The impact of endoscopic transsphenoidal pituitary adenoma surgery on endocrine function: a single centre study

Luke Galloway[1], Mohamed Ali[1], Andrew Lansdown[2], Peter Taylor[2,3], Aled Rees[2,4], John Stephen Davies[2], Caroline Hayhurst[1]

1. Department of Neurosurgery, University Hospital of Wales, Cardiff, UK
2. Department of Endocrinology, University Hospital of Wales, Cardiff, UK
3. Thyroid Research Group, Systems Immunity Research Institute, Cardiff University School of Medicine, Cardiff, UK
4. Neuroscience and Mental Health Research Institute, Cardiff University, Cardiff, UK

Corresponding Author:

Mr. Luke Galloway

Department of Neurosurgery,

University Hospital of Wales,

Cardiff,

Wales, UK,

CF14 4XW

Telephone: +44 7772306563

E-mail: lukegalloway14@hotmail.com

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Abstract

Introduction

The outcome for pituitary endocrine function following endoscopic transsphenoidal surgery remains unclear. This study aims to evaluate endocrine outcomes following endoscopic surgery in order to provide a benchmark to assist in the counselling of patients perioperatively.

Methods

A prospectively held pituitary database was retrospectively analysed for all adult pituitary adenoma patients undergoing endoscopic surgery from May 2011 – May 2017. All operations were performed by a single Neurosurgeon at a regional centre for pituitary surgery. Functioning and non-functioning adenomas were included. Hormonal status was assessed at most recent follow-up.

Results

145 patients (69 M, 76 F) were included in the study with a median age of 52 years. Median follow-up was 52 months. 88 patients (61%) had normal function preoperatively and 57 patients (39%) were hypopituitary preoperatively. Preoperatively, 29 patients (20%) had hypothalamo-pituitary-adrenal (HPA) axis dysfunction, 39 patients (27%) had thyroid axis dysfunction, 11 males (16%) and 7 females (9%) had gonadal axis dysfunction, and one patient had preoperative diabetes insipidus.

Postoperatively, 26 patients (18%) had a new deficiency in pituitary function, whilst 6 patients (11%) were restored to normal function. 19 patients (13%) had new HPA axis deterioration, 12 (8%) had new thyroid axis dysfunction, 8 males (11%) and 4 females (5%) had gonadal axis deterioration and 6 patients (4%) had new diabetes insipidus (DI).

Conclusions

The ability to restore pituitary function following endoscopic surgery remains limited, whilst new deficits still occur. It is essential that patients are counselled accordingly as hormonal replacement therapy can have a significant impact on quality of life. Larger longer-term collaborative studies of endocrine outcome in endoscopic pituitary surgery are needed.

Key Words

Pituitary; adenoma; endoscopic; surgery; endocrine; outcome.

Introduction

Pituitary adenomas represent approximately 15% of all intracranial neoplasms and have an estimated prevalence of 17%[21, 44]. Many pituitary adenomas are discovered as asymptomatic incidentalomas without clinical significance and do not require treatment[25]. However, adenomas may present clinically with symptoms of hormonal hypo- or hypersecretion or with symptoms of tumour mass effect such as headaches and visual disturbance[35].

Hypopituitarism in pituitary adenoma patients is common. Hypopituitarism is known to cause significant morbidity across the various pituitary axes if left untreated. Adrenal insufficiency can be fatal and is associated with a poor quality of life as well as a reduced life expectancy, whilst growth hormone (GH) deficiency can cause cardiac dysfunction and psychiatric impairment [17, 19]. Sexual dysfunction, fertility and symptoms of hypothyroidism also contribute to morbidity in hypopituitarism. Long-term replacement hormone therapy to treat hypopituitarism can have an impact on quality of life[29].

The outcomes of endocrine function following transsphenoidal surgery for pituitary adenomas has been documented in the literature, yet remain unclear[2, 3, 6, 7, 11, 13–16, 22, 24, 26, 30, 31, 36, 39, 46]. The majority of such studies have been in relation to microscopic surgery and are rarely comprehensive in terms of individual hormone profiles. Outcomes for endoscopic transsphenoidal pituitary adenoma surgery are more limited and the numbers studied are often very small. The endoscopic approach has increased focus on the potential to maximise tumour resection and preserve normal pituitary gland, due to the improved field of view, better illumination, and enhancement of identification of critical neurovascular structures[27].

The aim of this study was to examine outcomes and predictive factors for both the improvement and worsening of pituitary endocrine function following endoscopic transsphenoidal surgery (ETSS) in a specialist pituitary centre.

Methods

A prospectively held pituitary database was retrospectively analysed for all patients undergoing ETSS for pituitary adenomas from May 2011 to May 2017. No microscopic transsphenoidal surgery was performed at our centre during this period. All operations were performed by a single consultant neurosurgeon at a specialist tertiary university teaching hospital following patient discussion in a pituitary multidisciplinary team meeting (MDT). Both functioning and non-functioning tumours were included in the study and pre-operative and postoperative endocrinological outcome was recorded. All assessments were carried out by a specialist endocrinologist prior to further review in a combined clinic. Paediatric patients under the age of 18 years old were excluded from the study. All patients were followed up in outpatient clinics for a minimum of 12 months.

Data for the following variables were collated: age at surgery; sex; clinical diagnosis; length of hospital stay; tumour classification (microadenoma/macroadenoma); maximum tumour diameter; other magnetic resonance imaging (MRI) features (e.g. suprasellar extension, cavernous sinus invasion); extent of resection; preoperative hormonal status; postoperative hormonal status; most recent follow-up and total follow-up duration. The axes assessed included the hypothalamo-pituitary-adrenal (HPA) axis, the thyroid (HPT) axis, the gonadal (HPG) axes, and posterior pituitary function (evidence of diabetes insipidus). Due to the complexity in dynamic assessment of the growth-hormone axis, it was not included in this study.

All patients planned for surgical intervention underwent high-resolution MRI with dedicated pituitary sequences prior to surgery. All imaging was reviewed to locate areas of normal pituitary gland tissue to guide preservation of functional gland during tumour resection, whilst aiming for gross total resection of tumour.

Any patient requiring preoperative hormonal replacement therapy for any one or more of the pituitary axes were defined as having a preoperative endocrine deficit. Patients on hormone replacement for other known reasons (e.g. thyroxine for primary hypothyroidism) were not included in this definition. If following surgery and during the follow-up period patients were able to cease replacement medications, it was said that patients had exhibited recovery of endocrine function within that axis. Patients who had to stop hormone replacement for other reasons (e.g. testosterone for rising PSA or drug reactions) were not included in this definition.

For those patients who were not requiring hormone therapy prior to surgery, yet developed the need for replacement postoperatively, these patients were described as having worsening of endocrine function in the specified axis. All patients had endocrine assessment by an endocrinologist at 6 weeks, 3 months, 6 months then annually thereafter. Hormonal status was defined at the most recent follow-up clinic according to defined biochemical criteria from basal +/- dynamic testing.

All patients with a normal steroid axis preoperatively underwent a 9am cortisol blood test on day 1 postoperatively. If the cortisol result was less than 400 nmol/L then patients were started on either hydrocortisone (all patients before July 2016) or prednisolone (all patients after July 2016) as per our local endocrine protocol[8]. All patients were then followed up at 6-weeks in the endocrine clinic where they underwent a short synacthen test (SST) to assess HPA axis function. If an appropriate response then the steroid replacement was stopped. Patients that were found to have regained normal HPA axis function at their 6-week follow-up SST were not considered as having postoperative endocrine dysfunction.

Statistical analysis was performed using IBM® SPSS Statistics 23.0. Independent and paired t-tests were used as necessary, whilst chi-squared tests were performed for nominal data. Significance was confirmed with a P-value of <0.05.

Results

Patient Demographics

A total of 145 consecutive patients underwent ETSS for pituitary adenomas. The median age of patients at time of surgery was 52 years (range 18 – 81 years). Of the 145 total patients in the cohort, 76 were female and 69 were male. The median follow-up for all patients is 56 months (range 21 – 92 months).

77 patients (53%) had non-functioning adenomas (NFA) and 68 patients (47%) had functioning adenomas. Of these functioning adenomas, 37 patients had a confirmed diagnosis of acromegaly, 28 patients had Cushing's disease, 2 patients had prolactinomas, and 1 patient had a TSH-secreting pituitary adenoma. On preoperative MRI scans 109 (75%) patients had macroadenomas, 33 (23%) had microadenomas, and 3 patients (2%) displayed no evidence of tumour (Cushing's disease based on biochemical tests and inferior petrosal sinus sampling).

The median length of hospital stay for patients postoperatively was 4 days (range 2 – 56 days). The median maximal tumour diameter (MTD) was 21mm (range 3 – 51mm) (Table 1.).

Endocrinological Outcome: All Patients

88 (61%) patients were eupituitary preoperatively (56 females and 32 males with a median age of 48 years old). Of these, 17 patients (19%) had new endocrine disturbance at most recent follow-up, whilst 71 patients remained eupituitary. The 17 patients that had new endocrine dysfunction were composed of 7 (41%) females versus 10 (59%) males which was statistically significant ($p = 0.04$). The median age of these patients was 45 versus the remaining patients with retained normal function having a median age of 51 ($p = 0.7$) (Table 2.).

The median MTD for patients with normal endocrine function preoperatively was 18mm. The median MTD for those patients who retained normal function postoperatively was 17.5mm, whereas the median MTD for patients who had a deterioration in endocrine function postoperatively was 21.5mm ($p = 0.25$).

Of the 57 patients (37 male, 20 female, median age 59) who were hypopituitary preoperatively (39%), 6 patients (11%) exhibited improved endocrine function across one or more axes postoperatively. Of the same group of patients, 9 (16%) developed further worsening of endocrine function. The group of 6 patients that displayed improved function were comprised of 3 males and 3 females, whilst the cohort that had worsened function was made up of 6 males and 3 females ($p = 0.55$). The median age of those patients that had improved function versus worsened was 61 and 57, respectively ($p = 0.4$).

The median MTD for patients with abnormal endocrine function preoperatively was 23.5mm versus 18mm for the patients with normal function ($p = 0.001$). Of the patients who had abnormal endocrine function preoperatively, the 6 patients who displayed improvement in pituitary function had an MTD of 26mm, whilst the 9 patients who had deterioration in function also had an MTD of 26mm.

Non-Functioning Adenomas

A total of 77 patients were operated on for NFAs. 47 patients were male and 30 were female. The median age of patients with NFAs was 56.5 years (range 24 – 81 years). The main presenting feature in the NFA cohort was 37 patients (48%) with deterioration in vision, 18 (23%) with headache, 16 (21%) with symptoms of hypopituitarism, and 6 patients (8%) had incidentally discovered tumours. The rate of gross total resection (GTR) based on post-operative MRI was 77%.

Preoperatively, 46 patients (60%) were hypopituitary and 31 patients (40%) were eupituitary. The median age for the hypopituitary patients was 59.5 verses 55 for the eupituitary patients ($p = 0.184$), and the median MTD for the hypopituitary group was 26.5mm versus 28mm for the eupituitary group ($p = 0.115$).

Of the eupituitary patients, 7 (23%) had worsening of endocrine function postoperatively, whilst in the hypopituitary group 8 patients (17%) had further new endocrine deficits. 5 patients (11%) who were hypopituitary demonstrated improved function postoperatively. The median age for the group with worsening function was 58 years versus 61 years for those who had improved endocrine function, whilst the median MTD for the deterioration

group was 28.5mm versus 29mm for the improvement group. There was no significant relationship between extent of tumour resection and endocrine outcome.

Functioning Adenomas

Of the 68 patients with functioning adenomas 46 were female and 22 were male with a median age of 42 years (range 18 – 79 years), and a median MTD of 12mm (range 3 – 34mm). 11 patients (16%) required new hormone replacement therapy across one or more axes postoperatively. These patients included 8 females and 3 females with a median age of 38, and MTD of 9mm. These were not significant risk factors in the functional adenoma group.

In the acromegaly cohort, 28 (76%) patients achieved biochemical remission, whilst for patients with Cushing's disease, 22 (79%) were in biochemical remission. The 2 patients with prolactinomas and the TSH-oma patient all achieved remission. Of the 11 patients with new pituitary deficits, 9 have achieved biochemical remission. There was no relationship between achieving biochemical remission and postoperative endocrine outcome.

Pituitary Axis Outcome

Preoperative deficit rates for each pituitary axis were recorded. 29 patients (20%) had HPA axis dysfunction, 39 patients (27%) had thyroid axis dysfunction, 11 males (16%) and 7 females (9%) had gonadal axis dysfunction, and one patient had preoperative diabetes insipidus. (Figure 1).

In total, 26 patients (18%) had worsening of endocrine function postoperatively across one or more axis. 19 patients (13%) had new HPA axis deterioration, 12 (8%) had new thyroid axis dysfunction, 8 males (11%) and 4 females (5%) had gonadal axis deterioration and 6 patients (4%) had new DI, (figure 2).

Of the 6 patients who exhibited improvement to normal endocrine function, 3 had HPA axis improvement, 2 in the thyroid axis, and 1 male with gonadal axis improvement. There was no improvement in the one patient with diabetes insipidus preoperatively (Figure 2).

The patients who had worsening of function across the HPA axis consisted of 13 males and 6 females (p=0.04), with a median age of 48 verses 53 for patients with stable outcome (p=0.3), and a median MTD of 23mm compared to 20mm (p=0.6). Decline of function in the thyroid axis was experienced in 7 males and 5 females (p=0.72), with a median age of 46 years verses 51 (p=0.24), and a median MTD of 19mm verses 21 (p=0.94).

New hypopituitarism in the male gonadal axis consisted of 8 males at a median age of 62 years verses 48 (p=0.02). These patients had a median MTD of 20mm verses 22mm (p=0.8). New deficits in the female gonadal axis was composed of 4 females at an average age of 55 verses 52. (p=0.48), with a median MTD of 18mm verses 21mm (p=0.42). For new diabetes insipidus postoperatively, there were 3 male patients and 3 females. These patients had a median age of 54 years verses 51 (p=0.8) and a median MTD of 19mm verse 21 (p=0.92). Risk factors for each axis are outlined in Table 3.

Discussion

Pituitary adenomas are common and often require surgical intervention due to the over secretion of hormones or the mass effect elicited on surrounding structures. Rates of improvement in pituitary function following surgery have varied across a host of microscopic surgical series ranging from 7.4 – 65%[2, 32, 36, 39, 46]. This wide range displays the variability between series in terms of recovery of pituitary function. Endocrine outcome often appears sporadic and unpredictable and therefore it can be very difficult to counsel patients prior to surgery.

There are a small number of studies investigating pituitary function following transsphenoidal surgery. Jahangiri et al. performed a large study looking at 305 operations for 282 patients with NFA over a 5-year period at a dedicated pituitary surgery centre[30]. 295 of the cases were performed microscopically and the remaining 10 endoscopically. 50% of their NFA patients had preoperative endocrine deficits. This cohort was statistically more likely to be older, male, and have larger adenomas. There were no predisposing factors to preoperative hypopituitarism in the NFA group in our series, despite tumour size being a significant predictor when looking at all patients (both functioning and NFA). The study quotes recovery rates at 6-months postoperatively of 49% in thyroid axis, 3% in HPA axis,

and 36% and 13% in the male and female gonadal axes, respectively. These numbers are much larger than the figures seen across our series, but highlight the large differences in outcome in comparison to other microscopic transsphenoidal surgery series. The rates of new deficits were in keeping with those in our series with 42 of their 305 patients (14%) displaying worsening of pituitary function postoperatively.

A study by Laws et al. in 2016 is one of the only purely endoscopic series documented in the literature[36]. They report a smaller cohort of 80 patients with the aim of providing a benchmark in endoscopic surgery for endocrine outcome with both functioning and NFA's included. The series quotes recovery rates of 7.4% of their 27 patients with preoperative hypopituitarism. Of their 53 eupituitary patients, 2 (3.8%) had impaired pituitary function at most recent follow-up, whilst 5 of the 27 patients (18.5%) with deficits prior to surgery had further impairment of function postoperatively. These are more comparable figures to the outcomes recorded in our series with 16% of our patients with documented deficits preoperatively having further impairment of function. However, we have seen a higher proportion (19%) of preoperative eupituitary patients develop new dysfunction in our series. The Laws et al. study did not look at predictive factors of outcome.

A study from 2018 by Harary et al. investigated gland volume in relation to endocrine outcome for ETSS, suggesting that recovery of function may occur in the months or years following surgery[26]. Their study looked specifically at endoscopically operated NFA patients. 56.9% of patients had preoperative endocrine deficits in at least one anterior pituitary axis with older age and larger tumour diameter being significant predictive factors. Larger MTD was also associated with hypopituitarism in our series. In terms of postoperative endocrine outcome, Harary et al. quote a complete normalisation rate of 37.4% and an improvement rate of 17.6% for their patients with preoperative hypopituitarism. These rates of improvement are greatly higher than both our series and the series by Laws et al. They also report new deficits in 37 (23.1%) patients which is more in keeping with our series.

The reasons for poor recovery of pituitary function following transsphenoidal surgery have been previously hypothesised. It may be due to irreversible damage to functioning glandular

tissue secondary to the mass effect of the tumour, or due to gland necrosis from the disruption of the vasculature of the portal vessels and pituitary stalk[2]. In the endoscopic era, improved visualisation may allow for a more radical resection and thus potentially could cause more disruption to residual functional pituitary gland. However, a recent international review by Wang et al. displays equivalency in outcomes between endoscopic and microscopic transsphenoidal surgery in pituitary adenoma surgery[45]. Additionally, the risk of new DI postoperatively has been reported to be more prevalent in ETSS[4].

The group of patients that were hypopituitary preoperatively had larger tumours than those patients with normal function and this was statistically significant (p=<0.001). We do not report any other predictive factors for preoperative hypopituitarism, whilst other papers have found that increased age and male sex may have an impact on preoperative endocrine deficits[26, 30].

We report an overall worsening in endocrine function of 18% across the whole cohort. Laws et al. documented that 10 (12.5%) of their 80-patient cohort developed new deficits following surgery (including 2 patients with permanent diabetes insipidus). In our cohort, males who had normal endocrine function preoperatively were more likely to develop new hypopituitarism postoperatively and this was statistically significant (p=0.04). There were no other predictors of worsening of endocrine function across the whole cohort, including tumour size. Males have been implicated to not do as well in terms of pituitary function in other studies including Jahangiri et al., although in their series males were more likely to be hypopituitary preoperatively.

The GTR rate for NFA's was 77% in our series. The Laws et al. and Harary et al. studies focusing on endocrine outcome do not quote a gross total resection rate for their endoscopic series, and thus it is not possible to draw comparisons here. When looking at other endoscopic surgery reports in the literature focusing on extent of resection in pituitary adenoma surgery, achievable GTR rates are reported as approximately 69% - 74%[1, 18, 37, 42]. It is possible that our institutes higher GTR rate may have impacted on postoperative endocrine function resulting in a higher rate of new hypopituitarism in comparison to the Laws et al. study.

In our functional adenoma group, we report a biochemical remission rate of 79% in the Cushing's disease patients and 76% in the acromegaly group. The rate of remission in the Cushing's disease patients is comparative to the documented literature with remission rates in purely endoscopic surgery reported ranging from 76% - 84%[9, 10, 12, 41, 43]. Our acromegaly cohort also achieves comparable remission rates to those previously reported for endoscopic surgery ranging from 46% - 75%[5, 23, 28, 33]. In this group, we recognise the limitation that for those patients with hypersecretory syndromes, we are generally aiming for hyposecretion postoperatively and therefore deficits may be more frequent with a potential more radical approach to surgery.

The most common preoperative endocrine deficit across the pituitary axes was that of the thyroid axis, with 39 patients of the 57 hypopituitary group requiring thyroxine therapy preoperatively. The HPA axis was deficient in 29 patients requiring steroid therapy preoperatively. The thyroid axis was also the most commonly affected axis preoperatively in a number of other documented studies in the literature and is consistent with the findings in our series [2, 26, 30, 36]. Harary et al. state that gonadotropes and thyrotropes are the cell types that are most susceptible to compression by tumour and thus are therefore more commonly associated with endocrine deficits. The most common deficits in their series preoperatively were hypothyroidism (52%), male hypogonadism (40%), and adrenal insufficiency (35%).

There is a well-recognised pattern of pituitary function loss in all causes of hypopituitarism, with the exception of lymphocytic hypophysitis. This often starts with GH deficiency, followed by gonadotrophins, then TSH, and finally ACTH. The higher proportion of patients with central hypothyroidism postoperatively in our series may relate to a testing and/or treatment bias. This is explained by the ease in measuring a thyroid-function test in comparison to dynamic GH stimulation tests, and the relative safety in prescribing thyroxine compared to testosterone or oestrogen. We define the need for hormone replacement therapy as per physician discretion rather than stringent biochemical thresholds.

In our series, males were more likely to develop a new deficit in pituitary function across the HPA axis (p=0.04), whilst older males were more likely to acquire new deficits than younger male across the male gonadal axis (p=0.02). Jahangiri and Harary et al. did not find any predictors for new postoperative deficits, although Hararay et al. stated that larger postoperative gland volume and female sex were associated with lower odds of having a new postoperative deficit.

The thorough review of preoperative MRI was of paramount importance for every patient in the series to identify normal pituitary gland. In our experience, there was concordance between imaging and intraoperative localisation of normal gland. This aided in the preservation of normal pituitary versus tumour. We also consider our MDT approach to be imperative throughout the patient journey and teamwork is vital. There is indeed room for teamwork in endonasal endoscopic surgery between a neurosurgeon and an ear, nose, and throat surgeon[38, 40]. However, we continue with an experienced single-surgeon approach in our unit and do not feel that this has impacted on the outcomes in this study.

There are no large studies comparing a thorough assessment of endocrine outcome between the two approaches by the same surgeon or at the same centre. One study suggests that transition from a full microscopic approach to an endoscopic approach elicited similar surgical outcomes in both cohorts, whilst the endoscopic approach offered the advantage of reduced hospital length of stay and duration of surgery[20]. Another study by Kim et al. states that endoscopic surgery was a safe approach in the hands of an experienced surgeon for NFAs, yet their standard hormonal outcomes were not changed in comparison to documented microscopic surgical series[34].

Conclusions

Endoscopic transsphenoidal surgery is an established technique for pituitary adenoma resection. Despite thorough radiological planning and improved visualisation, recovery of pituitary function remains limited, whilst new deficits can often occur. Males were more likely to develop new endocrine deficits in our series. Patients need appropriate counselling prior to surgery to manage expectations regarding endocrine outcome. Larger longer-term collaborative studies of endocrine outcome in endoscopic pituitary surgery are needed.

Figure 1. Bar chart showing preoperative endocrine deficit rates across the various pituitary axes for all patients.

Figure 2. Bar chart displaying postoperative endocrine outcomes across the various pituitary axes for all patients.

Table 1. Patient demographics and tumour characteristics

Age (years)	
Median (range)	52 (18 – 81)
Gender	
Male	69 (48%)
Female	76 (52%)
Follow-up (months)	
Median (range)	56 (21 – 92)
Diagnosis	
Non-functioning adenoma	77 (53%)
Acromegaly	37 (26%)
Cushing's disease	28 (19%)
Prolactinoma	2 (1%)
TSH-secreting adenoma	1 (1%)
Maximal tumour diameter (mm)	
Median (range)	21 (3 – 51)
Tumour characteristics	
Macroadenoma	109 (75%)
Microadenoma	33 (23%)
Not visualised on imaging	3 (2%)

Table 2. Endocrinological outcome

Endocrine function preoperatively	
Normal	88 (61%)
Hypopituitary	57 (39%)
Endocrine function postoperatively (Normal preoperatively)	
Stable	71 (81%)
Worsened	17 (19%)
Endocrine function postoperatively (Hypopituitary preoperatively)	
Stable	42 (74%)
Worsened	9 (16%)
Improved	6 (11%)
Endocrine function postoperatively (Overall)	
Stable	113 (78%)
Worsened	26 (18%)
Improved	6 (11%)

Table 3. Results of statistical analysis for predictors of new hypopituitarism postoperatively across pituitary axes

Variable	HPA	Thyroid	Male gonadal	Female gonadal	Diabetes insipidus
Male sex	**0.04**	0.72	N/A	N/A	0.94
Age	0.3	0.24	**0.02**	0.48	0.8
Tumour size	0.6	0.9	0.8	0.4	0.84

*Statistically significant results of $p<0.05$ are listed in bold.

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Conflict of Interest - All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical Approval – Ethical approval was not required for this study.

Consent – For this type of study, formal consent is not required.

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