



Intraoperative parathyroid hormone monitoring in primary hyperparathyroidism; resolving controversies and debates

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Abstract

Intraoperative parathyroid hormone monitoring (IPM) has been increasingly considered as a valuable adjunct in surgery for primary hyperparathyroidism (PHPT). In view of the attributed extra cost and time, its routine use has been debated. Similarly, controversies have encompassed various aspects of IPM implementation. This article will display the up to date evidence relating to IPM use in different clinical scenarios, discuss the pros and cons of its controversial technical aspects, highlight the relevant recommendations and identify areas which need further research. The aim of this review is to help surgeons deciding whether IPM is needed in a particular PHPT patient and what is the optimal protocol to be followed in that patient.

Keywords: Intraoperative parathyroid hormone, Primary hyperparathyroidism, Parathyroidectomy

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Introduction

Surgery has been agreed as the definitive management for primary hyperparathyroidism (PHPT), however, the optimal surgical plan has usually been challenging. Such challenge stems primarily from the fact that, although, anatomically, four glands exist in 84% of individuals (1); PHPT is caused by pathology of single gland in up to 88% of cases (2). Additionally, although classic bilateral neck exploration (BNE) has been the standard of care for decades, its appeal and indications have been progressively decreasing in the era of minimally invasive parathyroidectomy (MIP) for what the latter has of many advantages; including minimal incision, minimal dissections and short hospital stays. This brings two requirements for optimal surgical management; 1) Confirmation of which gland is the culprit and should therefore be removed and 2) Exclusion of any possibility of additional hyper-functioning glands.

Despite the development of many perioperative tools, most importantly imaging localization studies, none has achieved 100% accuracy of localization. Combined ultrasound (US) and MIBI/SPECT have achieved an overall accuracy of 91% for preoperative localization of single gland disease (SGD) in some reports (3). Radio-guided surgery has achieved only 83% accuracy of localization in surgery for PHPT (4). Additionally, frozen section examination has not proved much usefulness in operative decision making because of its inconsistent diagnostic accuracy (5). By contrast, intraoperative parathyroid hor-

mone (ioPTH) monitoring (IPM) has been demonstrated to have an accuracy of up to 98.5% (4). Monitoring ioPTH has improved the surgical success rates of PHPT from 90%-95% to 100% in some series (6,7). However, since its advent, controversies have been evolving about the prudence of its use in various PHPT clinical scenarios, considering its inherent extra time and cost involved. Similarly, the optimal ioPTH protocol to be used has been a subject of considerable debate; what baseline should be considered? What drop should be viewed as satisfactory? And when decision should be made? Furthermore, should PTH be measured as “intact” or “whole”? In theatres or in the central laboratory?

Materials and Methods

In this review, we summarize the published results of these controversial and debatable issues and display the ongoing arguments with a view to resolve uncertainties and highlight recommendations that would help in better utilization of this intraoperative adjunct and subsequent optimization of the surgical plan for PHPT patients.

In order to approach this, we reviewed the literature from 2005 to 2015, by using the search terms “intraoperative parathyroid hormone monitoring” and “rapid parathyroid assay”. For this review, we used a variety of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). Eligible articles were those concerned with ioPTH debates of concern. Additional articles were extracted from the

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■ Implication for health policy/practice/research/ medical education

Since its advent, the use of intraoperative parathyroid hormone monitoring (IPM) has been a subject of continuous debates. The present article aims to guide surgeons tailoring IPM use to individual clinical scenarios and specific health care settings, through summarizing the state of art pertinent knowledge and highlighting the relevant recommendations. Additionally, the IPM- related arguments are discussed, with a trial to resolve some controversies, while gray-zone areas are emphasized for future research.

eligible article bibliographies for their relevance. A total of 77 articles were therefore used to construct this narrative.

When to use?

In this context, it is important to first define various possible ioPTH results (Table 1). In the table, the definition of “adequate” or “inadequate” decline varies according to ioPTH protocol followed (Table 2). Cure is usually defined when the patient remains eucalcemic for 6 months after surgery, while persistent disease is defined if hypercalcemia is encountered in the six months postoperatively.

Preoperative localization studies

Much of the debate about when to use IPM in surgery for PHPT is contributed by the results of preoperative localization studies in terms of addressing two points 1) How probable the disease would be multi-glandular (MGD) and 2) How IPM would change decision in terms of a. value added accuracy on account of true negative (TN) results and b. unnecessary BNEs caused by false negative (FN) results.

The term *equivocal* imaging has been coined if localization studies are formally reported as “negative” while remain suspicious by either the surgeon or the radiographer. In such scenario, ioPTH has significantly increased the like-

lihood of the procedure to be concluded as focused (8), supporting, therefore, its use in such cases.

In PHPT patients with *single positive* preoperative localization study, the risk of MGD has been reported by Sebag et al (9) to be 3.6%; justifying, therefore, the use of IPM in association with MIP. The latter is in agreement with Barczynski et al (10) who have reported an IPM value added accuracy of 18.9% in such cases. Stalberg et al (11), however, opined against the use of IPM if MIBI was unequivocally localizing; since they have documented only 1% value added accuracy at the expense of 9% unnecessary BNEs if IPM results have been used to make the operative decision. Again, the later opinion was subsequently challenged by Gill et al who have demonstrated failure of MIBI scan alone to predict MGD in 73% of time and the significantly improved operative success rate with IPM (12).

The inadequate accuracy of a single localizing study has prompted surgeons to use combination of imaging localization studies. Ultrasonography and scintigraphy have long been the most commonly used localizing studies on account of acceptable performance, cost and availability. The results of preoperative studies may match; either concordantly localizing or non localizing, or may contradict each other.

As low as 0% risk of MGD has been reported in association with *concordantly localized* PHPT (9); thus, giving more confidence for surgically addressing the culprit parathyroid by MIP and causing, however, more debate about whether IPM is indicated. On the one hand, retrospective studies from Hacıyanlı et al (13), Thakur et al (14) and Mownah et al (15) have reported excellent cure rates in concordantly localized cases without the use of ioPTH; suggesting, therefore, eliminating its use in such cases, in view of time and cost effectiveness. On the other hand, in Barczynski et al cohort of 260 PHPT patients with preoperative imaging concordantly suggestive of solitary adeno-

Table 1. Definitions of possible ioPTH results

Results	ioPTH decline	Outcome	
		Pathological	Clinical
True-positive	Adequate ioPTH decline	All pathological glands were removed	Disease cured
False-positive	Adequate ioPTH decline	Not all pathological glands were removed	Disease persisted
True-negative	Failure of ioPTH to decline adequately	Not all pathological glands were removed	Disease persisted
False- negative	Failure of ioPTH to decline adequately	All pathological glands were removed	Disease cured

Table 2. Different ioPTH protocols

Baseline	Time	PTH decline	Percentage of false results		Reference
			FP	FN	
Highest	5	≥50%	0.6	11	(54,67)
Highest	10	≥50%	0.4-0.9	2.3-2.6	Miami (16,54)
Highest	10	≥50% and within normal (≤65 pg/mL)	0.4	24	(51,54)
Highest	10	≥50% and below pre-incision	0.6	6	(29,54)
Highest	20	≥50% and/or within normal and/or ≥7.5 ng/L lower than T10	0	16.2	Rome (16,68)
Pre-incision	10	≥50%	0.3-0.4	7.3-16	Vienna (16,54,65)
Pre-excision	10	≥50%	0.6	15	(54,69)
None	15	Low normal (≤35 pg/mL)	0	35	Halle (16,65)

Abbreviations: FP, False positive; FN, False negative.

ma, IPM has picked 8 out of nine MGD cases; contributing a significant value of 3.1% in the reported overall success rate (99.6%) (16). In the latter study, consideration of delayed post-excisional values (15 and 20 minutes) has caused no necks to be unnecessarily explored. Consistently with the later study, in their retrospective analysis of 338 concordantly localized single gland PHPT, Riss et al have found that abstaining from IPM would have significantly raised the rate of persistent disease from 0.9% to 5.0% (17). Whether to employ IPM in PHPT patients with single unequivocally localizing study or two concordantly localizing studies remains highly debatable and depends largely on surgeon experience and discussion with the patients.

The results of preoperative imaging could occasionally, however, be *non-matching or discordant*. Three main patterns of discordance have been recognized by Smith et al, MIBI+/US-, MIBI-/US+ and contradictory MIBI/US; in which IPM has been reported to change the operative decision in 13%, 22% and 62% of cases respectively, leading to an overall success rate of 97% in this group of patients (18). Since the risk of MGD is known to be higher in MIBI -ve versus MIBI +ve cases, more MGD cases have been reported among patients with localizing US than localizing MIBI (36.2% vs 12%) (19,20). In the latter studies, the value added accuracy of IPM was notably and expectedly higher in MIBI-ve/US+ve than in MIBI+ve/US -ve cases (26.3% and 10% respectively) (19,20). Given the relatively high risk of MGD and the considerable value added by IPM in discordant cases, its use in such cases is therefore preferred.

On another perspective, preoperative imaging could be *non localizing or negative*, in which case the reported MGD risk is high (31.6%) (9) and basically the surgeon has no clue about which gland should be first explored; BNE is therefore indicated, another IPM debate turns up here.

Type of surgery

MIP versus BNE

On the one hand, despite being decreasingly indicated in the era of MIP, BNE has still been used as an initial surgery for PHPT patients with non informative localization studies or as an extension to initially focused approach in case of intraoperatively picked MGD. In those patients, in whom the neck is bilaterally explored by experienced surgeon the value of IPM has been questioned if 4 glands have been visualized (21). Some surgeons, however, have recommended using a post excision ioPTH measurement to intraoperatively pick possible “ectopic” or “supernumerary” which are potential sources of recurrence (22) or to assure the adequacy of resection (23). A similar debate has, on the other hand, been raised if MIP has been employed, since a satisfactory success rate of 98% has been reported without IPM (24); discouraging, therefore, its routine use. Consequently, a selective approach of not using IPM in concordantly localized PHPT has also been suggested to cut costs (25) or time (26). Multiple comparative studies

have, however, clearly demonstrated significantly higher cure rate in IPM guided versus non-guided MIP (97%-100% vs 90%-93% respectively) (6,7,27). To conclude, routine use of IPM has been recommended for all PHPT patients, especially those undergoing MIPs (28).

Initial versus reoperative surgery

Monitoring ioPTH in *initial parathyroidectomy* has been demonstrated to improve cure rate (18), though, admittedly the cure rate for such cases has been reported to be high even without IPM (24). On the contrary, *recurrent PHPT* represents a consistently challenging situation in which surgeons usually tend to use every possible adjunct to optimize the chance for cure. In their comparative study, Irvin et al (29) have demonstrated that employing IPM improved the success rate of reoperative parathyroidectomy from 76% to 94%. Such IPM-attributed success rate has latter been confirmed by Parikh et al (30). Conversely, however, Sebag et al (31) have shown that the IPM-attributed improvement of success rate of reoperative parathyroidectomy was not significant. Keeping in mind that subsequent neck entry is undoubtedly potentially more hazardous than the first time, and admitting the IPM demonstrated ability to define cure, its use would therefore be prudent for all reoperative PHPT patients (32).

How to use it?

What type of ioPTH decline?

Early report from Chapuis et al (33) required ioPTH to drop to a value within the normal range. However, subsequent reports have demonstrated up to 75% failure rate of this criterion when solely used for prediction of postoperative normocalcemia (34). An intraoperative drop of PTH to within normal range has not also been found to correlate with cure from PHPT (35). Such criterion is somewhat troublesome in itself, since up to 14% of PHPT patients may have normal preoperative PTH level; a fact that prompted investigators to require a certain percentage to ioPTH drop rather than a drop to within normal range. However, ioPTH drop by 50% but not to normal level has been found to be associated with 19 times greater likelihood of surgical failure than a drop by 50% and to normal (36); a (dual criterion), that requires ioPTH to drop both by percent and to normal, has therefore been suggested. Expectedly, such hardening of the cure criterion has been found to be associated with higher operative success rate by minimizing the false positive (FP) results. However, the latter would come at the expense of more unnecessary BNEs, brought by the elevated FNs. In their retrospective study, Carneiro et al (37) have not found a significantly higher recurrence rate among those having their ioPTH dropped by 50% and still above normal range, compared to dropped by 50% and to within normal range. Additionally, despite having a higher incidence of postoperatively elevated PTH, majority of patients in the former group maintained postoperative eucalcemia i.e. cure. In their comparative study of (percent drop criterion) versus

(dual criteria), Sugg et al (38) have demonstrated higher sensitivity of the former in SGD and the latter in MGD. Conclusively, therefore, based on preoperative localization studies and biochemical profile, it is reasonable to employ percent drop criterion if SGD is suspected and/or in cases of normo-parathyroid PHPT (39) and to add (the drop to within normal) requirement if MGD is suspected.

How low should we go?

If the (percent drop) is opted for IPM, it is important to determine what percentage ioPTH drops would be accepted to predict cure. A 50% drop (either solely or in combination with drop to normal range) has been used in most literature. However, greater ioPTH drops (e.g. by 75% or 80%) have been required by some surgeons with the intent of reducing the likelihood of FP results (40,41). Requiring greater percent drops is another approach to hardening the cure criteria, which admittedly would increase the validity of IPM in PHPT; however, this would inevitably increase the frequency of unnecessary BNEs. Therefore, greater ioPTH drops should be required on selective basis; PHPT patients 1) suspected to have MGD (42), which may have resulted in failed surgery if not properly addressed (43) or 2) had their surgery as BNE, as hardening the cure criterion in such situation would not entail any additional morbidity; rather, it is important to assure surgical adequacy (23).

Which baseline?

Subsequent to determining what percentage decline would be accepted, it is also important to set the baseline PTH level against which post excision values would be compared. Kantora et al (44) suggested the use of *work-up* PTH (wPTH) as the baseline, since this would have resulted in an equal number of FP results while maintaining the same accuracy, when compared to other proposed baselines. On account of the wide PTH fluctuation, the use of such PTH has been discouraged (45), while using a pre-incision measurement has been adopted by many authors (6,46).

When considering *pre-incision* measurement for baseline value, most literature tends not to mention the exact timing of withdrawing the blood samples in relation to anesthetic induction; some authors, however, clearly stated “before induction” (47) or “after induction” (48); another controversy, hence, turns up. In fact, the latter controversy has gained its importance, from recent reports of PTH rise in relation to anesthetic technique, a point that raised concern that induction-related effect on PTH kinetics may lead to an inappropriately set PTH baseline, which could potentially mislead subsequent interpretation of intraoperative result. Hong et al (49) have recommended that a pre-incision sampling should be prior to induction to avoid incorrect operative decision based on the deceptively elevated post-induction value. On the other hand, Grabutt et al (50) have recently demonstrated a significantly higher ioPTH overall accuracy when considering post-induction vs pre-induction pre-incision baselines.

A probable explanation to this apparent controversy is that the former study (49) has restricted the analysis of anesthesia related IPM performance to MGD cases, in which stricter protocol is required i.e. incorporating the deceptively higher post-induction PTH value would have led to a false satisfactory PTH percent decline being encountered at 10 minutes post-excision; therefore, inappropriately terminating the procedure. If a pre-incision level is to be considered a baseline, a prudent approach would therefore be to use the post-induction value except if MGD is suspected, in which case the lower pre-induction value would be preferably taken into consideration, as another approach to hardening the cure criteria. Another issue has been argued to probably confound the accuracy of the pre-incision measurement as a baseline; that is a rise of PTH level occasionally observed prior to gland excision (PTH spike). Such rise, in fact, is spurious since it does not result from an exaggeration of function of the overactive gland; rather, it represents a momentary burst of PTH into the blood stream secondary to gland manipulation. Yet, recognizing such spikes is clinically important since they may not allow the PTH level to decay satisfactorily by the due time after the pre-incision baseline; hence, a negative result could be incorrectly considered (i.e. FN), potentially leading to unnecessary BNEs (46,51).

Some authors have therefore preferred a *pre-excision*, rather than pre-incision, timing to withdraw a sample for a baseline value, while securing the possibility of picking up a probable spike (52). However, other authors have denied the detection of any such rise (53). Moreover, a significant drop at the pre-excision time point has been reported in other authors' experience; probably due to early inadvertent devascularization of the gland (54). In the latter case, a pre-excision sample would already have a deceptively reduced PTH level, which again if solely considered as a baseline, would subsequently lead to an adequate PTH decline to be incorrectly appreciated as inadequate (i.e. FN).

Conclusively, therefore, taking the baseline as the *highest* of pre incision/pre excision values, as initially proposed by Irvin et al (55), would reasonably achieve a better accuracy (98%), through minimizing the FNs; by allowing to appropriately consider a probable manipulation-induced PTH spike as a baseline (in which case a pre-excision value is considered) and by avoiding a probable devascularization induced PTH drop to be inappropriately considered as a baseline (in which case a pre-incision value is considered).

Lastly, not only the baseline has been recommended to be the higher among the pre-excision values, but also it has been allowed to be re-set to “*the 5-minute post-excision*” value if the latter demonstrated a rise, relative to the preceding readings. The latter approach “Wisconsin rule” has been reported to result in 100% cure rate among such cases (56).

When to decide?

Many time points have been used for ioPTH measure-

ment; as short as 3 minute post-excision (42) and as long as 30 minutes post excision (57). The role of IPM in assuring adequacy of resection in surgery for PHPT has its basis from the physiological fact that PTH has short half-life; 5 minutes on the average (58). Most authors, therefore, tend to test the ioPTH at 5 minutes after the pre-set baseline. Decision, nevertheless, is usually made based on 10 minutes sampling; giving few additional minutes to compensate for any possible confounders of ioPTH kinetics e.g. adenoma weight, vitamin D status (59) and body mass index (60). Other authors, however, have used a (12 minute) time point for their decision on account of the reported 4 to 10 minutes PTH half-life (26). Continued monitoring to 15 minutes after gland excision has been recommended in PHPT patients in whom slower PTH decline is anticipated (e.g. mild PHPT, chronic renal insufficiency) to avoid unnecessary BNEs resulting from FN (61,62). Other authors also used 15 minute measurement so as to reduce possible failures resulting from MGD missed by a FP ioPTH test at the 5 or 10 minute time points (63). Data from Proctor et al (34), however, failed to demonstrate any significant difference in the success rate when comparing 15 minute versus 10 minute measurements. Moreover, Calo et al (64) have reported that extending monitoring to 20 minutes, while increasing the operative time only modestly, would minimize the possibility of unnecessary BNEs. A 30 minute measurement has also been recommended in suspected MGD to ensure the operative success (42). Conclusively, longer waiting time for intraoperative decision making is recommended if MGD is suspected to avoid failure resulting from possible FP in a preceding measurement, or if slow PTH decay is expected to avoid unnecessary BNE resulting from possibly FN result.

Which protocol?

Varying combinations of the aforementioned debatable parameters have been used to formulate “protocols” or “criteria” to be followed in IPM (Table 1). Barczynski et al (16) and Carneiro et al (54) have evaluated these criteria and came to the conclusion that Miami criterion achieved the best overall accuracy, in terms of balancing FP rate (i.e. high specificity or avoiding missed adenomas) and FN rate (i.e. high sensitivity or avoiding unnecessary BNEs). However, some important issues need to be considered in the context of selecting the most appropriate criterion for a particular patient

A. Whether the disease is suspected to be multi-glandular: since BNE is usually planned in this situation, specificity issues become more important in order to minimize the risk of persistence, while sensitivity become less important since the neck is already bilaterally opened; hence the prudence of opting criteria with least or no FPs (e.g. Rome/Halle). Riss et al (65), however, have opined that a strictly defined baseline would improve the intraoperative diagnosis of MGD, hence the superiority of Vienna criterion in such cases.

B. Whether surgery is reoperative: The most important consideration in this situation is to minimize the chance

of subsequent, consequently hazardous neck entry; hence the need for stringent criterion to optimize the chance of cure; those with least FP i.e. entailing a “drop to within normal” component (32).

C. Whether a “spike” has been observed intraoperatively: a manipulation-induced rise of ioPTH has been detected in up to 12% of surgeries for PHPT. A pre-incision-based protocol (e.g. Vienna) has been observed by Riss et al (66) to elevate the risk of FN results in such cases; hence, better avoided; Miami protocol has been recommended instead.

What to measure?

Two main types of PTH assays have been recognized; intact and whole PTH assays. Intact PTH assay, also known as second generation assay, react not only with bio-active 1-84 PTH fragment, but also with non-active large carboxyl terminal PTH fragments, mainly 7-84 fragment. Whole PTH or third generation assay, on the other hand, exclusively react with the whole PTH molecule (1-84 fragment) (70). Yamashita et al (71) have demonstrated a slower intraoperative decline of intact versus whole PTH assays after adenectomy for PHPT; probably caused by longer half-life of 7-84 fragment. Such findings raised concern that the cross reactivity of intact PTH assay with the non-biologically active, yet slowly metabolized 7-84 fragment, may cause the PTH measurement at the 10 minute time point not to decline satisfactorily, resulting therefore in a FN result. While assays measuring whole, rather than intact, PTH have been clearly recommended for IPM in renal HPT surgery (72), it remains to be determined, however, whether the use of either assay would make a difference in PHPT surgery.

Which vascular access?

Some controversy has been raised concerning which vascular line should be used to withdraw blood samples for PTH measuring. In their study, Urquhart et al (73) found no significant difference in baseline and 10 minute post-excision PTH between arterial and venous samples. Subsequently, Abdel-Misih and colleagues (74) demonstrated that validity of the assay was not significantly altered by central versus peripheral venous sampling. Moreover, if the peripheral vein was no longer functioning, shifting to central venous sampling did not compromise the predictive value of IPM. Hence, for the purpose of IPM, arterial or venous lines, whether central or peripheral, can be safely used for blood sampling.

Where to measure?

Quick PTH assays used for measuring PTH intraoperatively were traditionally placed in the hospital central laboratories (CLs) where biochemists work, quite far from the site of the patient care. Measuring PTH near the site of the patient care (Point of Care Testing or PoCT) has recently gained much interest, which raised concern about its measurement accuracy, time and cost effectiveness in comparison with CL settings. In a comparative study by Terris group (75,76), PTH measured in the PoCT setting

showed an excellent correlation with results obtained from CL. In addition, PoCT setting has been demonstrated to have a time edge over the CL setting; saving, therefore, time for the already extra-time consuming IPM guided surgery (76,77). Cost effectiveness, however, has been controversial. In their cost effectiveness comparison, O'connell et al (77) have demonstrated the cost effectiveness of the CL setting, taking into account the more expensive equipment, reagents and dedicated OR technician needed for PoCT measurement of PTH. On account of PoCT attributed reduction of the operating time, Terris et al (75), on the contrary, concluded that the PoCT setting additionally had a cost reducing privilege. In the latter study, however, the "time is money" concept is assuming that ORs have been running at 100% efficiency. Conclusively, the current state of knowledge cannot recommend for or against the setting to be used for ioPTH and further prospectively designed comparative studies are needed to provide adequate evidence.

Summary

Guiding MIP by IPM is highly recommended for PHPT patients with *equivocal or discordant* imaging. If the disease is preoperatively localized through *unequivocal MIBI* scan or *concordant MIBI/US*, the use of IPM in guiding MIP is generally preferred, although this depends primarily on surgeon practice/experience and relevant discussion with the patients. In PHPT operated through *BNE*, the use of IPM is controversial if four glands have been intraoperatively visualized. For *reoperative* cases, every effort, including IPM use, should be employed to optimize the outcome.

Reduction of ioPTH by 50% at 10 minutes post-excision time point is generally used by most surgeons, on account of having the best balance between minimizing unnecessary explorations (FN) and minimizing failures (FP). Adding a drop to within *normal* range, requiring drop by *greater percent* and waiting *longer time* for decision making are all strategies meant to make the cure criteria more strict, and should be employed selectively, mainly in cases in which MGD is suspected. Taking the highest PTH level attained intraoperatively as a *baseline* has been shown to have the highest success rate and should therefore be employed.

Arterial or venous *samples*, drawn from peripheral or central lines can be used for ioPTH measurement. Measuring *whole* PTH is theoretically advantageous over measuring *intact* PTH; however, whether this would significantly impact results of PHPT surgery needs prospectively designed comparative studies. In comparison with *CL* setting, measuring PTH through *in-theatre* setting is accurate, time effective and cost effective if theatres are run at full efficiency.

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Author's contribution

MSS is the single author of the manuscript.

Conflicts of interest

Author declares no conflict of interest.

Ethical considerations

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