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**Title**

# Diagnostic accuracy of CT in patients with non-specific symptoms of cancer referred directly to CT from general practice: a retrospective follow-up study


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## Abstract

### Background

The Urgent Referral Cancer Patient Pathway for Non-Specific Symptoms and Signs of Cancer (NSSC-CPP) was introduced in Denmark in 2012 to reduce delay in cancer diagnosis. In the Zealand region, it includes direct referral from GPs to contrast-enhanced CT of thorax, abdomen, and pelvis (ceCT-TAP). In 2013, the NSSC-CPP cancer prevalence was 20%, but easy access to CT may change referral patterns.

### Aim

To examine cancer prevalence, diagnostic accuracy of ceCT-TAP, and changes in NSSC-CPP referral patterns.

### Design and Setting

Retrospective cohort study from the Zealand region of Denmark.

### Method

We included patients referred by GPs with non-specific symptoms or signs of cancer from 1 July to 31 December 2019. Primary endpoints were cancer prevalence and diagnostic accuracy of ceCT-TAP. Secondary endpoints were cancer types, referral trends from 2012–2019, and prevalence of GP-reported symptoms and clinical findings. Patients were followed until cancer diagnosis or up to 12 months after ceCT, whichever came first.

### Results

729 referrals were recorded, a fivefold increase compared to 140 in the same period in 2013. Malignancy was diagnosed in 95 patients (13%). Twelve patients had a false-negative ceCT-TAP result, yielding a negative likelihood ratio for malignancy of 0.15.

### Conclusion

Despite a fivefold increase in GP referrals for ceCT-TAP since 2012, it remains an important diagnostic tool, identifying malignancy in one in seven patients. However, as the negative likelihood ratio was >0.10, a normal ceCT-TAP does not convincingly rule out cancer and should not stand alone as the only decision-support tool.



**Keywords**: Denmark; cancer; cancer patient pathway; computed tomography; diagnostic radiology; general practice.

## How this fits in

This retrospective study validates the efficacy of ceCT-TAP within Denmark's NSSC-CPP, identifying malignancies in 13% of GP-referred cases despite a fivefold referral increase since 2012. It highlights the pathway's role in facilitating earlier cancer detection, yet underscores ceCT's limitations (LR- 0.15), as certain malignancies remain undetected, necessitating a multimodal diagnostic approach to enhance accuracy.

## Introduction

Absence of organ-specific symptoms in cancer is associated with longer time to diagnosis and treatment onset, which in turn is associated with advanced cancer stage at diagnosis and poorer survival rates [1][2][3].

To address this a Non-Specific Symptoms And Signs Of Cancer Pathway (NSSC-CPP) was implemented in 2012 in Denmark.
In the NSSC-CCP, the GP follows a two-step process. Step 1 includes medical history, physical examination and a recommendation of performing a standardized blood test panel. If inconclusive, a contrast-enhanced computed tomography of the thorax, abdomen and pelvis (ceCT-TAP) is performed (step 2).
We have previously reported the key role of ceCT-TAP in the NSSC-CCP and found that 20% were diagnosed with malignancy in a 2013-2015 cohort [4]. The negative likelihood ratio of ceCT-TAP in the NSSC-CCP was 0.1 with 98% negative predictive value, thus a normal CT efficiently ruled-out malignancy [4].

In 2015, NICE altered the recommendation of active work-up from 5% to 3% risk of cancer [5], and an unpublished internal survey from our unit suggested a marked increase in patients referred for ceCT-TAP in NSSC-CCP. Thus, with the present study we aimed to investigate both trends in cancer prevalence and number of referrals as well diagnostic accuracy of ceCT-TAB and as prevalence of GP-reported symptoms and signs at referral to ceCT-TAP.

## Methods

### Design and patient population

This retrospective single-centre cohort study included patients ≥18 years referred by their GP in NSSC-CPP to a CT of chest, abdomen and pelvis (ceCT-TAP) at the Department of Radiology (Zealand University Hospital, Roskilde and Køge, Region Zealand, Denmark) between July1st to December 31st, 2019. Temporal trend of prevalence of referral to ceCT-TAP was reported annually from 2012-2019 (July 1st to December 31st).

All citizens in Denmark have access to tax-paid, free-for-all health care, which is organized into five regions of which Region Zealand serves a population of 835,000 inhabitants. General practitioners (GPs) serve as primary care gatekeepers, initiating and coordinating referrals. Based on NSSC-CPP results, the GP decides treatment and care, or referral to specialized hospital department.

The Danish Patient Safety Authority and the Danish Data Protection Agency approved the study before collection of data was carried out.

### Computed tomography

Contrast-enhanced CT (ceCT) scans of the chest, abdomen, and pelvis were performed using multi-row detector scanners (Philips or Siemens). Intravenous contrast was administered in the portal-venous phase for the thorax and abdomen and in the arterial phase for the liver, except in patients with an estimated glomerular filtration rate (eGFR) below 30, who were scanned without contrast. All scans were reviewed by a team of general radiologists.

### Categorization of ceCT-TAP results

Radiological findings from ceCT-TAP scans were categorized into four groups based on the original descriptions provided by an experienced oncological radiologist (Hanne Sandstrøm, HS), who was blinded to clinical data:

1. No cancer and no abnormal findings,
2. No suspicions of cancer, but findings that for other reasons warrant further workup (eg. aortic aneurysms),

3. Possible cancer, abnormal findings that could be malignant,

4. Probable cancer.

Re-evaluation: ce-CT initially categorized as group 1 or 2 were re-evaluated if a diagnosis of cancer was made during the study period to determine if the cancer was identifiable in retrospect. The same oncological radiologist (HS) performed re-evaluation.

**Data collection**

**Patient identification and data collection**

Patients were identified using a unique code for NSSC-CPP ceCT-TAP of the chest, abdomen, and pelvis in the Radiology Information System (RIS). No efforts were made to identify incorrectly tagged ceCT scans. Patient data were retrieved from electronic patient records and national health databases, including RIS, Picture Archiving and Communication System (PACS), the regional electronic health record system EPIC, and the Danish Pathology Database (excluding non-melanoma skin cancer).

The date of the ceCT-TAP scan was defined as day 0, and a cancer diagnosis within the subsequent 12 months was considered the diagnostic outcome.

All cancers within the subsequent 12 months were retrieved from the Danish Pathology Database.

**Patient Symptoms and Clinical Findings**

Symptoms and clinical findings reported by the general practitioner (GP) at the time of referral were extracted from the original ceCT referral texts, which were written in free-text format without the use of checkboxes.

**Blood Test Data**

We recorded whether patients had undergone a full blood test panel as recommended by NSSC-CPP guidelines. This panel includes red and white blood cell counts with differentials, platelets, renal function tests (including total calcium and albumin), liver function tests, C-reactive protein, glucose, pancreas-specific amylase, lactate dehydrogenase (LDH), myeloma protein, immunoglobulins G, A, and M, and coagulation factors II, VII, and X.

As data on patients who did not proceed to ceCT-TAP within the NSSC-CPP were unavailable, we could not accurately assess the diagnostic performance of blood tests for malignancy.

### Statistics

Statistical analysis was performed using Microsoft Excel for Windows XP. Categorical variables were described discrete values (%), and intergroup difference analysed with T-test. Continuous variables were described as means. Intergroup differences were assessed using Pearson's *Chi*$^2$ test and Fisher's exact test. Statistical significance was ascribed at $p < 0.05$.

To account for multiple testing, we applied a false discovery rate (FDR) correction (Benjamini-Hochberg method) to all p-values across the 35 variables examined. A q-value < 0.05 was considered statistically significant. True positive ceCT-TAP scan was defined as a radiological classification of groups 3 or 4 and with a cancer diagnosis within the following 12 months. True negative ceCT-TAP scan was defined as a radiological classification to groups 1 or 2 and no cancer diagnosis within the following 12 months. Based on these categorizations, we calculated true-positive, true-negative, false-positive, false-negative, sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), positive predictive values (PPV), and negative predictive values (NPV). Additionally, we calculated a worst-case scenario in which fatalities in patients not diagnosed with cancer, were considered false-negative cancer cases [6].

## Results

### Study population

A total of 729 patients having ceCT-TAP from July 1$^{st}$ to December 31$^{st}$ 2019 were identified: 34 were excluded from further analysis due to duplicate referrals, non-attendance, or cancellations (Appendix Figure 1), thus totally 729 cases were eligible for inclusion. Figure 1 illustrates the annual increase in referrals, corresponding to a fivefold increase from 2012.

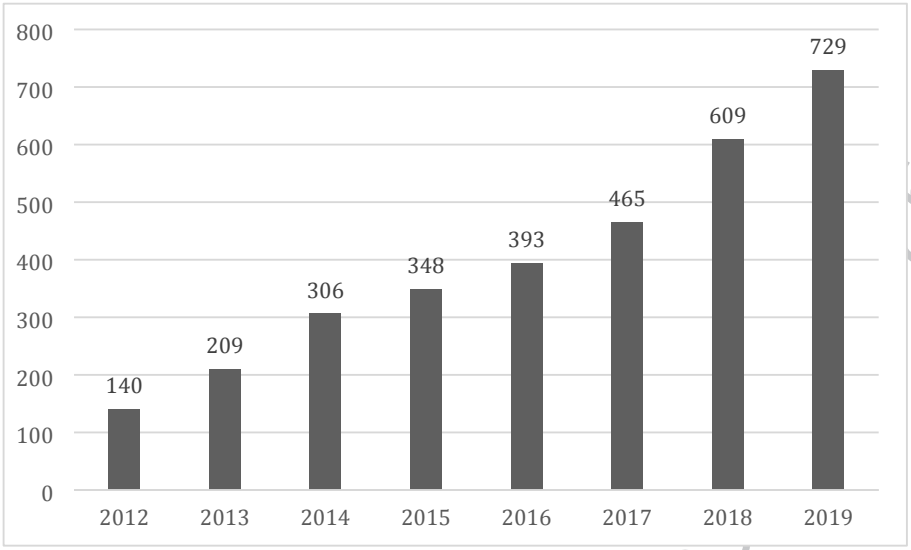


*Figure 1. Annual increase in referrals from 01 July to 31 December (half-year interval chosen to compare with our 2013 report [4])*

**Cancer prevalence (primary endpoint)**

Totally 95 (13%) subjects were diagnosed with cancer. The diagnostic properties of ceCT-TAP are shown in Table 1 In total, 52 patients died during the 12-month follow-up period, of whom 37 (65%) were diagnosed with cancer. A worst-case scenario - in which fatalities in patients not diagnosed with cancer were considered as false-negative cancer cases - did not significantly change the diagnostic properties (see Appendix Table S1).

**Table 1** Diagnostic rates of ceCT-TAP for malignancy

| | **Diagnosed with malignancy** | **No malignancy** | *Total* |
|---|---|---|---|
| **Malignancy suspected (Groups 3 and 4)** | 83 | 88 | *171* |
| **Malignancy not suspected (Groups 1 and 2)** | 12 | 546 | *558* |
| | | | |
| **Sensitivity** | 0.87 | **Specificity** | 0.86 |
| **Positive predictive value, PPV** | 0.49 | **Negative predictive value, NPV** | 0.98 |
| **Positive likelihood ratio, LR+** | 6.3 | **Negative likelihood ratio, LR-** | 0.15 |

**ceCT-TAP classification and post-CT referrals**

Table 2 shows the radiological classification of ceCT-TAP into increasing likelihood of malignancy. Most patients were classified as having a normal CT (group 1) and of these only 33% were referred for further work-up. Table 2 shows a positive and significant correlation between the severity of radiological findings (CT groups) and the likelihood of referral for further diagnostic workup ($p$ <0.005, $Chi^2$-test). However, Table 2 also shows that 20% of patients referred in an organ-specific cancer pathway had a CE without cancer suspicion.

**Table 2.** Radiological classification of ceCT-TAP and later referral patterns

| ceCT-TAP result category | Group 1: No abnormal findings | Group 2: Abnormal findings but cancer unlikely | Group 3: Abnormal findings: cancer possible | Group 4: Abnormal findings: cancer likely |
|---|---|---|---|---|
| **Total patients (%)** | 423 (58.0) | 134 (18.4) | 85 (11.5) | 87 (11.9) |
| **No referral** | 286 (67.6) | 42 (31.3) | 13 (15.5) | 1 (1.1) |
| **Referrals** | | | | |
| **Organ-specific cancer pathway** | 31 (7.3) | 17 (12.7) | 38 (45.2) | 61 (70.1) |
| **Unknown primary tumor** | 20 (4.7) | 12 (8.9) | 10 (11.9) | 2 (2.3) |
| **Non-cancer pathway** | 85 (20.1) | 62 (46.3) | 20 (23.8) | 9 (10.3) |
| **Generalists in tertiary care (Diagnostic Centre)** | 1 (0.2) | 1 (0.7) | 4 (4.8) | 14 (16.1) |

Table 3 shows the distribution of cancer diagnoses and that pancreatic cancer (17%), lung cancer (14%) and haematologic malignancy (13%) were the most predominant. Table 3 also depicts that twelve patients in groups 1 and 2 (no suspicion of cancer) were diagnosed with malignancy in the study period. In retrospect one case of lung cancer and one case of oesophageal cancer were reclassified as probable cancer (group 3). The remaining ten cancers were not visible in retrospect: haematological cancer ($n$=6), rectal cancer, cerebral glioblastoma, breast cancer, and malignant melanoma ($n$=1 each). Of notice, only eight had the mandatory blood test panel prior to ceCT-TAP.

**Table 3.** Prevalence of malignant diagnoses stratified by ceCT-TAB result

| Type cancer | Malignancy not suspected, Groups 1 + 2 | Malignancy suspected, Groups 3 + 4 | Overall prevalence, % |
|---|---|---|---|
| Pancreatic cancer | 0 | 16 | 17% |
| Lung cancer | 1 | 12 | 14% |
| Haematological cancer | 6 | 6 | 13% |
| Colorectal cancer | 1 | 10 | 11% |
| Urogenital cancer | 0 | 11 | 11% |
| Breast cancer | 1 | 8 | 9% |
| Upper gastrointestinal cancer | 1 | 5 | 6% |
| Malignant melanoma | 1 | 1 | 2% |
| Unknown origin cancer | 0 | 1 | 1% |
| Other: rare cancers * | 1 | 13 | 15% |
| **Total** | **12** | **83** | **100%** |

* Rare cancers: Groups 1+ 2: Glioblastoma (*n*=1); Groups 3+4: Cholangiocarcinoma (*n*=6), Hepatocellular carcinoma (*n*=3), Sarcoma (*n*=2), Liposarcoma (*n*=1), and Thyroid carcinoma (*n*=1).

Table 4 shows that patients diagnosed with cancer were older and had significantly higher 12-months-mortality. Table 4 also depicts symptoms and signs reported by the GP at referral for ceCT-TAP. Totally, in 138 cases (19%) GPs reported a 'gut feeling' of cancer, and was one of few symptoms and signs associated with malignancy. After correction for multiple comparisons, only patient's age, and reported anemia or GP's 'gut feeling' remained statistically significant. The positive and negative likelihood ratios for GP's 'gut feeling' were only 1.7 respectively 0.86.

**Table 4:** Association between a final diagnosis of malignancy and gender, age, and symptoms and signs as reported by GP at ceCT-TAP referral.

| | **Malignancy diagnosed** *n*=95 (13%) | **No malignancy** *n*=634 (87%) | *P*-value |
|---|---|---|---|
| Gender (female) % | 55 (49.5) | 347 (54.7) | 0.56 |
| Age (years) | 72 (43-94) | 65 (20-94) | **<0.005** |
| Full blood test panel before ceCT (%) | 55 (49.5) | 314 (57.9) | 0.13 |
| Died within 12 months from ceCT (%) | 37 (38.9) | 17 (2.7) | **<0.005** |

| From GP report: symptoms (%) | | | |
|---|---|---|---|
| Weight loss | 48 (50.5) | 278 (43.8) | 0.22 |
| Affected general condition | 16 (16.8) | 102 (16.1) | 0.85 |
| Fatigue | 30 (31.6) | 199 (31.4) | 0.97 |
| Vertigo | 2 (2.1) | 32 (5.0) | 0.20 |
| Excessive sweating | 8 (8.4) | 75 (11.8) | 0.33 |
| Patient noticed a tumor | 4 (4.2) | 6 (0.9) | **0.03** |
| Respiratory symptoms | 25 (26.3) | 141 (22.2) | 0.38 |
| Digestive system symptoms | 47 (49.5) | 303 (47.8) | 0.76 |
| Cardiovascular symptoms | 0 (0.0) | 21 (3.3) | 0.05 |
| Urinary tract symptoms | 4 (4.2) | 12 (1.9) | 0.15 |
| Neurological symptoms | 0 (0.0) | 10 (1.6) | 0.25 |
| Musculoskeletal symptoms | 14 (14.7) | 114 (18.0 | 0.44 |
| Skin symptoms | 2 (2.1) | 13 (2.1) | 0.29 |
| Reproductive system symptoms | 1 (1.1) | 1 (0.2) | 0.77 |
| No symptoms | 1 (1.1) | 11 (1.7) | 0.15 |
| Other symptoms | 1 (1.1) | 3 (0.5) | 0.52 |
| **From GP report: signs (%)** | | | |
| Affected general condition | 27 (28.4) | 65 (10.3) | **<0.005** |
| GP registered weight loss | 0 (0.0) | 2 (0.32) | 0.59 |
| Anemia | 15 (15.8) | 51 (8.0) | **<0.005** |
| GP felt tumor | 15 (15.8) | 37 (5.8) | **<0.005** |
| Abnormal blood samples | 32 (33.7) | 126 (19.9) | **<0.005** |
| Respiratory | 2 (2.1) | 32 (15.1) | 0.11 |
| Digestive system | 19 (20.0) | 67 (10.6) | **0.01** |
| Cardiovascular | 1 (1.1) | 5 (0.8) | 0.39 |
| Urinary tract | 0 (0.0) | 2 (0.3) | 0.76 |
| Neurological system | 0 (0.0) | 1 (0.2) | 0.87 |
| Musculoskeletal system | 0 (0.0) | 19 (3.0) | 0.1 |
| Reproductive system | 1 (1.1) | 1 (0.2) | 0.23 |
| Skin | 1 (1.1) | 3 (0.5) | 0.34 |
| No findings | 22 (23.2) | 304 (47.9) | **0.01** |
| GP's ***'gut feeling'*** | 28 (29.5) | 110 (17.6) | **<0.005** |

## Discussion

### Summary

This study shows that despite a fivefold increase in GP referrals for ceCT-TAP in the NSSC-CPP from 2012 to 2019 due to non-specific symptoms and signs, the prevalence of detected malignancy declined only modestly from 20% to 13%. This corresponds to an increase in numbers-needed-to-scan from five to seven, which remains substantially lower than in screening programmes, where values typically range from 100 to 500 [7–9]. The absolute number of cancers detected also increased, likely reflecting earlier recognition of suspicious symptoms rather than a true increase in cancer prevalence [10]. We speculate that in 2013, more patients were diagnosed later in their disease trajectory, either due to organ-specific symptoms or during emergency admission with more pronounced systemic symptoms [10,11]. Being diagnosed during an emergency hospital admission carries a worse prognosis than during planned admissions, where emergency admission can indicate poor physical or psychosocial resources [11].

Diagnostic accuracy analysis revealed insufficient likelihood ratios to confidently rule cancer in (LR+ <10) or out (LR– >0.1) [19]. Not all cancer types are readily detectable on ceCT-TAP, as lesions may be located in non-scanned regions (e.g., brain, skin, or extremities) or be radiologically occult (e.g., bone marrow). This was seen in 10 of the 12 missed cancers in our cohort, including haematological, rectal, glioblastoma, breast cancer, and malignant melanoma, some of which could represent aggressive interval cancers developing during the 12-month follow-up [12]. PET-CT has shown promising results in the NSSC-CPP setting, with improved specificity and accuracy, and a non-significant trend toward higher sensitivity compared to ceCT-TAP [13].

Symptoms reported by GPs were heterogeneous, with weight loss being the most frequent (44.7%), although it was not associated with increased cancer risk [14,15]. A GP's "gut feeling" remained a strong predictor of malignancy, but with LR+ and LR– far from conclusive [16–18].

In 77% of patients, ceCT-TAP did not indicate cancer; however, findings often prompted further evaluation for other conditions, with 27% referred to non-cancer pathways. In 58.2%, no abnormal findings were detected, and 67.2% of these had no further hospital follow-up. This highlights the relevance of ceCT-TAP in ruling out cancer and detecting other significant conditions, although this was not the primary focus of the study. Overall, one in seven patients referred had cancer, confirming ceCT-TAP as an important diagnostic tool, albeit not a standalone one.

**Strengths and limitations**

Strengths of this study include a clearly defined cohort of consecutive patients within a predefined timeframe, minimal missing data, complete follow-up, and access to regional electronic patient records and national pathology data. All patients were identified via procedure codes, and none were lost to follow-up. Statistical methods followed well-established standards, including rigorous criteria for reporting diagnostic accuracy (LR+ and LR–) [19].

Limitations include reliance on GP-reported symptoms as stated in CT referrals, which may differ from patient-reported symptoms [20–22]. Lack of access to GP medical records could mean that additional symptoms or clinical findings were not captured. The dataset is pre-COVID-19; however, Grønnemose et al. reported stable referral numbers between 2018 and 2021, with only a transient drop in cancer prevalence in 2020 [23]. Referral bias may also have influenced which symptoms were reported, as GPs might prioritize those likely to result in accepted referrals [26].

**Comparison with existing literature**

Several studies have observed declining cancer prevalence with increased familiarity with referral pathways [23–26]. Grønnemose et al., studying another Danish region where GPs cannot directly refer to ceCT-TAP, observed a more marked drop in malignancy prevalence from 40% in 2014 to 19% in 2021 [23]. In that cohort, 75% of patients were GP-referred, corresponding to 14 out of 19% diagnosed with cancer, which is similar to our 13%. Differences between studies may reflect regional organization of diagnostic work-up, as the other study's hospital-based diagnostic centre also received referrals from hospital departments, unlike our direct GP referral system.

Types and distribution of cancers remained largely consistent with prior years. Pancreatic and lung cancers remained most common, both of which are associated with vague or non-specific symptoms in advanced stages [14]. Haematological cancers were as prevalent as lung cancer at 12-month follow-up, but only 50% were visible on initial ceCT-TAP, reflecting the limitations of this modality for early detection.

Diagnostic accuracy of ceCT-TAP alone remains insufficient to guide further work-up, as LR+ was below 10 and LR– above 0.1 [19].

PET-CT has shown promising results in the NSSC-CPP setting, demonstrating significantly better specificity and accuracy, along with a non-significant trend toward higher sensitivity

compared to ceCT[13]. Thus, PET-CT may offer diagnostic advantages, but economic, logistical, and clinical considerations must be carefully weighed before broad implementation in the NSSC-CPP pathway *[13].*

GP-reported “gut feeling” continues to be a strong predictor of malignancy, consistent with prior studies [16–18], although it cannot independently confirm or exclude cancer. Other reported symptoms, such as weight loss, were not consistently associated with cancer, aligning with findings by Lebech et al. [14] but differing from de Chiffre et al. [15].

**Implications for research and/or practice**

Our data show that GP use of ceCT-TAP in the NSSC-CPP has increased markedly since 2012, reflecting earlier recognition of suspicious symptoms and possibly increased clinical confidence in referral pathways. One in seven patients was found to have cancer, confirming ceCT-TAP as a clinically relevant decision-supporting tool. However, because a normal ceCT-TAP does not convincingly rule out cancer (LR– >0.1), it should not be used in isolation. Clinical judgement, patient history, physical examination, and complementary investigations remain essential.

Future research should explore integrated diagnostic strategies, potentially incorporating PET-CT and structured clinical algorithms, to improve early cancer detection in patients with non-specific symptoms. Further studies may also investigate optimal thresholds for referral to balance early diagnosis with healthcare resource utilization, considering both cancer and non-cancer outcomes. Finally, evaluating patient trajectories after non-cancer findings on ceCT-TAP may help optimize follow-up protocols and enhance patient-centered care.

## Declaration

- **Ethics approval and consent to participate:** The Danish Patient Safety Authority and the Danish Data Protection Agency, which is an independent authority that supervises compliance with the rules on protection of personal data, approved the study before data collection was carried out (approval No REG-012-2021). All methods were performed in accordance with the relevant guidelines and regulations. Neither patients nor the public were involved in the planning of the study.

- **Consent to Publication:** Not applicable.

- **Availability of data and materials:** Data are available from the corresponding author, Mads Rømer Skøtt, upon reasonable request.

- **Competing interests:** None declared.

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