The Synergism of Somatostatin, Melatonin, Vitamins Prolactin and Estrogen Inhibitors Increased Survival, Objective Response and Performance Status In 297 Cases of Breast Cancer

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Abstract

Background: Breast cancer is still the leading cause of death in women world-wide.

Study question: Our purpose is to improve survival, objective response and quality of life with a non-toxic biological therapy.

Study design: The DBM (Di Bella Method) with MLT (Melatonin), Retinoids, solubilized in vitamin E, D3, and C, Folates, proteoglycans and calcium, has a differentiating, cytostatic, anti-angiogenic, immune-modulating, factorially synergic effect, simultaneously reinforcing the functions which physiology considers to be essential for life. With Somatostatin/Octreotide, prolactin and estrogen inhibitors, DBM has an antiproliferative, antiangiogenic and antimetastatic effect. These molecules govern negatively pituitary secretions like GH-PRL, whose mitogenic properties are enhanced by the combination of ovarian hormones such as estrogen. The negative regulation of GH extends to IGF-1, EGF (Epidermal Growth Factor), VEGF (Vascular Endothelial Growth Factor), and GH-dependent growth factors. The DBM (Di Bella Method) uses minimal metronomic apoptotic, non-cytotoxic and non-mutagenic doses of cyclophosphamide. The tolerability of which is enhanced by MLT and by the vitamins included in the DBM. We report a retrospective observational study with 5-year follow-up, carried out on 297 patients affected by breast cancer and treated with the Di Bella Method biological therapy.

Results and conclusion: complete and stable objective responses without cytolytic chemotherapy, in some cases even without surgery or radiotherapy, with a generalized improvement in quality of life and no significant and/or prolonged toxicity. The most important 5-year survival rate was 69.4% at stage IV cancer versus 26.3% reported by the National Cancer Institute.

Keywords: Breast cancer; Somatostatin; Retinoids; Prolactin' inhibitors; Melatonin

Introduction

Breast cancer is usually treated with surgery, which may be associated singly or in various forms with chemotherapy, estrogen block, radiotherapy and selective monoclonal antibodies for epidermal growth factor receptors (EGFR). Breast cancer is the most frequent form of cancer in women and the leading cause of death in women.

Numerous *in vitro* studies carried out on various cell lines have demonstrated the marked anticancer effects of DBM components', clarifying the mechanisms of action and paving the way to the achievement of encouraging results in clinical practice [1-16]. We report a retrospective observational study with 5-year follow-up, carried out on 297 patients affected by breast cancer and treated with the Di Bella Method biological therapy.

Materials and Methods

Enrolment criteria of 297 cases of breast cancer

Only patients with a histological diagnosis of breast cancer and disease characteristics that could be measured according to the Response Evaluation Criteria in Solid Tumors (RECIST) were enrolled [17].

The study included 297 patients suffering from breast cancer and each one of these were subject to blood chemistry, hystological and immunoistocheminal tests expected for this pathology.

The patients were divided into three groups according to the stage of their breast cancer at the start of the treatment.

- The first group, Regional Breast Cancer, consisted of patients whose tumor was limited to a single anatomical district.

- The second group, Local Breast Cancer, consisted of patients whose tumor had spread to the lymph nodes.

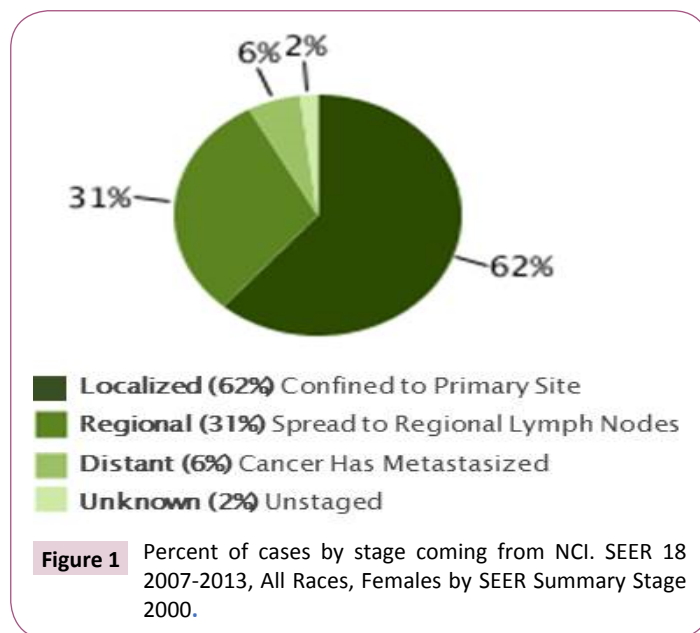- The third group, Advanced Breast Cancer, consisted of patients with metastases.

The DBM was administered in one of the following forms:

1) First-line treatment, for patients who had previously undergone only surgery

2) Second-line treatment, for patients who had previously followed traditional adjuvant oncological protocols for a maximum of 6 months.

3) Last-resort treatment, for patients with stage IV cancer who had undergone repeated multi-chemo/radiotherapy treatments for more than a year.

The objective clinical responses were statistically classified in three groups: REGRESSION, STABILITY, PROGRESSION. Among the effects of the DBM, toxicity and quality of life were also evaluated. RELATIVE survival was also assessed, i.e. the percentage of patients still alive 5 years after the diagnosis of breast cancer, compared to the average survival of a group of women of the same age, from the same geographical area, and in good health. This last index was then compared with the results published by the National Cancer Institute (**Figure 1** statistical analysis of cases by stage), the leading American agency for the collection and management of data relative to cancer patients **(Figure 1)**.

Enrolment criteria 40 cases of breast cancer-Sub-analysis

A sub-analysis is setup with only 40 cases, treated with DBM in Exclusive Therapy. In the present study only patients with an Eastern Cooperative Oncology Group (ECOG) status 2 were diagnosed with histologic diagnosis of breast cancer and measurable disease characteristics in accordance with the Solid Tumors Response Evaluation Criteria (RECIST) [17]. Another requirement for enrollment was the absence of standard therapeutic regimens (surgical interventions, polycotherotherapy, radionuclide therapy, monoclonal antibodies), and to accept, with

Figure 1 Percent of cases by stage coming from NCI. SEER 18 2007-2013, All Races, Females by SEER Summary Stage 2000.

prior informed consent, the administration of biological therapy as a first-line treatment. The 40 cases are classified according to the type of response received during the observation period (according to the RECIST criteria):

- OVERALL RESPONSE=CR(Complete) - PR(Partial) – SD (Stable Disease)-PD (Progressive Disease)

- DFS=Disease-Free Survival

- PFS=Progression-Free Survival

Therapeutic treatment

All the patients received a daily combination of Somatostatin/octreotide, Melatonin, Retinoids solubilized in Alpha Tocopherol Acetate, dopaminergic agonists, estrogen inhibitors and minimal doses of cyclophosphamide.

These components were administered as follows:

Gradual oral dosages of:

- Retinoic acid, [ATRA-All Trans Retinoc Acid] 0.25 gr (488.372 IU), + axerophthol palmitate 0.25 gr (909000 IU) + Betacarotene 1 gr (3 334 000 IU) solubilized in alpha tocopherol acetate 500 gr, stoichiometric ratio 1:1:4:2)(1×106 IU); fasting, once a day for seven days, then twice a day for 7 days; from week 3 for the rest of the treatment period, 3 times a day, orally.

- Dihydrotachysterol 10 drops with each administration of retinoids (15 200 IU), 30 drops a day.

- Somatostatin at gradually increasing doses (1 mg for the first 7 days, increasing 1 mg for week, to 3 mg at day 21).

- Tetracosactide acetate (0.25 mg) added every other day to the syringe with somatostatin, compatibly with pressure and glycemia.

- Octreotide long-acting release (LAR) (20 mg) every 3 weeks, intramuscular.

- Triptoreline analogues LH- FSH (**Follicle-Stimulating Hormone**) 3.75 mg every 4 weeks, intramuscular.

- Melatonin hydrosolubilized in hydrogen bond with Adenosinae, stabilized with Glycine in 5 mg tablets, orally: 3 tabs (15 mg) at midday and in the evening at meals plus 10 tabs (50 mg) before going to bed (average total daily dose=80 mg).

- Cabergoline orally with the main meal, 1 mg (equal to 1\2 tablet) twice a week.

- Bromocriptine (2.5 mg) orally, half a tablet morning and evening.

- Anastrozole 1 mg tablet.

- Cyclophosphamide (50-100 mg) orally, variable dosage: start with 1 tablet with the main meal for 1 week, then 1 tablet in the morning and the evening one day and the next day just in the evening.

- Hydroxyurea 500-1000 mg/day; replace with Endoxan if not tolerated or if cerebral metastases are present due to the ability of hydroxyurea to pass through the blood-brain barrier.

- Ascorbic Acid (Vit C) orally: 1/2 teaspoon (4 gr) in a glass of water during the midday and evening meals together with:

- Calcium lactate gluconate +calcium carbonate equal to 1000 mg of calcium, half a sachet in the same glass.

- Chondroitin sulfate (500 mg) one tablet in the morning, at midday and in the evening, with meals.

- Ferrous Sulphate (329,7 mg) one tablet 2 – 3 times a week, depending on sideremia and hemochrome values.

- Calcium levofolinate one 22 mg tablet a day.

- Ursodeoxycholic acid (UDCA) 300 mg to contrast the choleretic and cholagog inhibition of the SST (Somatostatin) and/or octreotide.

- **Taurine** 1500-2000 mg/day when necessary, to improve cardiac and hepatic function.

Therapeutic treatment has been administered continuously, even after complete remission, and its effects are appropriately and consistently monitored over time, through chemotherapy and with the aid of instrumental diagnostics.

As long as the tumor is in progress, the therapy should be given without any variation, or with the possible changes that may be made on the course, and only after obtaining complete remission over time can be appropriately reduced in a very gradual manner until reaching a "maintenance" therapeutic threshold, also calibrated on the basis of individual individual staging and histological features. Somatostatin was administered subcutaneously by means of a timed 10-hour syringe, taking into account the short half-life (3 minutes) and concurrent GH night-time peak.

Evaluation of safety and toxicity

For the toxicity evaluation, only the side effects that could have been due to this specific treatment were considered (degrees of correlation: possible, probable or certain, expressed as absolute frequency (n), relative frequency (%), and 95% confidence interval (CI), as described by the National Cancer Institute (NCICTC) criteria (http://www.eortc.be/services/doc/ctc/).[1]

All patients therefore gave their informed consent to participate in the study.

The most frequent toxicity phenomena found in the study, grade I and II, were the following:

- Hematological toxicity: Leucopenia 33%,

- Gastrointestinal: nausea 25%,

- Drowsiness (36%).

These phenomena were the only ones observed, and generally there was a subsequent, progressive and gradual adaptation and improvement within a few weeks. A reduction, delay or temporary suspension of treatment due to toxicity has been necessary in patients with leucopenia (cyclophosphamide suspension until recovery of leukocyte counts) and in cases of severe gastrointestinal effects (Somatostatin).

Such circumstances, though limited, have occurred much more frequently and more clearly, especially in patients with critical stage, advanced especially if chemotherapy/radiotherapy/monoclonal antibodies are pre-treated.

There have been no deaths associated with the treatment.

Results and Discussion

Table 1 shows the clinical result in terms of REGRESSION, STABILITY and PROGRESSION of the disease. The best clinical outcomes were achieved, as expected, in the first group of patients, those with Regional Breast Cancer, with a clinical response of regression always greater than 80%. In the second group of patients with locally advanced cancer, the most promising results were seen with the DBM administered in the second-line form, where 87.5% of patients achieved regression. As regards the patients with advanced stage breast cancer, both the first and second-line forms of treatment achieved regression in 20% of cases, while the success rate was only 10% in patients who had repeatedly undergone multiple sessions of chemo- and radiotherapy, were no longer responsive and were generally in critical conditions before starting the DBM **(Table 1)**.

In order to compare our results with NCI data, a preliminary

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[1]**Note:** This is a study on the combined use of drugs that have already passed all the reliability and anticancer tests. Thus, since all the drugs have been extensively tested and their use has been approved by the international health organizations, and here they are merely used in a new combination, it was decided not to submit the study protocol to an ethics committee. The study was carried out in accordance with The Good Clinical Practices directives and the Declaration of Helsinki.

Table 1 Percentage of patients with remission, stability and progression, after DBM with different treatment modality (exclusive, adjuvant or 2nd/ 3rd line therapy), for different staging at the date of enrolment.

Staging at the date of Enrolment	Treatment Modality	Patients n.	Result	%
Early Stage Breast Cancer (Stage I - II - III)	Exclusive Therapy	27	Remission=23	81.50%
			Stability=1	3.70%
			Progression=3	14.80%
	Adjuvant Therapy	87	Remission=74	81.50%
			Stability=2	2.30%
			Progression=11	12.60%
	2nd/ 3rd Line Therapy or Supportive	34	Remission=28	82.40%
			Stability=5	14.70%
			Progression=1	2.90%
Locally advanced	Exclusive Therapy	4	Remission=1	25%
			Stability=1	25%
			Progression=2	50%
	Adjuvant Therapy	8	Remission=7	87.50%
			Progression=1	12.50%
	2nd/ 3rd Line Therapy or Supportive	3	Remission=1	33.30%
			Progression=2	66.70%
Metastatic Breast Cancer	Exclusive Therapy	9	Remission=2	22.20%
			Stability=2	22.20%
			Progression=5	55.60%
	Adjuvant Therapy	18	Remission=4	22.20%
			Stability=1	5.60%
			Progression=13	72.20%
	2nd/ 3rd Line Therapy or Supportive	104	Remission=11	10.60%
			Stability=20	19.20%
			Progression=73	70.20%
Stage not defined		3	-	-
Total		297		

Table 2 Statistical Observation on Survival (Observed and Relative) at 5 years after diagnosis and initial stage: (Localized=confined to primary site - Regional=extended to regional lymph nodes - Distant=metastatic tumor).

MDB- Observed and Relative Survival (5 years)				
Initial diagnosis	Observed patients N.	Survived patients n.	Observed Survival (%)	Relative Survival (%)
Localized	52	49	94.2%	98.1%
Regional	91	77	84.60%	88%
Distant	15	10	66.70%	69.40%
Undefined initial diagnosis	29	27	93.1%	96.2%
SubTotal	187	163	87.2%	90.4%
Others (data/diagnosis <5years)	107	-	-	-
No classiable	3	-	-	-
Total	297	-	-	-

Relative Survival is obtained for every stage and reported in **Table 2**. In **Figure 2** is shown an evaluation of the percentage of women still alive 5 years after diagnosis, treated with the DBM, versus data on official oncological treatment reported by the National Cancer Institute. DMB method appears more efficient for the treatment of distant tumor in particular **(Table 2) (Figure 2)**.

Sub-analysis

This sub-analysis highlights:

• Clinical Target Benefit (CR - PR - SD) in 85% of patients with initial stage disease (I - II - IIIA)

• a percentage of 44% positive results (2 PR-2 SD) in the 9

metastatic tumor patients and an average survival time of approximately 30 months (75-42-42-41-24-21-17-6 -6).

Based on the classification criteria used by N.C.I (Project SEER 18 - 2007-2013), the 40 cases are also classifiable:

• 19 localized tumors (11 CR - 6 PR - 1 SD - 1 PD).

• 12 locoregional tumors (5 CR - 2 PR - 1 SD - 4 PD).

• 9 metastatic tumors (2 PR - 2 SD - 5 PD).

By identifying Progressive Survival Survival (PFS) - Free Disease Survival (DFS) and Global Response (OR) as the primary endpoint, the following summary was elaborated **(Table 3)**.

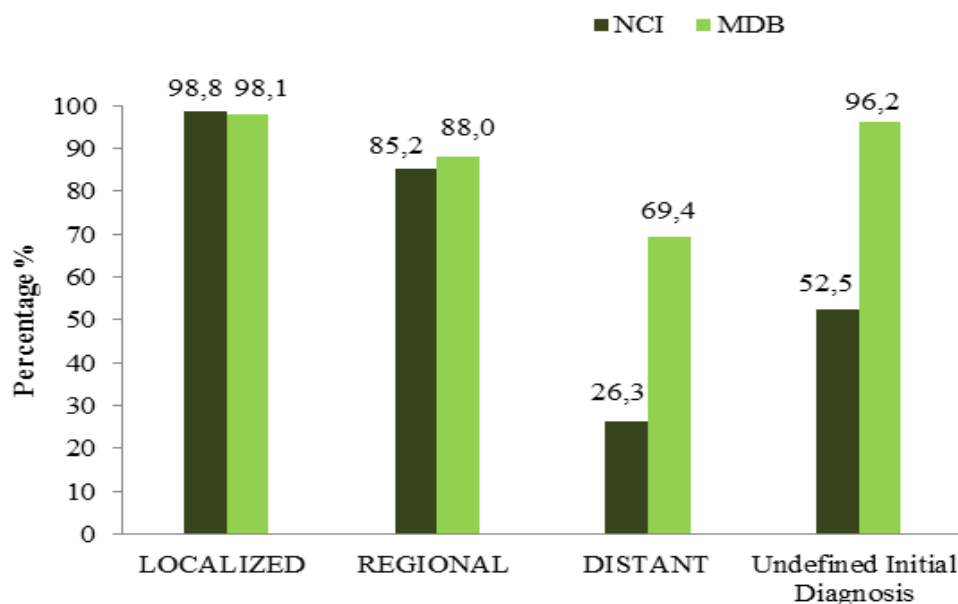**Relative Survival – Comparative Graphics (NCI vs MDB)**

| **Figure 2** | Comparative graphics of breast cancer survival 5 years after diagnosis between DBM oncological treatment and official oncological treatment reported by Nation Cancer Institute. The statistic evaluation depends from the type of tumor (localized, regional and distant). |

Table 3 Observation of therapeutic response of 40 cases of breast cancer treated with only DBM.

Identity and Staging					Overall Response (Global Response)				Maintenance of clinical remission					PFS			
Patient ID	Age at Diagnosis	Age at Enrolment	Grade	Stage	CR	PR	SD	PD	Start therapy	Stable response over time	Temporary answer	No answer	DFS (month)	Conclusion of the observation	Observation period (months)	PFS (month)	PFS / observation period
138	51	51	n.d.	IIA	X	-	-	-	Dec-04	X	-	-	105	Nov-14	119	119	100%
586	62	68	n.d.	IV	-	X	-	-	Dec-06	X	-	-	_	Oct-10	42	42	100%
601	52	52	G2	I	X		-	-	Mar-06	X	-	-	104	Still under obser	118	118	100%
614	56	56	n.d.	IIA	-	X	-	-	Jul-06	X	-	-	_	Jul-11	60	60	100%
657	57	57	n.d.	IIA	-	X	-	-	Jun-06	X	-	-	_	Oct-07	17	17	100%
799	42	43	G3	IIIC	-	-	-	X	Jan-07	-	X	-	_	May-08	18	2	11%
895	72	72	n.d.	IIIB	-	-	-	X	Mar-07	-	-	X	_	Feb-08	5	0	0%
970	69	69	G3	IV	-	-	-	X	Apr-08	-	X	-	_	Sep-09	17	2	12%
994	54	55	G3	IV	-	-	-	X	May-09	-	X	-	13	Jan-15	75	41	55%
1101	50	51	nd	IIB	X	-	-	-	Mar-07	X	-	-	106	Still under obser.	117	117	100%
1941	47	47	n.d.	IIA	X	-	-	-	Apr-09	X	-	-	45	Sep-13	65	65	100%
2178	68	68	n.d.	IIA	-	X	-	-	Jun-09	X	-	-	_	Still under obser.	81	81	100%
2224	52	65	G1	IV	-	-	-	X	Aug-09	-	X	-	_	Aug-11	24	10	42%
2580	55	55	G2	IIIA	-	-	-	X	Mar-10	-	X	-	_	Jul-13	40	0	0%
2708	37	37	G2	IIB	-	X	-	-	May-10	X	-	-	_	Sep-12	27	27	100%
2898	55	55	G2	I	X	-	-	-	Sep-10	X	-	-	5	Nov-13	22	22	100%
3029	45	45	G1	IIA	X	-	-	-	Dec-10	X	-	-	48	Still under obser.	72	72	100%
3048	49	49	G3	IIB	X	-	-	-	Dec-10	X	-	-	34	May-14	42	42	100%
3056	62	62	G2	IIB	-	X	-	-	Dec-10	X	-	-	_	Still under obser.	92	92	100%
3361	34	35	G2	IIIB	X	-	-	-	Feb-11	X	-	-	59	Still under obser.	74	74	100%
3617	41	41	G1	IIA	X	-	-	-	Jul-11	X	-	-	48	Still under obser.	60	60	100%
3696	53	53	G2	IIA	X	-	-	-	Sep-11	X	-	-	9	Nov-12	14	14	100%
3734	37	39	n.d.	I	-	X	-	-	Oct-99	X	-	-	_	Still under obser.	171	171	100%
3950	64	64	n.d.	IIA	-	-	-	X	Dec-11	-	X	-	_	Jan-15	36	25	69%
4253	49	56	G1	I	-	X	-	-	Mar-12	X	-	-	_	Still under obser.	57	57	100%

Identity and Staging					Overall Response (Global Response)					Maintenance of clinical remission				PFS			
4358	43	43	G2	IIIA	X	-	-	-	Apr-12	X	-	-	41	Still under obser.	45	45	100%
4548	45	45	n.d.	IIB	-	-	-	X	Jul-12	-	X		_	Still under obser.	57	25	44%
4614	48	48	n.d.	I	X	-	-	-	Sep-12	X	-	-	42	Still under obser.	54	54	100%
4688	67	67	G3	IIIB	-	-	X	-	Sep-12	X	-	-	_	Nov-15	36	36	100%
4851	31	31	n.d.	IIB	X	-	-	-	Aug-12	X	-	-	22	Oct-14	26	26	100%
4967	64	65	n.d.	IIA	X	-	-	-	Mar-12	X	-	-	19	Still under obser.	51	51	100%
4971	46	46	G3	IV	-	-	-	X	Feb-13	-	X	-	_	Aug-16	42	16	38%
5502	59	59	G2	I	-	-	X	-	Sep-13	X	-	-	_	Still under obser.	38	38	100%
5779	60	60	G3	IV	-	-	X	-	Sep-13	X	-	-	_	Mar-14	6	6	100%
5826	64	64	G2	IV	-	-	X	-	Jun-13	X	-	-	_	Still under obser.	41	41	100%
6167	48	48	n.d.	IIA	X	-	-	-	Oct-13	X	-	-	24	Still under obser.	41	41	100%
6287	68	68	G2	IIA	X	-	-	-	Jul-12	X	-	-	19	Still under obser.	56	56	100%
6435	41	42	n.d.	IV		X	-	-	May-15	X	-	-	-	Still under obser.	21	21	100%
6514	54	54	n.d.	I		X	-	-	Mar-13	X	-	-	-	Still under obs.	50	50	100%
6624	47	48	G2	IV	-	-	-	X	May-14	-	-	X	_	Nov-15	6	0	0%

CR=Complete Response; PR=Partial Response; SD=Stable Response; PD=Progressive Response; DFS=Disease Free Survival; PFS=Free from Progressive Survival.

Conclusion

The DBM therapy proposes to counter the progression of the neoplastic phenotype by:

a) Inhibiting the neoplastic proliferation by cell processes of apoptosis/necrosis and depletion of hormones and cell growth factors;

b) Countering the marked mutagenic tendency by direct activation of the DNA repair systems, and by epigenetic cell programming.

c) Blocking neoplastic progression by reducing the formation of new blood vessels (Neoangiogenesis-Lymphoangiogenesis) and of cell motility phenomena (migration), essential for neoplastic dissemination

d) Reinforcing natural defense mechanisms against neoplastic aggression (natural and acquired immunity and improvement of vital functions).

In cases of breast cancer monitored at 5 years, the DBM biological multitherapy significantly improved quality of life, objective response and survival with respect to the same stages of breast cancer treated with conventional oncological protocols. The negative regulation of the main interactive mitogen systems - GH–GF–Prolactin-Estrogen – by means of somatostatin and analogues, D2R agonists, aromatase inhibitors, analogues of LH-FSH, together with the differentiating, cytostatic, homeostatic action of Retinoids, Vitamins E, D3, and C, Folates, Ca, MLT (Melatonin), Proteoglycans with factorial interaction, without significant toxicity, made this result possible [18-22]. We report these therapeutic results to improve the prognosis of tumors in general and of breast cancer in particular. Breast cancer remains the leading cause of death worldwide in women, demonstrating the deficiencies of the current measures of cancer prevention and treatment and the need to overcome these serious limits of oncological therapy by taking advantage of still underestimated scientific evidence.

Acknowledgements

Conflict of Interest

No conflicts of interest to disclose.

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