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Development of a disease-specific quality of life questionnaire module for patients with gastrointestinal neuroendocrine tumours

A.H.G. Davies[a,b,l], G. Larsson[f], J. Ardill[e], E. Friend[c], L. Jones[d], M. Falconi[g], R. Bettini[g], M. Koller[h], O. Sezer[i], C. Fleissner[i], B. Taal[j], J.M. Blazeby[k], J.K. Ramage[a,c,]*
On behalf of the EORTC Quality of Life Group

[a]*Institute of Liver Studies (Carcinoid Clinic), King's College Hospital, Denmark Hill, London SE5 9RS, UK*
[b]*North Hampshire Hospital, Aldermaston Road, Basingstote RG24 9NA, UK*
[c]*Department of Gastroenterology and Hepatology, North Hampshire Hospital, Aldermaston Road, Basingstoke, Hampshire RG24 9NA, UK*
[d]*University Hospital Aintree and Royal Liverpool University Hospital, Liverpool, UK*
[e]*Regional Regulatory Peptide Laboratory, Royal Hospitals Trust and Department of Medicine, Queen's University, Belfast, UK*
[f]*Department of Endocrine Oncology, 30 B2, University Hospital, Uppsala, Sweden*
[g]*Department of Surgical and Gastroenterological Sciences, University of Verona, Verona, Italy*
[h]*Institute of Theoretical Surgery, Philipps-University Marburg, Marburg, Germany*
[i]*Department of Oncology and Haematology, University Hospital Charite, Berlin, Germany*
[j]*Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Plesmanlaan, Amsterdam, The Netherlands*
[k]*Clinical Sciences at South Bristol and Department of Social Medicine, University of Bristol, Bristol, UK*

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ABSTRACT

Quality of life (QoL) measurements are increasingly being used as an end point in cancer clinical trials. Standard generic QoL questionnaires may not assess symptoms produced by neuroendocrine tumours. Here we report the development of a disease-specific quality of life score questionnaire for patients with neuroendocrine tumours of the gut to supplement the EORTC core cancer questionnaire, the QLQ-C30. Phases 1–3 of the EORTC quality of life group guidelines for module development were used to design the new questionnaire. Forty-one relevant issues (questions) were generated after an extensive literature search. Following interviews of 15 health care workers and 35 patients, a 35 question provisional questionnaire was constructed. This was translated into seven European languages and pre-tested in 180 patients resulting in a 21-item module that will be validated in an international clinical trial. The EORTC QLQ-NET21 provides a site-specific module to supplement the QLQ-C30 for patients with neuroendocrine tumours.

* *Corresponding author.*
E-mail addresses: alsan@magdave.freeserve.co.uk (A.H.G. Davies), John.Ramage@nhht.nhs.uk (J.K. Ramage).
[1] Tel./fax: +44 1752 769719.
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1. Introduction

Quality of life measurements are increasingly being used as an end point in clinical trials especially those involving patients with malignant diseases. A limited amount of research has been published about quality of life (QOL) in patients with carcinoid and neuroendocrine tumours and to our knowledge there is no disease-specific quality of life score questionnaire for these patients.[1–7] Neuroendocrine tumours of gut origin give rise to symptoms not only from the presence of tumour in the liver (pain, ascites, pressure) but also from the output of the various hormones secreted by these tumours. The symptom complexes associated with the syndromes and their treatments are relatively specific, setting them apart from gastrointestinal malignancy in general. The most common set of symptoms are from carcinoid syndrome – skin flushing, diarrhoea and wheezing due to the production of serotonin.[8,9] Syndromes from secreting pancreatic NET's[10,11] include Zollinger–Ellison syndrome (gastrointestinal ulceration, diarrhoea),[12,13] insulinoma (hypoglycaemia, fits, collapses and sweating),[14,15] glucagonoma (diabetes and rash),[16,17] VIPoma (severe secretory diarrhoea),[18–20] and somatostatinoma (gallstones, steatorrhoea).[21–23] Other rarer syndromes result from ectopic secretion of adrenocorticotropic hormone (ACTH), parathyroid releasing hormone (PTRH) and growth hormone releasing hormone (GHRH).[24] Although carcinoid and neuroendocrine tumours exhibit very different symptoms, the QoL issues may be similar and this has been suggested by previous work.[3] Many of the treatments are associated with side effects: somatostatin analogues can cause malabsorption, diarrhoea and gallstones; interferon causes fever, nausea, lethargy and lymphopenia;[25] radionuclide therapy causes marrow suppression; and Yttrium-Octreotide can cause renal failure.[26–28] Embolisation causes pain and fever and the mortality is similar to that of liver resection at 4–6%.[29–31] It has been difficult to show significant survival benefits of many treatments, and those that do prolong life may actually reduce QOL. It is clear that both quality and quantity of life are important factors when deciding on funding expensive treatments and adequate assessment of the former are needed to justify the huge expense of these therapies. Patients are being encouraged to have more of a say in the care and treatment they receive and are being empowered in this by patient support groups and "physician–patient" partnerships. It is hard for patients to make up their minds about treatment on the basis of survival figures alone. Patients will want to know how they will actually feel in the later stages of the disease and how the treatment will affect their quality of life. Currently, studies of therapy do not address this systematically. It is important to develop a QOL measure that is representative of the patients' feelings to empower them in decision-making about their care.

Current core cancer QOL questionnaires such as the EORTC QLQ-C30 and FACIT questionnaire do not address any of the above symptoms that are specific and problematic to patients with carcinoid and neuroendocrine tumours. There is therefore the need to develop a disease-specific quality of life module to supplement a core questionnaire. This study aimed to develop a module for patients with neuroendocrine tumours of gut to supplement the core questionnaire, the EORTC QLQ-C30.

2. Patients and methods

2.1. Design

The guidelines developed by the EORTC quality of life group for questionnaire development were followed (Table 1).[32–34] This paper describes the development of the module up to phase 3. Phase 4 involves psychometric testing and this will be carried out in the near future.

2.2. Subjects

The inclusion criteria for patients in phases 1–3 were: (1) patients with histologically proven metastatic carcinoid with/without secretion of 5HIAA; (2) neuroendocrine tumours with primary anywhere in the gut or pancreas; (3) bronchogenic

Table 1 – Guidelines for the development of an EORTC disease-specific quality of life module

Phase	Aim	Process
1	Generation of QoL issues	1. Literature search 2. Interviews with health care providers 3. Patients' interviews 4. Analysis of qualitative and quantitative data 5. Adaptation of the list
2	Operationalisation – construction of a provisional questionnaire	1. Consultation of the EORTC QLG item bank for existing items 2. Construction of new items 3. Translation of the provisional questionnaire by the translation committee
3	Pre-testing to identify and solve potential problems	1. Administration of questionnaire to patients 2. Structured interviews with each patient 3. Qualitative and quantitative analysis of the data 4. Modification of the questionnaire 5. Formal development report to the EORTC QLG
4	International field-testing	Psychometric testing of the content reliability, validity, sensitivity and cross-cultural applicability

carcinoid with liver metastasis; (4) patients without another concurrent malignancy; (5) patients not confused and able to participate in an interview study; and (6) patients with written informed consent.

The inclusion criterion for health care workers was any health care worker (specialist nurse or consultant) who regularly cared for patients with carcinoid and neuroendocrine tumours.

2.3. Data analysis

2.3.1. Phases 1–2 data analyses

Descriptive analysis was used to analyse results of the interviews in phases 1–3. In phase 1 patients and health care workers rated the questions according to their importance/relevance in terms of the quality of life for this group of patients on a 4-point Likert scale from 1 – not at all, 2 – a little, 3 – quite a bit, to 4 – very much. The list of questions generated was split into two sections: the first was made up of questions general to patients with carcinoid and neuroendocrine tumours; and the second section being questions for patients with specific syndromes (e.g., gastrinoma, insulinoma). Patients were also asked to select five questions they would choose to stay in the final questionnaire, if they were allowed only five, and also to select five questions or issues that were not included in either the proposed questionnaire or the QLQ-C30 that they thought were important. Finally, they were asked if they had any other comments to make.

The mean relevance ratings for each question by each group and the number of times it was prioritised for inclusion were calculated. The mean scores for each question from both groups were then combined and an average score calculated. Questions that scored less than 1.9 were deleted.

The scores were considered in conjunction with qualitative analysis of the comments made by both groups during the interviews.

2.3.2. Phase 3 data analyses

After completion of phases 1 and 2, the provisional module, the QLQ-NET35 was translated into seven European languages. After scoring the questions using the same scale as in phase 1, patients were asked to answer six other questions to determine whether any of the questions were difficult, annoying, confusing, upsetting, intrusive or if they had any other comments. They were asked if any of the questions were irrelevant and finally if there were any issues that they thought were relevant that were not included in our provisional questionnaire.

The criteria for accepting issues at this stage were: mean score >1.5; range >2 points; prevalence >30%; and rated a priority for inclusion by patients or health care workers in phase 1. Items that met 2 or less of these criteria were considered for deletion in conjunction with qualitative comments made by patients during the interview.

3. Results

Literature search: Previously developed EORTC disease-specific modules were reviewed for issues relevant to patients with carcinoid and neuroendocrine tumours not already included or sufficiently dealt with in the generic cancer questionnaire the QLQ-C30. These included the breast QLQ-BR23, head and neck cancer QLQ-H&N35, lung cancer QLQ-LC13, oesophageal cancer QLQ-OE24 and ovarian QLQ-OV28.

A Medline search for publications in English on carcinoid and neuroendocrine tumours from 1996 to September 2001 was carried out and 950 articles were found. When quality of life, psychosocial deprivation, social adjustment, and illness were added this was narrowed down to 22 relevant articles.

ClinPSYC from 1990 to September 2001 was also searched. Two thousand four hundred and eighty (2480) articles for quality of life and three thousand five hundred and seventy-four (3574) for neoplasms were found. Combining the two resulted in 267 articles. All abstracts were reviewed and relevant articles retrieved.

Forty-one (41) questions/issues for the patients and health care workers in phase 1 were generated (Table 2).

'Weakness' was included in the questionnaire for phase 1 interviews. This question has already been sufficiently dealt with in the QLQ-C30 and it was therefore eliminated and not included in the analysis.

3.1. Interview with health care workers

Fifteen health care workers, 8 doctors and 7 nurses with experience in treating patients with carcinoid and neuroendocrine tumours were interviewed. There were 8 (4 doctors and 3 nurses) from the United Kingdom (UK); 6 (2 doctors and 4 nurses) from Sweden; 1 doctor from Germany and 1 from Norway. The mean scores by health care workers are shown in Table 3.

3.2. Interview with patients

Thirty-five (20 male and 15 female) patients were interviewed in phase 1. Thirty-two patients were interviewed in the hospital clinic and 3 at home. There were 8 from Northern Ireland, 11 from Sweden and 16 from United Kingdom. The mean age was 60 years (SD ± 9.66) with a range of 42–83.

There were 24 carcinoid, 5 non-secretory NETs, 2 insulinoma patients, and 1 of each gastrinoma, glucagonoma, VIPoma and a mixed pancreatic NET. The mean scores by patients are shown in Table 3.

3.3. Analysis and adaptation

The mean scores by each group (patients and professionals) on the 4-point Likert scale were calculated for each question. The means were then combined to form an average of the mean score for each question (Table 3). The time frame was one week for all questions but one (change in sexual activity) which was four weeks as is was decided by the group that one week was too short a time for someone to notice a change in sexual activity. The original intention was to delete all questions scoring an average of less than 2 but because headache (scoring 1.9) was selected twice by the patients as one of the most important issues in terms of quality of life this issue was included. The following were deleted: "felt dizzy", "poor body image", "had fever", "skin

Table 2 – List of issues generated in phase 1

General issues for neuroendocrine tumours	
Single item and symptom scales	
Flushing	Cough
Wheezing	Weakness (HCW only)
Abdominal pain	Sweating at night
Bloating of abdomen	Fever
Wind	Dizziness
Weight	loss Muscle pain
Ankle swelling	Joint pain
Bone pain	Headache
Had difficulty remembering things (Patients' only)	
Functional issues	
Emotional function:	Social function:
Anxiety about recurrent disease	Limited ability to see friends
Concern for family members	Limited ability to travel
Anxiety about dying	
Worrying about events at the next appointment	
Attitude towards treatment/treatment related	
Painful injection sites	
Scarring from operations	
Poor body image	
Multiple infections	
Fear of side effects of therapy	
Anxiety about which treatment is best	
Skin rashes	
Satisfaction with care scales/issues	
Satisfaction of care	
Problems with investigations (tests, etc.)	
Concern about late diagnosis (in the past)	
Information/communication scales/issues	
Lack of information about disease	
Sexuality	
Change in sexual activity	
Specific issues	
Insulinoma	
Fear of fits – symptom scale	
Fear of collapses – symptom scale	
Sweating – symptom scale	
Glucagonoma	
Worry about skin rash – treatment related	
Zollinger–Ellison	
Unable to eat – physical function	
Dyspepsia (indigestion) – symptom scale	
Vomiting – symptom scale	

rashes", "scarring from operations", "ankle swelling", "had a cough" and "multiple infections". From the specific syndrome questions all the questions scored over 2 but because glucagonoma patients are very rare and we interviewed only 1 patient (with no hope of getting more in phase 3) it was decided to delete the glucagonoma-specific question "worry about skin rash".

3.4. *Additions*

Only two issues (not included in both the QLQ-C30 and the proposed new questionnaire) were suggested on two occasions by healthcare workers to be added to the final list of issues. These were: (1) "Concern about inheritance", which was added as a second question to "concern for family"; and (2) "Concern about the effect of the disease on other systems/organs". All the other additional issues were selected only once both by patients and healthcare workers.

3.4.1. *Phase II – Operationalisation*

After deletion and addition of new items the resulting questionnaire was of 35 questions (Fig. 1). The EORTC Quality of Life Group item bank was consulted to check for similar and approved quality of life score questions from previously validated questionnaires.[35] All the questions from the questionnaire with similar meanings were changed to the wording in the item bank. There were 25 similar questions and the wordings from the item bank were adopted. They were questions no. 31, 34, 35 to 44, 46, 49, 50, 52, 54, 55, and 57 to 63 (see Fig. 1). The two new questions added were no. 45 'Did you worry about passing the disease on to your children?' and no. 53 'Did you worry about the effect of your disease or treatment on other organs or parts of your body?'

"Concern for family" was reworded into two questions from the item bank: no. 43 'Were you concerned about disruption of family life?' and no. 44. 'How distressing do you feel your illness or treatment has been to those close to you?'

3.5. *Translation*

The provisional questionnaire was translated into seven European languages (Dutch, French, German, Italian, Spanish, Swedish and Norwegian) by the EORTC's Quality of Life Group translation procedures.[36,37] The new translations were pilot tested on 10–15 patients in each language group to check for translation problems before the questionnaire was finalised.

A total of 180 patients from five European countries were interviewed and six were excluded because they did not meet the inclusion criteria (none had evidence of metastatic disease). The socio-demographic and clinical characteristics of the patients are shown in Table 4.

After quantitative analysis (using the five criteria noted in methods) and considering qualitative comments made by patients the questionnaire was reduced to 20 questions. From the qualitative analysis, patients were concerned about weight gain as well as weight loss. This was particularly true for patients on somatostatin-analogue therapy. Therefore a new question: no. 46. 'Has weight gain been a problem for you?' was added. The option not applicable (N/A) was added to 4 questions. This is because it was noticed that many patients may score certain questions as "not at all" when in fact the question is "not applicable". For analysis it is important to make this distinction, hence the new category of N/A.

The new questionnaire – GINET21 – with 21 questions has three defined multi-item symptom scales (endocrine – 3 ques-

Table 3 – Mean scores from health care workers and patients in descending order of the average mean score of the two groups

List of issues	Mean score		
	Patients	Health care providers	Average
Flushing	2.34	3.73	3.04
Satisfaction of care	2.58	3.47	3.03
Anxiety about recurrent disease	2.46	3.2	2.83
Concern for family members	2.76	2.8	2.78
Tummy pain	2.14	3.2	2.67
Lack of information about disease	2.12	3.13	2.62
Concerned about late diagnosis	2.2	2.92	2.56
Had anxiety about dying	2.27	2.73	2.51
Wind	2.57	2.33	2.45
Anxiety about which treatment is best	2.2	2.67	2.43
Limited ability to travel	2.2	2.67	2.43
Change in sexual activity	2.17	2.55	2.36
Bloating of abdomen	1.89	2.73	2.31
Weight loss	1.6	2.93	2.26
Fear of side effects of therapy	1.91	2.6	2.26
Had muscle pains	2	2.47	2.23
Felt worried about events at the next appointment	1.94	2.5	2.22
Painful injection sites	1.94	2.47	2.21
Sweating at night	1.91	2.47	2.19
Had problems with investigations (tests)	1.6	2.75	2.17
Had joint pains	1.89	2.4	2.14
Wheezing	1.35	2.8	2.08
Limited ability to see friends	1.71	2.42	2.07
Bone pain	1.66	2.2	1.93
Had headache	1.8	2	1.9
Felt dizzy	1.71	2.07	1.89
Poor body image	1.6	2	1.8
Had fever	1.26	2.33	1.79
Skin rashes	1.6	1.93	1.76
Scarring from operations	1.63	1.8	1.71
Ankle swelling	1.37	2	1.68
Had a cough	1.49	1.87	1.68
Multiple infections	1.4	1.8	1.6
Specific symptoms			
Sweating	2.67	2.64	2.65
Fear of fits	2.33	2.91	2.62
Unable to eat	2	2.5	2.25
Vomiting	1.67	2.7	2.18
Fear of collapses	1.67	3.27	2.47
Dyspepsia (indigestion)	1.67	3.2	2.43
Worry about skin rash	1	3.1	2.05

tions, gastrointestinal – 5 questions, and treatment related side effects – 3 questions), two single item symptoms (bone/muscle pain and concern about weight loss), two psychosocial scales (social function – 3 questions, disease-related worries – 3 questions) and two other single items (sexuality and communication).

4. Discussion

The QLQ-GINET21 is a disease-specific module for patients with gut related carcinoid and neuroendocrine tumours to be used in conjunction with the EORTC QLQ-C30. It contains specific disease and treatment-related issues, and covers emotional and social well-being in patients with neuroendocrine tumours not adequately covered by QLQ-C30. It has been developed using standard guidelines for questionnaire development. The developmental process did not only depend on published literature but encompassed the views of health professionals and patients from five European countries and rigorous peer review. It therefore provides high content validity and sensitivity together with cross-cultural applicability.

There are many generic tools to measure quality of life but these instruments do not cover specific issues that may affect patients with a particular disease as a consequence of the disease or its treatment. The EORTC QLQ-C30[38] is a widely used generic questionnaire for cancers and it has been developed to be modular, with the core questionnaire being supplemented by disease-specific modules containing those aspects of quality of life relevant to patients with a specific type or site of cancer.[39] Few reports have been published in which health-related quality of life

EORTC QLQ – NET35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Did you have hot flushes?	1	2	3	4
32. Have you noticed or been told by others that you looked flushed/red?	1	2	3	4
33. Did you have trouble with wheezing?	1	2	3	4
34. Did you have abdominal pain?	1	2	3	4
35. Did you have a bloated feeling in your abdomen?	1	2	3	4
36. Were you troubled by passing wind/gas/flatulence?	1	2	3	4
37. Have you lost weight?	1	2	3	4
38. Have you had bone aches or pain?	1	2	3	4
39. Have you had aches or pains in your muscles or joints?	1	2	3	4
40. Did you have night sweats?	1	2	3	4
41. Did you have headaches?	1	2	3	4
42 Were you worried about the tumour recurring in other areas of the body?	1	2	3	4
43. Were you concerned about disruption of family life?	1	2	3	4
44. How distressing, do you feel, your illness or treatment has been to those close to you?	1	2	3	4
45. Did you worry about your children developing the disease?	1	2	3	4
46. Have you been worried about dying?	1	2	3	4
47. Have you worried about events at the next appointment?	1	2	3	4
48. Did you have any limitations in your ability to travel?	1	2	3	4
49. Have you had trouble having social contact with friends?	1	2	3	4

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
50. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
51. Did you have any anxiety about not receiving the best treatment?	1	2	3	4
52. Have you had a problem from repeated injections?	1	2	3	4
53. Did you worry about the effect of your disease or treatment on other organs or parts of your body?	1	2	3	4
54. Were you satisfied with the care you received from your doctors?	1	2	3	4
55. Did you worry about the results of your examinations and tests?	1	2	3	4
56. Did you have problems with your investigations (tests)?	1	2	3	4
57. Has the information given about your physical condition and treatment been adequate?	1	2	3	4

During the past four weeks:	**Not at all**	**A little**	**Quite a bit**	**Very much**
58. Did you experience any change in your sexual activity?	1	2	3	4

During the past week: "Zollinger-Ellison Syndrome/Gastrinoma":	**Not at all**	**A little**	**Quite a bit**	**Very much**
59. Have you had acid indigestion or heartburn?	1	2	3	4
60. Have you felt nauseated?	1	2	3	4
61. Have you vomited?	1	2	3	4
62. Have you had trouble eating?	1	2	3	4

During the past week: "Insulinoma":	**Not at all**	**A little**	**Quite a bit**	**Very much**
63. Did you have seizures?	1	2	3	4
64. Were you afraid you were going to collapse?	1	2	3	4
65. Did you sweat at anytime of the day?	1	2	3	4

Fig. 1 – Phase 3 questionnaire for pre-testing.

have been addressed in patients with neuroendocrine tumours.[1–7,40] No general conclusion could be drawn from those reports as different health-related quality of life instruments were used and the questionnaires were not specific enough for patients with neuroendocrine tumours. The only cancer specific questionnaire used in these patients in the past is the EORTC QLQ-C30 but it is limited by the fact that it does not cover specific and detailed issues like flushing, abdominal pain, discomfort in joints and muscles, effect of the disease on sexual behaviour, worry that family can not cope with the illness, worry that the illness will get worse and worry about recurrence. There is therefore a need for a disease-specific quality of life score questionnaire for these patients.

The limitations of our work is that this questionnaire will not be applicable to patients with glucagonoma/insulinoma as only one patient with glucagonoma was interviewed and the one specific question for these patients was deleted. The number of insulinoma patients was so low, and with such diverse symptoms, it was not practical to include specific questions for these patients. Originally it was intended to have extra questions specifically for gastrinoma patients but

Table 4 – Socio-demographic and clinical details of patients interviewed

	Total	174
Mean age (range) at diagnosis	Years	53.4 (17–80)
Mean age (range) at interview		58.19 (19–81)
Gender (male/female)	Male	85 (48.9%)
	Female	89 (51.1%)
European country	Country	No. of patients (%)
	Mainland, UK	61 (35.1)
	Northern Ireland	25 (14.4)
	Sweden	30 (17.2)
	Netherlands	25 (14.4)
	Germany	17 (9.8)
	Italy	16 (9.2)
Diagnosis	Carcinoid	85
	Non-secretory	55
	Insulinoma	7
	Gastrinoma	20
	VIPoma	4
	Glucagonoma	1
	Ppoma	2
Karnofsky score	Mean (SD)	82.62 (15.27)
	Range	30–100
Embryonic origin	Foregut	74
	Midgut	64
	Hindgut	10
	Ovaries	2
	Unidentified origin	24
Metastasis	Liver	128
	Lymph node	17
	Liver and bone	7
	Liver and lung	2
	Peritoneal	2
	Bone	1
	No metastasis	17

NB: Foregut = pancreas, lung, oesophagus to jejunum.
Midgut = ileum to right colon.
Hindgut = right colon to anus.

the questions thought to be specific to gastrinoma turned out to be useful for other NET patients so were included in the main questionnaire.The EORTC QLQ-GINET21 will now undergo international field-testing that will ensure psychometric testing of the reliability, validity and sensitivity of the module in assessing QoL in patients with carcinoid and neuroendocrine tumours in clinical trials.

In summary, EORTC QLQ-GINET21 is the only quality of life score questionnaire available for patients with gut related carcinoid and neuroendocrine tumours. This supplement to the core questionnaire should improve the sensitivity and specificity to detect small changes in quality of life as a result of treatment or disease progression.

Conflict of interest statement

None declared.

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