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Incidental detection of colorectal lesions on ^{18}F-FDG-PET/CT is associated with high proportion of malignancy: A study in 549 patients

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ABSTRACT

Background and study aims Further diagnostics of incidental colorectal lesions on ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is questionable. Therefore, we aimed to evaluate the clinical importance of incidentally detected colorectal lesions on FDG-PET/CT.

Patients and methods In the North Denmark Region, a retrospective study was performed among 19,987 patients who had an FDG-PET/CT from January 2006 to December 2015. Among these patients, we identified patients with a colonoscopy within 12 months from the PET/CT scan and a description of incidental colorectal PET-avid lesions on the PET/CT. PET findings were compared with colonoscopy-detected lesions and eventually histopathology.

Results Incidental PET-avid lesions were observed in 549 patients. Colonoscopy revealed lesions in 457 (83 %), among whom 338 patients had a final histopathological diagnosis. Malignant and premalignant lesions were found in 297 patients (54 % among patients with a PET-avid lesion). The lesions were cancer in 76 patients and adenoma in 221 patients of whom 30 had high-grade and 191 low-grade adenomas. The findings changed patient management in 166 cases (30 % of all patients with a PET-avid lesion). A colonoscopy-based surveillance program was initiated for 80 % of patients with high-grade adenoma. No patients with PET-avid lesions but normal colonoscopy developed colorectal cancer during 3 years of observation (median observation time 7 years).

Conclusions Incidental colorectal FDG uptake was infrequently observed, but when present, it was associated with a high rate of malignant or premalignant lesions. Our results indicate that patients with incidental colorectal FDG uptake should be referred to diagnostic work-up including colonoscopy.

Introduction

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computer tomography (PET/CT) is an established imaging modality in detection of a variety of malignancies and infectious diseases [1–3]. From time to time, imaging shows incidental sites of pathological uptake that may represent malignant or premalignant lesions. Incidental findings have been described in a number of organs, e. g. the adrenal glands (malignancy rate 20 %) and the thyroid (malignancy rate 50 %) [4–6].

This indicates that malignancy rates of incidental FDG-PET/CT lesions may vary among organs. Incidental uptake on FDG-PET/CT in the colon or rectum has been described in several studies [7]. Focal colorectal FDG uptake can indicate a variety of lesions, both benign and malignant. The risk of malignant and premalignant lesions reported ranges from 16 % to 100 %. In some cases, the nature of the FDG uptake is unclear [8, 9]. To reveal the nature of the incidental PET-avid lesions, further diagnostic work-up is needed. In the colon or rectum, this primarily includes colonoscopy with biopsy and histopathologic assessment [10, 11].

Previous studies included a limited number of patients. In a systematic review of 26 studies, the median number of included patients was 35. Only four studies included >100 patients, one with a maximum of 239 patients [7]. Only a few studies performed diagnostic work-up of patients with incidental colorectal FDG uptake but negative colonoscopy, or performed systematic colonoscopy in all the included patients with incidental FDG uptake [9]. Some studies stated that incidental colorectal FDG uptake can be nonspecific and that physiological FDG uptake is often observed in the colon and rectum [12–14]. Other studies reported a strong correlation between incidental colorectal FDG uptake and the lesion observed during colonoscopy [15–18]. Yet no management algorithm exists to suggest the optimal management of patients with incidental colorectal PET-avid lesions, and the decision whether to perform further diagnostic evaluation can be difficult [7].

To the best of our knowledge, we present data from the largest study of patients with incidental colorectal FDG-PET-avid lesions. All followed up by colonoscopy per institutional practice and year-long follow-up for patients with negative colonoscopy to evaluate the clinical importance of incidental colorectal PET-avid lesions.

Patients and methods

Patients

We reviewed files from all patients undergoing an FDG-PET/CT scan from January 2006 to December 2015 at Aalborg University Hospital, Denmark and who subsequently had colonoscopy within 12 months. Patients were identified by an electronic search of the procedure codes for FDG-PET/CT and colonoscopy. This hospital is the only site with PET/CT in the North Denmark Region, which has a population of approximately 600,000 inhabitants. The PET/CT scan reports of potentially eligible patients were reviewed by one person (SJK) for details on incidental findings in the colon or rectum. Any reporting of focal incidental uptakes in the conclusion or description of the PET/CT scan was included. Lesions finally characterized as physiological diffuse uptake by the nuclear medicine physicians were not regarded as incidental findings. Exclusion criteria were a present or prior history of colorectal cancer or inflammatory bowel disease.

PET/CT scan

The PET/CT was acquired on a VCT discovery True 64 PET/CT (GE Healthcare, Chicago, Illinois, USA) in accordance with institutional procedures (370 MBq of FDG, scan at 60 minutes, blood glucose of 11 mmol/L or less). The CT scan was performed as low-dose CT or diagnostic, contrast-enhanced CT depending on the reason for the referral and the time since the most recent diagnostic CT had been obtained. PET images were fused with CT and read visually and were semi-quantitatively assessed using a GE Advantage Workstation (GE Medical Systems, Milwaukee, Wisconsin, USA). Per institutional practice, two independent readers trained in radiology and nuclear medicine read the PET/CT scans and reached a conclusion in consensus.

Colonoscopy findings

Colonoscopy was performed using a flexible endoscope per common regional instructions at three hospitals in the North Denmark Region. Bowel preparation was carried out according to regional guidelines. The colonoscopy was performed by trained endoscopists. A few patients (n = 12) with an initial incomplete colonoscopy were referred to further examination where a sufficient colonoscopy was performed in all cases.

All colonoscopies were retrospectively reviewed through medical records to identify colorectal lesions revealed during colonoscopy in patients with incidental colorectal FDG uptake. The colorectal lesions were grouped as per their appearance on colonoscopy as likely cancer, premalignant, non-neoplastic and benign lesions. This in accordance with the phenotypic presentation of the lesions described in the colonoscopy description, which was based on the guidelines from the Danish Colorectal Cancer Group (DCCG). In patients with more than one lesion, only the most severe lesion was considered in the analysis.

The medical records for patients with incidental colorectal FDG uptake but a negative colonoscopy were reviewed to check for later discovery of colorectal lesion. The medical records were reviewed until May 2019.

Histopathological findings

Biopsy was performed in all patients with suspicious malignant or premalignant lesions (n = 393) on colonoscopy except from one patient with disseminated lung cancer who had three suspicious colonic adenomas. The lesions judged as benign by colonoscopy were, per institutional practice, not routinely biopsied.

Histopathological investigation of the biopsies was performed using the World Health Organization histological classification of tumors of the colon and rectum (4th edition). Specimens were categorized as cancer (colorectal cancer (CRC) and non-CRC), premalignant adenomas, non-neoplastic polyps and benign lesions. Premalignant lesions were categorized according to the evaluation of low or high degree of neoplastic dysplasia [19–21]. Benign lesions were subdivided into inflammation, diverticulosis [22] and other less common benign lesions.

Patients with cancer of the colon or rectum or adenomas were reviewed to check for indication for treatment [23].

Statistical analyses

Descriptive statistics including prevalence, positive predictive value (PPV) and sensitivity with a 95 % confidence interval (95 %CI) were used.

STATA version 14 (StataCorp LP, Texas, United States) was used for the statistical analyses; all statistical analyses were consulted with a biostatistician at Department of Biostatistics, Aalborg University Hospital, Denmark.

Approvals

Retrospective studies do not require ethical approval in accordance with Danish national legislation. The Danish Data Protection Agency approved the study (study ID 2015–176) and provided a waiver for informed consent regarding access to patient files.

Results

Patients

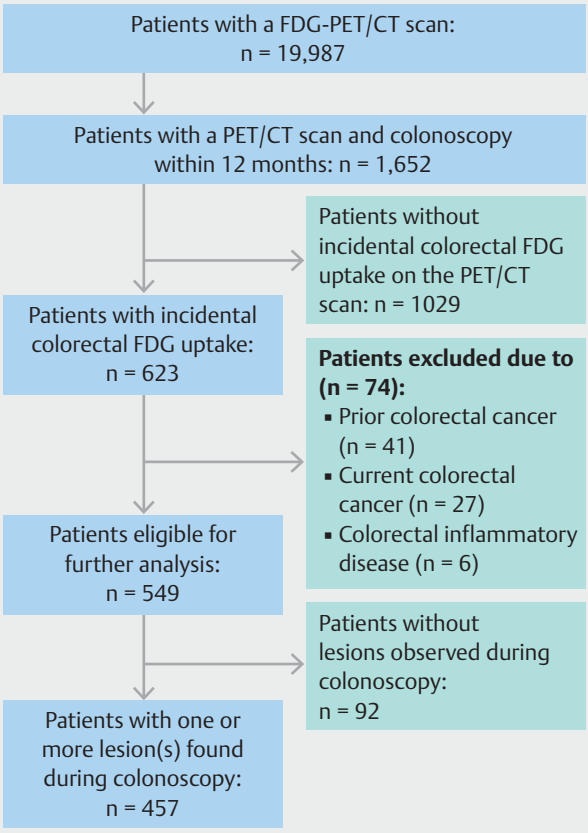
During the observation period from 2006 to 2015, an FDG-PET/CT scan was performed in 19,987 patients of whom 1,652 patients had a colonoscopy within 1 year from the PET/CT scan (median 22 days, range 1–350 days) (▶ **Fig. 1**). In total, 623 patients had incidental colorectal FDG uptake. Among these patients, 74 were excluded, most frequently due to a previous CRC. Thus, 549 patients were eligible for further analyses (mean age 68.5 years, standard deviation (SD) 9.5, 302 males and 247 females). The prevalence of incidental colorectal FDG uptake leading to colonoscopy was 2.7 %.

Most patients (457/549 patients, 83.2 %) with incidental colorectal FDG uptake had one or more lesions detected at colonoscopy (Patient example in ▶ **Fig. 2**). Among the 457 patients, 229 patients had one lesion and 228 had two or more lesions. A total of 917 lesions were found. The PPV and sensitivity for detection of any type of lesion from incidental colorectal FDG uptake were 83 % (95 %CI [80;86]) and 66 % (95 %CI [62;69]), respectively. Classification of lesions by colonoscopy is represented in ▶ **Table 1**.

Ninety-two patients had a negative colonoscopy of whom none were diagnosed with CRC within a median follow-up time of 7.2 years (range 3.4–12.6 years). Thirteen patients (14.1 %) had developed benign or low-grade dysplastic lesions as evidenced by colonoscopy within the follow-up period (mean 4.7 years; range 1.1–9.5 years).

Histopathological findings

For the 457 patients, the colorectal lesion was assessed with a biopsy in 338 (338/457 patients, 74.0 %). A biopsy was performed in all patients with a suspected cancer or a premalignant lesion (n = 297) on colonoscopy, except from one patient with disseminated lung cancer who had three suspected colonic adenomas. The non-neoplastic and benign lesions were less frequently histopathologically assessed by a biopsy. A biopsy was taken from 26 of the 61 patients with a non-neoplastic lesion (42.6 %) and from 15 of the 98 patients with a benign lesion judged by colonoscopy (15.3 %). A total of 338 patients had a final histopathological diagnosis.

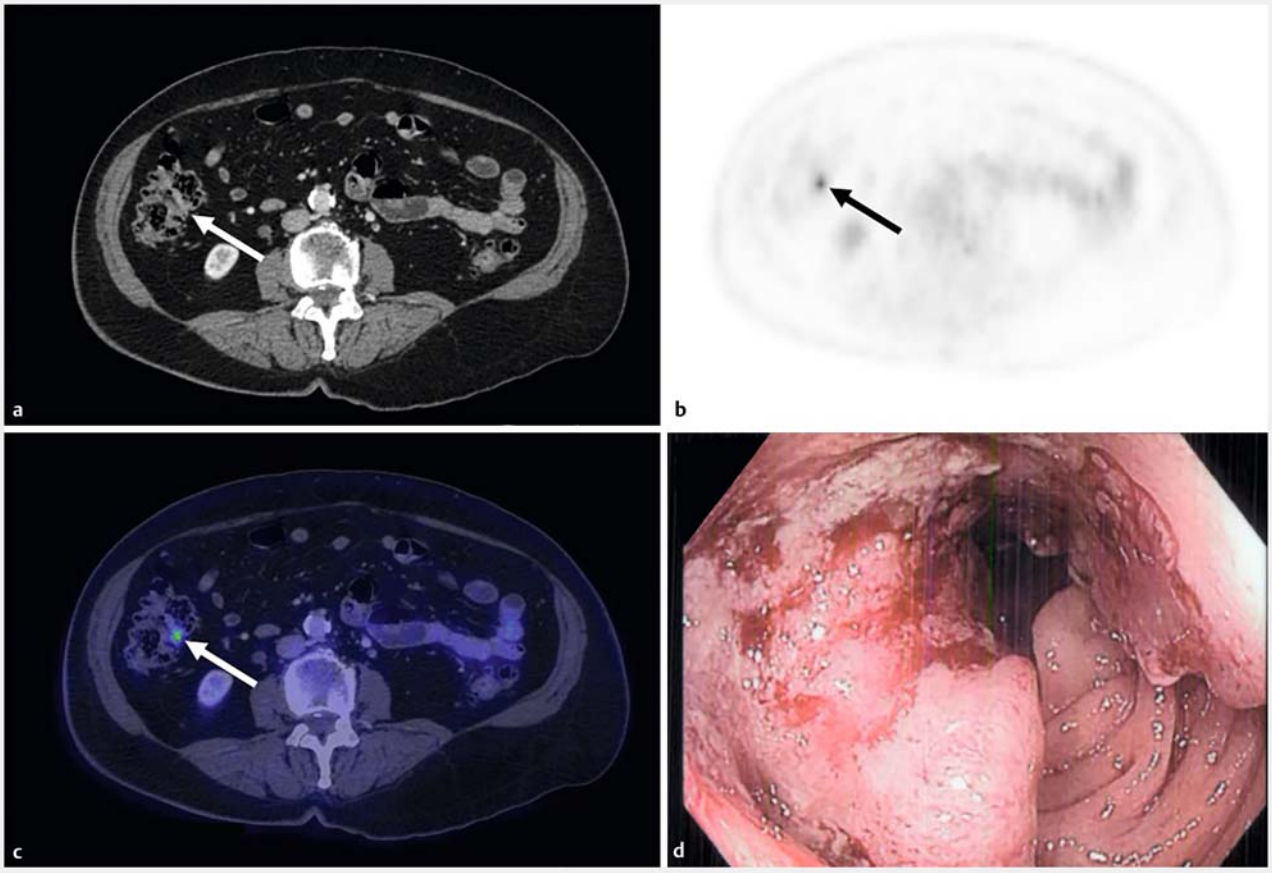


▶ **Fig. 1** Flowchart of the inclusion and exclusion process.

Among these 338 patients, 76 patients were diagnosed with cancer, 67 patients with CRC, eight patients with non-CRC (types of cancer: Mantel cell lymphoma, malign melanoma, squamous cell carcinoma, neuroendocrine cancer, medullary carcinoma, malign lymphoma), and one patient with CRC as well as non-CRC (Mantel cell lymphoma). A total of 221 patients were diagnosed with a biopsy-verified high- to low-grade adenomas, 30 patients with high-grade adenomas and 191 patients with low-grade adenomas. The PPV and sensitivity for detection of a cancer or premalignant lesion from incidental colorectal FDG uptake were 72 % (95 % CI [68;75]) and 57 % (95 % CI [53;60]), respectively; and for detection of a CRC 12 % (95 %CI [10;15]) and 10 % (95 %CI [8;12]), respectively. A total of 41 patients had a biopsy-verified non-neoplastic or benign lesion. The histopathological classification of the lesions is represented in ▶ **Table 2**.

Change of patient management

The overall findings had a notable impact on patient management, both at the time of the diagnosis and at follow-up. Among the 76 patients with an incidental cancer in the colon/rectum, 37 patients underwent intended curative treatment (surgery incl. chemotherapy before surgery, radiation therapy)



▶ **Fig. 2** An 86-year-old women had an ^{18}F-fluorodeoxyglucose positron emission tomography/computer tomography (FDG-PET/CT) scan because of a gynecological cancer. There was incidental FDG uptake in the sigmoid colon. The patient underwent colonoscopy-assisted biopsy, which showed colorectal cancer. **a** The CT image showing a colorectal lesion with an arrow indicating the site of most intense FDG uptake on the fused image. **b** The PET image. **c** Fused PET/CT image showing FDG uptake (standardized uptake value, SUV 18.5) in the recto sigmoid transition (white arrow). **d** Colonoscopy image showed the colorectal lesion.

and 29 patients received palliative treatment. Ten patients had no further treatment due to primary cancer prognosis or comorbidity (9 patients with CRC, 1 patient with non-CRC). In total 37 of the 76 patients had a change in patient management.

Because of the findings during colonoscopy and pathology, a surveillance program with colonoscopy was initiated in 24 of 30 patients (80 %) with high-grade dysplasia adenomas and in 105 patients of the 191 patients (55 %) with low-grade dysplasia adenomas.

Discussion

To the best of our knowledge, this study is the largest study of patients with incidental colorectal FDG-PET-avid lesions followed by colonoscopy per institutional practice and year-long follow-up for patients with negative colonoscopy. Pathology showed cancer or premalignant lesions in nearly 300 of 549 patients with PET-avid colonic accidental findings, including 67 patients with CRC and 30 patients with high-grade adenoma. In the majority of the patients, patient management was changed because of the pathology findings. This underlines that incidental FDG-PET-avid lesions in the colon should be followed up with colonoscopy and with histopathological assessment in case of suspicion of malignancy.

The wide use FDG-PET/CT imaging introduced the dilemma of incidental PET-avid lesions, which poses challenges to clinicians. The prevalence of incidental colorectal PET-avid lesions is, however, relatively low. In a review, studies from 2002 to 2012 [9], reported detection rates of incidental colorectal PET-avid lesions within a range of 0.4 % to 16.3 %. A meta-analysis by Treglia et al. reported a pooled prevalence of 3.6 % [9]. In the present study, we observed colorectal PET-avid lesions leading to colonoscopy among 2.7 % of the patients undergoing FDG-PET/CT for various reasons. The risk of incidental PET-avid lesions turning into malignant lesions is often the reason for referral to further diagnostic work-up. Risk of malignant and premalignant lesions was reported in the literature with a range of 16 % to 100 % of the cases. A meta-analysis based on 23 eastern and western studies described a pooled risk of malignant and premalignant lesions of 68 % [9]. In the present study, we found a risk of malignant lesions of 12 % and of premalignant lesions (adenomas) of 72 %. This illustrates a strong correlation be-

▶ **Table 1** Clinical characterization of lesions by colonoscopy in patients with incidental colorectal FDG uptake (n = 549).

Population	Colonoscopy
Malignant lesion	
▪ Cancer, n (%)	76 (13.8 %)
Premalignant lesion	
▪ Adenoma, n (%)	222 (40.4 %)
Non-neoplastic lesion	
▪ Hyperplastic polyp, n (%)	22 (4.0 %)
▪ Sessile serrate polyp, n (%)	5 (0.9 %)
▪ Unclassified polyp, n (%)	34 (6.2 %)
Benign lesion	
▪ Diverticulosis, n (%)	82 (14.9 %)
▪ Acute or chronic inflammation, n (%)	9 (1.6 %)
▪ Others (e. g. chronic inflammatory bowel disease), n (%)	7 (1.3 %)
No lesions detected	
▪ n (%)	92 (16.8 %)

▶ **Table 2** Final histopathological diagnosis of the biopsy-verified lesions discovered during colonoscopy in patients with incidental colorectal FDG uptake (n = 338).

Population	Histopathology
Malignant lesion (cancer)	
▪ CRC adenocarcinoma, n (%)	67 (19.8 %)
▪ Non-CRC, n (%)	8 (2.4 %)
▪ CRC and non-CRC, n (%)	1 (0.3 %)
Premalignant lesion (adenoma)	
▪ High-grade adenoma, tubular adenoma, n (%)	21 (6.2 %)
▪ High-grade adenoma, tubulovillous adenoma, n (%)	6 (1.8 %)
▪ High-grade adenoma, villous adenoma, n (%)	3 (0.9 %)
▪ Low-grade adenoma, tubular adenoma, n (%)	176 (52.1 %)
▪ Low-grade adenoma, tubulovillous adenoma, n (%)	7 (2.1 %)
▪ Low-grade adenoma, serrate adenoma, n (%)	5 (1.5 %)
▪ Low-grade adenoma, villous adenoma, n (%)	3 (0.9 %)
Non-neoplastic lesion	
▪ Hyperplastic polyp, n (%)	21 (6.2 %)
▪ Sessile serrate polyp, n (%)	5 (1.5 %)
Benign lesion	
▪ Acute or chronic inflammation, n (%)	8 (2.4 %)
▪ Others (e. g. chronic inflammatory bowel disease), n (%)	7 (2.1 %)

CRC, colorectal cancer.

tween incidental colorectal abnormalities detected on FDG-PET/CT images and colorectal lesions confirmed at histopathological assessment, where malignant and premalignant lesions often are diagnosed.

No published international management algorithm exists to inform management of patients with incidental colorectal FDG uptake. At our institution, all patients with incidental colorectal PET-avid lesions are automatically referred to colonoscopy. The findings of our study support that whenever a focal hot spot is detected within the large bowel or rectum, further diagnostic work-up such as colonoscopy and histopathological assessment should be performed to exclude malignant or premalignant lesions. Contingent on this is, however, that patients are deemed fit for further diagnostic work-up or have a reasonable prognosis for the lesions [24]. Salazar Andia and colleagues showed that PET/CT modified the diagnostic and treatment management in approximately 90 % of the patients undergoing colonoscopy for PET-avid lesions [17]; and Valente MA showed change in treatment of 85 % of patients with a diagnosed CRC [25]. This is somewhat in line with our findings. We observed a change in patient management for 37 of the 76 patients (49 %) diagnosed with a cancer in the colon or the rectum. A surveillance program with colonoscopy was established for 80 % of the patients with high-grade adenoma and 55 % of the patients with low-adenoma.

Most studies on FDG-avid colon lesions include a limited number of patients [7]. This study is the largest study of its kind with more than twice the number of the patients reported previously [26]. All the included patients with incidental colorectal FDG uptake described on the PET/CT scan were referred to colonoscopy with later histopathological assessment of the lesion in 74 % of the patients; such a systematic approach has not been conducted in previous studies [9]. Only four studies described a follow-up colonoscopy in patients with incidental colorectal FDG uptake but no lesions were discovered during the diagnostic colonoscopy [8, 27–29]. None of these four studies observed colorectal lesions at the follow-up colonoscopy. In our study, we observed no cases of colorectal cancer or high-grade adenoma at a follow-up colonoscopy after at least 3 years in patients with FDG uptake but negative diagnostic colonoscopy.

The study design of the present study was that of a historical cohort study, and the data was collected from the different registers at the university hospital. Even though it was institutional practice to perform colonoscopy in the case of FDG-avid colonic lesions, it can be hypothesized that for various reasons some patients did not receive a colonoscopy. The true epidemiology and malignancy rates of FDG-avid lesions should likely be examined in a prospective cohort. Colonoscopy revealed lesions in most, but not all patients with FDG-avid lesions. The true nature of the PET-avid lesions in patients with a negative colonoscopy remains unknown. However, none of nearly hun-

dred patients without colonoscopic findings developed colorectal cancer during an observation period at least 3.4 years, indicating that colonoscopy was sufficient as an investigative modality of FDG-avid lesions. Biopsy was not sampled for all lesions, especially not for apparently benign lesions detected during the colonoscopy. This practice was not unique for our study; such practice was described in other studies as well [17]. However, it is a limitation of our study.

Several patients presented with more than one lesion during colonoscopy. Every attempt was made to explore findings at the PET with the localization at colonoscopy, which is also described in the literature [30]. We did not explore the association of the anatomical location of the PET-avid lesions with individual findings on colonoscopy and the final pathological reference. Here, we focused on the clinical impact of PET-avid incidental findings on the final outcome at the patient level. A separate paper is in preparation for lesion analysis.

Conclusion

Our study demonstrated that incidental colorectal FDG uptake was infrequently observed. However, when present, it was associated with a high risk of cancer and/or high-grade adenomas leading to change of patient management. It is recommend that patients with incidental colorectal FDG uptake be referred to colonoscopy in all cases where the patient is considered suitable for further treatment. We encourage societies to issue recommendations for handling of FDG-avid colonic lesions.

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Competing interests

Drs. Kousgaard, Petersen, and Thorlacius-Ussing have received grant support, un related to the study. Dr. Petersen has received fees for speaking at meetings arranged by Astellas Pharma, Sanofi-Genzyme, Janssen Pharma, and Bayer, and has been a paid participant at conferences organized by Sanofi-Genzyme and Bayer; and receives consulting fees from KLIFO Drug Development Council, Copenhagen and ljpmedical, Aalborg, Denmark.

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