	
6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
7	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> None	
8	Patents planned, issued or pending	<input checked="" type="checkbox"/> None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input checked="" type="checkbox"/> None	
11	Stock or stock options	<input checked="" type="checkbox"/> None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None	

Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Journal Pre-proofs