Original Article

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Clinical relevance of ^{18}F-FDG-PET/CT incidental findings

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ABSTRACT

INTRODUCTION: The use of positron emission tomography with 2-deoxy-2-18F-fluoro-D-glucose integrated with CT (18F-FDG-PET/CT) in oncology is common. Unexpected incidental findings are occasionally recognised and can represent clinically relevant lesions or conditions. This study aims to assess the occurrence, clinical significance and economic impact of incidental 18F-FDG-PET/CT findings.

METHODS: PET/CT of 670 cancer patients was evaluated in consensus by two experienced specialists within nuclear medicine and radiology. Foci with an abnormally increased 18F-FDG uptake and/or CT changes not related to the patients` disease were reported. Thirty-five foci in 29 patients were assessed and their cost and impact on patient management were analysed with up to 32 months of follow-up. A supplementary literature review was conducted using PubMed, Embase and Web of Science and the results were compared with ours.

RESULTS: A total of 28 foci (80%) were clinically relevant and elicited management or follow-up including four malignancies and 18 premalignant and six benign lesions. Seven foci were without pathology. The estimated additional cost was 1,984 US$ per focus. In the literature review, 642 of 1,090 foci (59%) were relevant, distributed as 270 malignancies, 166 premalignant and 206 benign lesions, whereas 448 foci were without pathology.

CONCLUSIONS: Incidental 18F-FDG-PET/CT findings should be investigated despite the occurrence of false-positive findings, additional time consumption and cost as they may represent obscure malignancies and premalignant or benign conditions needing treatment.

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Abbreviations

FDG = flouro-deoxy-glucose
FN = false negative
FP = false positive
NPV = negative predictive value
PClR foci = probable clinically relevant foci
PET = positron emission tomography
PPV = positive predictive value
SPM = second primary malignancy
TN = true negative
TP = true positive

Positron emission tomography (PET) and CT are diagnostic modalities usually combined in a PET/CT examination using ^{18}F-flouro-deoxy-glucose (^{18}F-FDG). ^{18}F-FDG-PET provides information about cellular metabolism, and CT visualises morphological details of organs and tissues [1-3]. ^{18}F-FDG is used as a marker of glucose metabolism [2], and areas of increased uptake are suspect for malignancy, especially if correlated with morphological CT changes. Non-malignant disorders like infection and inflammation may also show abnormal ^{18}F-FDG accumulation, and physiological uptake mimicking pathological accumulation can occur leading to PET misinterpretation [4, 5].

^{18}F-FDG-PET/CT is valuable in the detection, staging and control of malignant diseases [6] and is also sensitive for detection of incidental clinically relevant foci [7]. Thus, in a study evaluating aneurysm wall inflammation by ^{18}F-FDG-PET/CT, malignancy was detected in six of 26 (23.1%) patients. The malignancies had not been detected by CT and X-ray performed before the PET/CT [8].

Our study aimed to assess the occurrence and clinical and economic impact of incidental findings by ^{18}F-FDG-PET/CT in a patient group and relate these findings to current knowledge obtained by a literature review. To our knowledge, this is the first study comparing the results of a current investigation of such findings with data collected by a literature review.

METHODS

Patients and statistical analyses

^{18}F-FDG-PET/CT of 670 consecutive patients with known or suspected malignancy was evaluated in consensus by two specialists in nuclear medicine and radiology. They systematically reported incidental foci of probable clinical relevance (PClR foci) defined as foci with an increased ^{18}F-FDG uptake compared with the mediastinum and the liver [9] and/or CT changes that were probably unrelated to the present disorder. The incidental findings were analysed based on the patients' medical records with a median follow-up of 19.5 months (range: 6-32 months). The final diagnoses were based on histopathological results, imaging and/or clinical follow-up.

Approval was obtained from the Danish Data Protection Agency.

A PClR focus was considered a true positive (TP) if clinically relevant and unrelated to the patient's disease whether malignant, premalignant or benign, and was considered a false positive (FP) if not associated with pathology. The positive predictive value (PPV) was calculated as follows: . The negative predictive value (NPV) could not be obtained as false-negative (FN) and true-negative values (TN) were unknown although foci with hypo- or iso-FDG metabolism were taken into account.

The χ^2-test and Fisher's exact test were used to compare our findings with the literature review. A p-value < 0.05 was considered significant.

Imaging procedures

The patients fasted six hours before their ^{18}F-FDG injection, securing blood glucose levels < 7 mmol/l (150 mg/dl). Patients on insulin therapy had the usual insulin dose after breakfast, followed by four hours of fasting before ^{18}F-FDG administration. The patients rested for one hour before the examination to reduce muscular activity and were encouraged to void in order to minimise bladder activity.

^{18}F-FDG was produced in-house (average of 5 MBq/kg; total activity of 200-600 MBq). Imaging was performed 60 minutes after the intravenous (IV) ^{18}F-FDG administration. With the patients in supine position and the arms above the head, a topogram was obtained to secure body coverage from the base of the skull to the mid-thigh, followed by acquisition of attenuation correction low-dose CT maps (3-5 mSv),

and PET acquisition over 5-6 bed positions with 3 min. per position. Image fusion was performed using an iterative algorithm.

A diagnostic CT was performed either immediately after or 2-4 weeks before the PET/CT, using IV iodixanol 270 mg/ml, 2 ml/kg, flow rate 4 ml/sec, 120 kV, 200 mAs, beam collimation 24 × 1.2 mm, slice thickness 2 mm and CT dose index volume approx. 13.5 mGy.

Economic impact

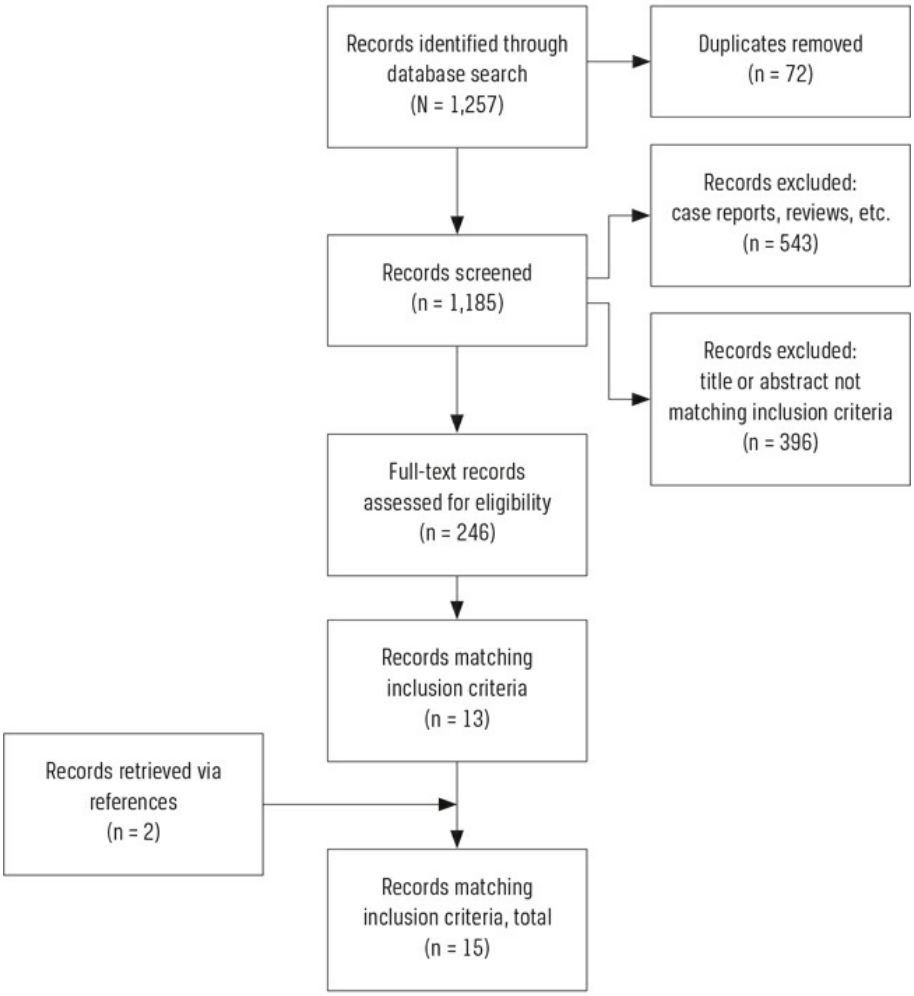
Data regarding management of PCIR foci (investigations and treatments) were available via the electronic patient journal system and their cost was collected via the interactive Danish diagnosis-related group system and calculated in US dollars.

The literature search

The literature search (Figure 1) was performed as follows: 1) in PubMed, using the search string ("Positron Emission Tomography Computed Tomography"[Mesh]) AND "Incidental Findings"[Mesh]; 2) in Embase.com via ELSEVIER using the words PET, CT AND incidental finding in the advanced search field; 3) in Web of Science, selecting ALL FIELDS and using search words PET-CT AND incidental findings. The searches were restricted to the period from 1 January 2006 to 1 May 2019, to humans and English language. The publications were subjected to the following inclusion criteria: original studies including PET/CT performed with ^{18}F-FDG and contrast-enhanced CT and a percentage of incidental findings investigated > 30% in oncology patients.

Trial registration: not relevant.

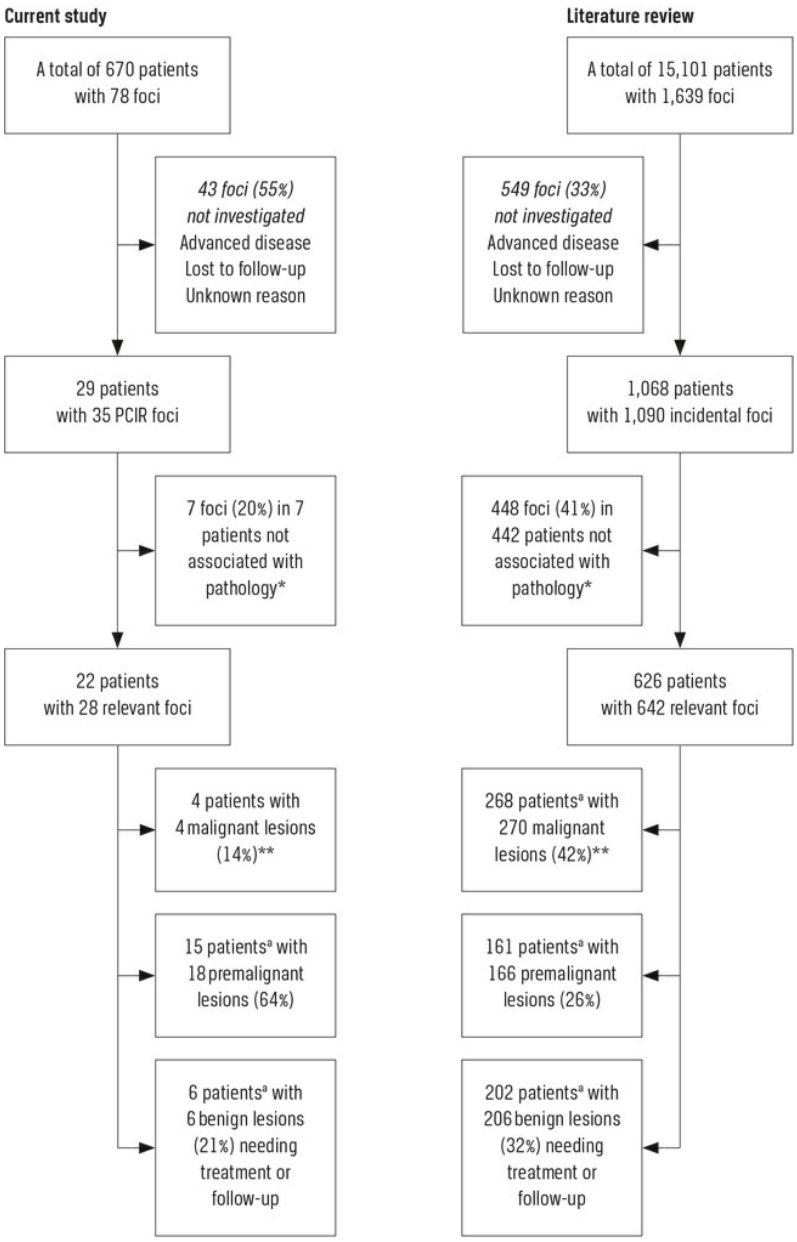
FIGURE 1 / Flow diagram presenting the literature search.



RESULTS

Figure 2 shows the division of our material. A total of 35 PClR foci in 29 patients (19 males and ten females; mean age 64.5 years, range: 47-86 years) were investigated further. They were referred for PET/CT for evaluation of lymphoma (n = 17), suspected malignancies (n = 5), head and neck malignancies (n = 5) and gastrointestinal cancer (n = 2). The indications for PET/CT were staging (n = 14), post-therapy control (n = 10) and diagnosis (n = 5).

FIGURE 2 / Flow diagram giving an overview of current patients and their probable clinically relevant (PCIR) foci compared with previously reported patients retrieved from the literature review.

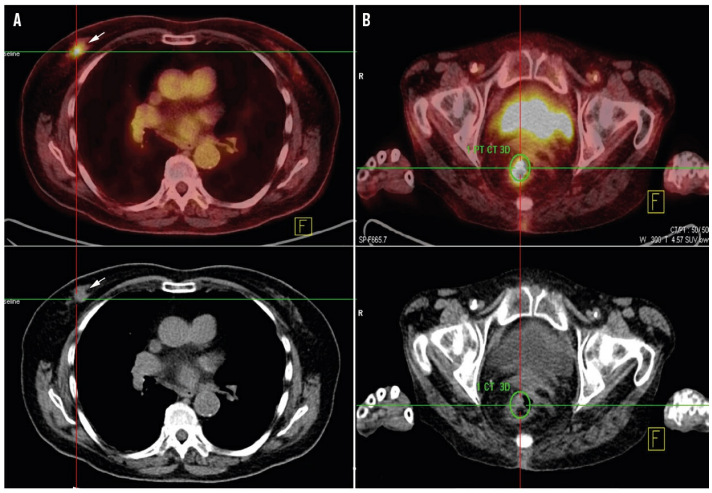


*) $p < 0.05$; **) $p < 0.01$.
a) Some of the patients had 2 incidental findings.

There were four malignancies (11.4%), 18 premalignant lesions (51.4%) and six benign lesions (17%). Seven foci were FP, encompassing four foci in the gastrointestinal tract and a focus in the prostate, testis and a mediastinal lymph node, respectively.

The four malignancies consisted of rectal, breast (**figure 3**), sigmoid and lung cancers. They were all removed surgically or endoscopically, without recurrence after 20-32 months. There were 13 colorectal polyps (size 0.5-4 cm), all of which were removed endoscopically, with no re-growth by control colonoscopy during 21-28 months.

FIGURE 3 / A. A fused PET/CT image of the chest (upper image) with low dose CT image (lower image) of a 72-year-old female presenting with dysphagia. A PCIR focus in the right breast with high [18F]FDG-uptake on PET and correlated with a morphological change (mass) on CT (arrows). The final diagnosis was invasive ductal carcinoma. **B.** A fused PET/CT image of the pelvis (upper image) with low dose CT image (lower image) of a 67-year-old female with known oral cavity cancer. A PCIR-focus in the rectum with high [18F]FDG-uptake and uncertain CT changes (circle) was diagnosed as rectal adenocarcinoma.



Three PClR foci were located to the thyroid. One patient had oncocytoma and inconclusive histopathology regarding malignancy. A left-sided thyroid lobectomy was performed; with no recurrence for 14 months. Two patients had adenomas; one without uptake of ^{99m}Tc-tracer, hence requiring control. It was unchanged after 22 months.

Gastroscopy with biopsy-detected peptic ulcer in two patients with PClR foci in the stomach. They received proton pump inhibitor and an ulcer eradication regime, respectively.

Four PClR foci were located to the recto-sigmoid area, two were diagnosed as diverticulitis by histopathology after sigmoid resection, and two were diagnosed as diverticulosis by colonoscopy.

Two patients had PClR focus in the kidney encompassing a renal cyst Type 2F [10] and an oncocytoma. The cyst had a diameter of 4.5 cm and multiple septa by CT and presented with a low ^{18}F-FDG uptake. It was unchanged by follow-up CT at 20 months. The oncocytoma was unchanged by ultrasound (US) at two years.

The prevalence of our 28 TP foci was 4.2% with a PPV of 80%, encompassing malignant, premalignant and benign lesions. Therapy was initiated for 25 lesions. Six surgical procedures were performed: a rectum resection and two sigmoid resections (8,034 US$ each), a lobectomy and a breast resection (4,967 US$ each) and a hemi-thyroidectomy (2,192 US$), 14 colonoscopies with polypectomy (1,461 US$ each), two gastroscopies with therapeutic regimes (1,458 US$ each), in addition to other monitoring procedures (total cost 5,344 US$). The total cost of investigating the seven FP foci was relatively low, 4,528 US$ (average 647 US$). The estimated total cost of all procedures was 69,471 US$ (1,984 US$ per incidental finding).

The literature search produced 1,257 publications (Figure 1). The excluded publications included 72 duplicates; 543 case reports, reviews or guidelines; and 396 publications where the title or abstract did not include data regarding analysis of the incidental ^{18}F-FDG-PET/CT findings in cancer patients. Full-text analysis of the remaining 246 studies left 13 studies matching our inclusion criteria. Another two studies were retrieved via references (Figure 1). In the 15 studies analysed, 15,101 cancer patients (age range: 16-93 years) had 1,639 incidental foci. A total of 549 foci were not investigated due to advanced diseases or for unknown reason or were lost to follow-up; 1,090 PClR foci in 1,068 patients were investigated, revealing

270 (25%) malignancies, 166 premalignant lesions (15%) and 206 (19%) benign lesions needing treatment (PPV 59%) (Table 1), whereas 448 foci were FP (Figure 2). The 549 foci that were not investigated imply a risk of bias. If they were all TP, the PPV would be 0.73, and if FP the PPV would be 0.39. Similar calculations in our data produced a PPV of 0.83 if the foci that were not evaluated had all been TP and 0.28 if they had been FP.

TABLE 1 / Overview of current study results compared with the results of the 15 previous studies analysed. The values are n (%).

Reference	Malignant findings & PPV	Premalignant findings & PPV	Benign findings & PPV	Relevant findings & PPV, total
Current study	4 (11.4)	18 (51.4)	6 (17.1)	28 (80)
Conrad et al, 2016 [11]	5 (16)	9 (29)	7 (22.6)	21 (68)
Even-Sapir et al, 2006 [12]	44 (36.6)	16 (13)	33 (27.5)	93 (77)
Sato et al, 2010 [18]	8 (57)	-	-	8 (57)
Britt et al, 2018 [19]	12 (25.5)	-	-	12 (25.5)
Casselden et al, 2019 [20]	4 (5.4)	9 (12)	25 (34)	38 (51.4)
Moletta et al, 2018[a]	25 (45.5)	4 (7.3)	5 (9)	34 (61.8)
Özkol et al, 2009[a]	17 (23)	9 (12.2)	26 (35)	52.2 (70)
Cohen et al, 2018 [14]	10 (77)	-	-	10 (77)
Sone et al, 2014[a]	56 (26.5)	14 (6.6)	-	70 (33.2)
Sebro et al, 2013[a]	10 (33)	4 (13)	1 (3)	15 (50)
Chopra et al, 2012 [15]	8 (8)	32 (31.5)	26 (25)	66 (63.5)
Gill et al, 2012 [16]	4 (40)	2 (20)	1 (10)	7 (70)
Malik et al, 2012 [17]	7 (16)	9 (21)	-	16 (37)
Tae et al, 2014[a]	8 (6)	-	-	8 (6)
Beatty et al, 2009 [13]	38 (28.5)	-	-	38 (28.5)

PPV = positive predictive value.
a) Please contact the corresponding author for further information.

Our frequency of FP findings was significantly lower than frequencies reported in the previous studies ($\chi^2 = 6.3$; $p < 0.05$) (Figure 2). There was no significant difference if TP malignant and premalignant lesions were grouped together or regarding benign lesions, but the frequency of TP malignant foci in our study was significantly lower than in the previous studies (Fisher's exact test, $p < 0.01$).

DISCUSSION

In our study, 28 of 35 PClR foci were clinically relevant whether malignant, premalignant or benign (PPV = 80%). In the reviewed articles, 642 of 1,090 foci were clinically relevant (PPV = 59%, range: 6-77%) [11-20]. The PPV values could be higher in case of a high percentage of TP findings among the foci that were not investigated. The same applies to our material. The differences in PPV may be due to differences in study design, study populations and PClR/incidentaloma definition. Some studies mentioned only second

primary malignancies (SPMs), detected by PET/CT in 25.5% of head and neck cancer patients [19]. Others reported malignant and premalignant lesions in 37% of patients referred to PET/CT for the staging of oesophageal cancer [17]. The frequencies of SPMs, premalignant and clinically relevant benign findings have been reported to be high in two studies, encompassing 21 of 31 melanoma patients (68%) [11] and 93 of 120 patients (77.5%) in a study similar to ours, including patients with a wide spectrum of malignancies [12] (Table 1).

Despite the discrepancy between our results and those of previous studies, it is obvious that relevant incidental ^{18}F-FDG-PET/CT findings are common in cancer patients, justifying further investigation. Fifteen of our PClR foci were colorectal lesions (42.8%) compared with 47.6-50% in other studies [11, 18]. In our study, follow-up colonoscopy after removal of polyps revealed no recurrence after up to 24 months, corresponding to previous results where the majority of polyps and cancers were removed radically at premetastatic stages [11, 18]. Endoscopic removal of such lesions can decrease the incidence of colorectal cancer by 53%.

There was one lung cancer (2.9%) and one breast cancer (2.9%) in our study compared with 1.5-10% [13, 18-20] and 1.9-5.2% [12, 13, 15], respectively, in the previous studies. Both current cases were without recurrence for 20 months and 36 months, respectively.

In our study, 8.5% of the lesions were located to the thyroid compared with 0.9-31.6% in the other studies [12, 15-17, 20]. Our patients had no sign of recurrence for up to 22 months.

Two current PClR foci were located to the kidney (5.7%) compared with 0.9-5.4% in the reviewed studies [12, 13]. The renal PClR foci, a renal cyst type 2F and an oncocytoma were unchanged by US and CT after 20 months and 24 months, respectively. This is in accordance with the 5-10% malignant potential of renal cysts type 2F [10] and the rare malignant potential of renal oncocytoma.

There were six inflammatory lesions (17%) in our study compared with 2.5-16.2% in previous studies [11, 12, 15, 20]. The lesions included two gastric ulcers and four diverticulitis/diverticulosis cases in the large bowel. The role of ^{18}F-FDG-PET/CT in the diagnosis of such lesions is unclarified; however, increased FDG uptake in inflamed tissues is common and can mimic malignant lesions [4, 5].

There were seven FP PClR foci in our study located to the rectum, colon, lymph nodes and testes; sites where physiological uptake is common [3]. In comparison, 448 of the reported 1,090 foci were FP [11-13, 15-20]. They were therefore significantly more frequent than in our material.

Our study aimed to investigate incidental findings by ^{18}F-FDG-PET/CT in cancer patients as they may have a 30% higher risk of developing SPMs than a comparable population. Such SPMs can be curatively treated if discovered at early stages. Moreover, cancer patients can have non-malignant findings needing treatment.

The average cost of the management of our PClR foci was 1,984 US$ per focus, and it was lowest for FP lesions and highest for necessary surgical procedures. Others have reported an average cost of 283 US$ (range: 248-311 US$). This difference may possibly be explained by different levels of health service and health insurance, resulting in cost differences between countries.

Our study had several limitations. It was designed as a single-centre study with follow-up analysis. Many PClR foci were not investigated due to advanced malignancies (Figure 2). The follow-up period of the investigated foci was only up to 32 months. Findings that were considered to be related to the known malignancy were not investigated; hence, it remains unclear whether these findings represent spread of the primary malignancy or synchronous conditions. Malignant lesions may manifest hyper-, iso- or hypo-FDG metabolism [12]. We considered FDG hypermetabolism as indicative of a relevant finding whether malignant or benign. Although lesions with iso- or hypo-FDG metabolism were also included when

presenting pathology by CT, the exact values for TN, FN and NPV were not obtainable.

CONCLUSIONS

Despite the occasional occurrence of FP findings, time and money consumption, incidental findings by ^{18}F-FDG-PET/CT should be assessed to final diagnoses as they may represent malignant, premalignant or benign conditions needing treatment, also in patients with known malignancies.

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LITERATURE

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A full list of references can be obtained by request to the corresponding author.

SUPPLEMENTARY MATERIAL