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Adrenal incidentalomas and effectiveness of patient pathway transformation

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ABSTRACT

INTRODUCTION. A total of 10% of older individuals harbour adrenal incidentalomas and need dedicated adrenal CT to exclude malignancy and biochemical evaluation. These investigations tax medical resources, and diagnostic delay may cause anxiety for the patient. We implemented a no-need-to-see pathway (NNTS) in which low-risk patients only attend the clinic if adrenal CT or hormonal evaluation is abnormal.

METHODS. We investigated the impact of a NNTS pathway on the share of patients not requiring an attendance consultation, time to malignancy and hormonal clarification, and time to end of investigation. We prospectively registered adrenal incidentaloma cases (n = 347) and compared them with historical controls (n = 103).

RESULTS. All controls attended the clinic. A total of 63% of cases entered and 84% completed the NNTS pathway without seeing an endocrinologist; 53% of consultations were avoided. Time-to-event analysis revealed a shorter time to clarification of malignancy (28 days; 95% confidence interval (CI): 24-30 days versus 64 days; 95% CI: 47-117 days) and hormonal status (43 days; 95% CI: 38-48 days versus 56 days; 95% CI: 47-68 days) and a shorter time to end of pathway (47 days; 95% CI: 42-55 days versus 112 days; 95% CI: 84-131 days) in cases than controls ($p \leq 0.01$).

CONCLUSION. We demonstrated that NNTS pathways may be an efficient way of handling the increased burden of incidental radiological findings, avoiding 53% of attendance consultations and achieving a shorter time to end of pathway.

FUNDING. Supported by a grant from Regional Hospital Central Denmark, Denmark. The study was approved by the institutional review boards of all participating hospitals.

TRIAL REGISTRATION. Not relevant.

A healthcare system challenged by a changing population demography, limited availability of healthcare workers and limited funding calls for innovation and challenges the wisdom of established clinical routines. Incidental radiological findings are an ever-increasing problem due to increased CT use and resolution. In Denmark, CT use rose by 250% from 2003 to 2014 [1]. Corresponding international data support a continued annual increase of 3.4-5.2% (40-66% increase per decade) [2]. Incidental findings are present on approximately 40% of all CTs [3]. Furthermore, 3% of people aged 50 years and 10% of older individuals harbour adrenal incidentalomas (AIs) [4].

With a few exceptions, all patients with AIs should undergo a dedicated adrenal CT imaging to exclude malignancy (reported in 3% of cases) along with biochemical evaluation to exclude hormonal hypersecretion including primary hyperaldosteronism (PHA) (3%), pheochromocytoma (7%) and hypercortisolism (12%), particularly mild autonomous cortisol secretion [4]. The investigation of AIs requires medical resources, causes anxiety and may result in inconvenience for the patient. These figures underpin the need for a more rational use of health resources.

We suggest a no-need-to-see (NNTS) patient pathway in which the patient is discharged from the outpatient clinic without seeing a physician in case of an adrenal CT with normal attenuation values and normal hormonal evaluation. The design of NNTS patient pathways requires knowledge of the *a priori* risk of disease, risk factors and diagnostic caveats; and an understanding of the sensitivity and specificity of the diagnostic modalities applied.

We hypothesised that a NNTS pathway would reduce attendance consultations without affecting time to clarification of hormonal or malignancy status.

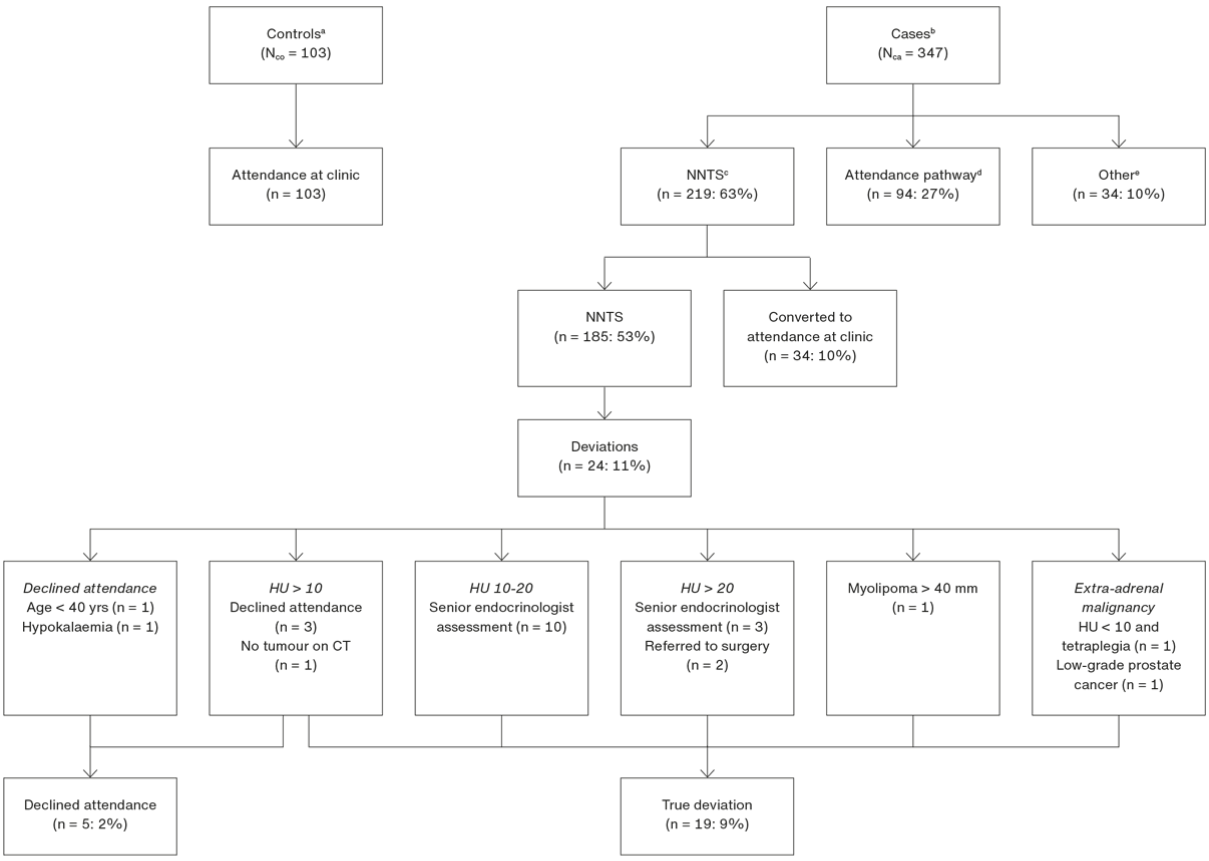
METHODS

Participating hospitals and study period

The endocrine outpatient clinics at three regional hospitals and at Aarhus University Hospital, Denmark, participated, representing a catchment population of 816,691 persons. The inclusion period was 12 months from inclusion was initiated in each centre. Patients were followed until a conclusion was reached regarding their malignancy status and hormonal hypersecretion, or until the pathway concluded because of the patient's wish or due to death.

Cases were registered consecutively and prospectively. All patients were adults referred with AIs described as ≥ 10 mm to one of the four participating outpatient endocrine clinics and assigned to one of three pathways; NNTS, "Attendance-pathway", or "Other ″based on the patient's individual risk profile as presented in **Figure 1**.

FIGURE 1 Patients by pathways.



HU = Hounsfield units; NNTS = no-need-to-see.
a) Retrospectively identified patients with adrenal incidentalomas during 2018.
b) Consecutively and prospectively registered, adults referred with adrenal incidentalomas described as ≥ 10 mm.
c) Low-risk patients defined as follows: > 40 yrs of age, no recent or current malignancy, no hypokalaemia except what is explainable by diuretics or hypomagnesaemia, no treatment-resistant hypertension, treated with < 4 antihypertensive agents irrespective of type, no hypertension before the age of 35 yrs.
d) Patients not designated as low-risk patients.
e) Patients not meeting the NNTS pathway criteria and who did not attend the clinic due to, e.g., critical comorbidities.

Controls were retrospectively identified patients with AIs investigated at either Viborg or Silkeborg regional hospital during 2018 (n = 103), all following the "*Care as usual*" pathway with attendance at the clinic.

The project was approved by the institutional review boards of all participating hospitals in accordance with Danish legislation on quality control studies.

The study cohort, adrenal CT, biochemical work-up and data collection are described in detail in the supplementum and summarised in Figure 1 and Supplementary Figure 1 (https://content.ugeskriftet.dk/sites/default/files/2023-05/a10220645-supplementary.pdf)

Deidentified participant data may be obtained upon reasonable request to Regional Hospital Midt but are not publicly available.

Statistics

Statistical computations were conducted using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Variables were compared by Student's independent t-test, the Mann-Whitney U test or Kruskal-Wallis test, as appropriate. For categorical variables, Fisher's exact test was applied and calculated both with missing values as a separate category and without missing values.

Time-to-event analysis was conducted using the Kaplan-Meier method with right censoring. Test for statistical significance was evaluated as log rank test. $p < 0.05$ was considered statistically significant and adjusted for

multiple comparison by applying Bonferroni correction.

Trial registration: not relevant.

RESULTS

A total of 450 patients were enrolled, encompassing 347 cases and 103 controls comparable in terms of age, sex, tumour size and type 2 diabetes and osteoporosis data. Cases had a higher prevalence of hypokalaemia ($p = 0.01$) and more often an available normal blood pressure (BP) measurement ($p < 0.001$) (**Table 1**). A trend was observed towards a higher prevalence of recent or present non-adrenal malignancy at the time of referral in cases than in controls ($p = 0.09$) (Table 1).

TABLE 1 Descriptives. Pre-intervention control cohort (2018) versus cases after intervention from 2019.

			p value	
	2019-: cases	**2018: controls**	**incl. NAs**	**excl. NAs**
N	347	103		
Age, median (range), yrs	65 (31.5-91.3)	66.4 (32.6-88.5)	0.3	-
Males, %	47	37	0.09	-
Tumour size, median (range), mm	18 (9-85)	18 (10-60)	0.4	-
HU ≤ 10, n (%)			0.3	0.3
Yes	240 (69.2)	64 (62.1)		
No	95 (27.4)	34 (33.0)		
NA	12 (3.5)	5 (4.9)		
Bilateral, n (%)			0.5	0.5
Yes	64 (18.4)	22 (21.4)		
No	281 (81.0)	80 (77.7)		
NA	2 (0.6)	1 (1.0)		
Washout, n (%)			0.09	0.04
Yes	58 (61.1)	14 (41.2)		
No	22 (23.2)	14 (41.2)		
NA	15 (15.8)	6 (17.6)		
Type 2 diabetes, n (%)			0.7	-
Antidiabetic medicine/elevated HbA_{1c}	50 (14.4)	13 (12.6)		
No anti-diabetic medicine & normal HbA_{1c}	297 (85.6)	90 (87.4)		
Osteoporosis, n (%)			0.6	-
Treatment	37 (10.7)	10 (9.7)		
No osteoporosis treatment	309 (89.0)	92 (89.3)		
NA	1 (0.3)	1 (1.0)		
Normal blood pressure measurement, n (%)			< 0.001	< 0.001
Yes	151 (43.5)	25 (24.3)		
No	164 (47.3)	76 (73.8)		
NA	32 (9.2)	2 (1.9)		
Hypertensive status, n (%)			0.1	0.3
Before age 35 yrs	3 (0.9)	0		
Not within target range	17 (4.9)	2 (1.9)		
None of those above	275 (79.3)	92 (89.3)		
NA	52 (15.0%)	9 (8.7)		
Hypokalaemia, n (%)			0.01	0.007
Large potassium supplement	5 (1.4)	2 (1.9)		
Spontaneous	31 (8.9)	1 (1.0)		
No	308 (88.8)	99 (96.1)		
NAs	3 (0.9)	1 (1.0)		
Malignancy; recent or present, n (%)			0.09	0.05
Yes	54 (15.6)	8 (7.8)		
No	288 (83.0)	93 (90.3)		
NA	5 (1.4)	2 (1.9)		

HU = Hounsfield units; NA = non-applicables.

Radiological characteristics were comparable with respect to Hounsfield units (HU) ≤ 10 and bilateral tumours. Benign washout was more prevalent in cases than in controls (p = 0.04) (Table 1). The nature of the incidentalomas was comparable (overall p = 0.3) (**Table 2**). No cases of overt cushing or adrenal cortical carcinoma were detected. The prevalence of mild autonomous cortisol secretion was comparable between cases and controls (p = 0.2) (Supplementary Table 1).

TABLE 2 Statistic significance. Overall: p = 0.8, incl. non-applicables (NAs): p = 0.3.

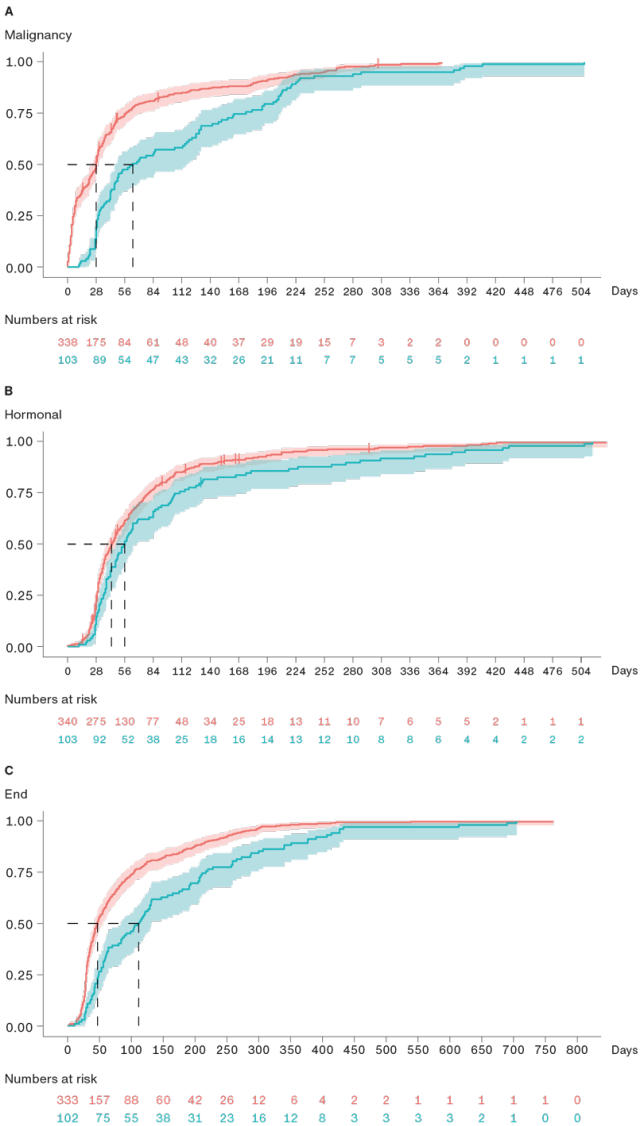
	2019 -: cases, n (%)	2018: controls, n (%)	p value[f]
Benign without hypersecretion[a]	298 (86)	93 (90)	0.1
Pheochromocytoma[b]	6 (2)	3 (3)	0.07
Hyperaldosteronism[c]	3 (1)	1 (1)	0.09
Other[d]	25 (7)	6 (6)	0.1
Metastasis[e]	2 (1)	0	0.1
NAs	13 (4)	0	
Total	347 (100)	103 (100)	

a) Adrenocortical adenoma according to post-operative histology results in 1 case and 1 control.
b) All pheochromocytoma according to post-operative histology results.
c) 1 post-operative histology diagnosis in agreement with Conn's syndrome.
d) 1 myelolipoma according to post-operative histology results.
e) 1 adenocarcinoma and 1 renal cell carcinoma according to post-operative histology results.
f) Fisher's exact test.

Transformation effect of the no-need-to-see pathway

Time-to-event analysis revealed a shorter time to clarification of malignancy (28 days; 95% confidence interval (CI): 24-30 days versus 64 days; 95% CI: 47-117 days), hormonal status (43 days; 95% CI: 38-48 days versus 56 days; 95% CI: 47-68 days) and to end of pathway (47 days; 95% CI: 42-55 days versus 112 days; 95% CI: 84-131 days) in cases than in controls ($p \leq 0.01$) (**Figure 2**).

FIGURE 2 Kaplan-Meier time-to-event plot. The Y axis represents the proportion of patients. The X axis represents time. Vertical lines: right-censored individuals. Dotted black lines: medians. Red line: cases. Blue line: controls. Ribbon: 95% confidence interval. **A.** Time to malignancy clarification. **B.** Time to hormonal clarification. **C.** Time to end of pathway. **D.** Table of medians (95% confidence intervals) and log rank test p values adjusted for multiple comparisons by the Bonferroni method.



D

Days to ...	September 2019 -: cases	2018: controls	p value	p value, Bonferroni
Malignancy clarification	28 (24-30)	64 (47-117)	< 0.001	< 0.001
Hormonal clarification	43 (38-44)	56 (47-68)	0.006	0.01
End of pathway	47 (42-55)	112 (84-131)	< 0.001	< 0.001

All controls attended the clinic. The distribution of the 347 cases was as follows: 219 cases (63%) entered the NNTS pathway; 94 cases (27%), the Attendance pathway (Figure 1 and Supplementary Table 2). A total of 34 cases were categorised as *Other* (10%). In all, 185 consultations (53%) were avoided, with 84% (185/219) of the NNTS group completing their patient pathway without seeing an endocrinologist (Figure 1). The remaining 34 cases (16%) were "*Converted to attendance at clinic*" due to either HU > 10 (n = 4), uncontrolled hypertension (n = 3), young age (n = 1), 1 mg dexamethasone suppression test (DST)/urinary free cortisol suspicious for cushing (n = 14), elevated metanephrines and elevated 1 mg DST (n = 4), symptoms and elevated U-catecholamines (n = 1), HU > 10 and elevated 1 mg DST/metanephrines (n = 5), elevated metanephrines (n = 1), or size > 4 cm (n = 1).

Time-to-event analysis supported that compared with the Attendance pathway and the Other group, the NNTS group was the main driver behind the shorter investigation time in cases than in controls ($p \leq 0.01$) (Supplementary Figure 2).

Deviations from the no-need-to-see algorithm and patient safety assessment

We evaluated whether patients who were non-eligible according to the protocol entered the NNTS pathway and found 24 such patients with details given in Figure 1. In summary, five patients declined seeing an endocrinologist (2%) and 19 patients had a true deviation from the algorithm (9%).

Screening of hypersecretion including primary hyperaldosteronism

In 98% (339/347) of cases and 91% (94/103) of controls, the consulting endocrinologist found no indication for PHA screening because of severe comorbidity, advanced age, no hypertension, less than four antihypertensive drugs or because the patient declined investigation ($p = 0.006$). In 5% ($n = 16$) of cases (NNTS = 2%, Attendance pathway = 10%, and Other = 6%) and 9% of controls, further investigation with an aldosterone/renin ratio was required ($p = 0.1$, excluding case subgroups; and $p = 0.01$, including case subgroups; data not shown).

Hypercortisolism

In 93% (322/347) of cases and 96% (99/103) of controls, screening for hypercortisolism was undertaken ($p = 0.3$). All, except three cases and three controls with missing screening for hypercortisolism, were explained by either advanced age ($n = 2$), severe comorbidity ($n = 9$), oral prednisolone without possibility for discontinuation ($n = 2$), patient declined ($n = 9$) or adrenal CT after entering the pathway showing a tumour < 10 mm ($n = 1$). No significant difference was observed within the case subgroups (NNTS, Attendance pathway, and Other; $p = 0.5$; data not shown).

Screening for pheochromocytoma was performed in 97% of the cases and 96% of the controls. All but one of 11 cases and three of four controls were explained by advanced age, severe comorbidity or declining patients. No significant difference was observed between the case subgroups (NNTS, Attendance pathway, and Other; $p = 1$)

Adrenal incidentalomas overlooked on previous CTs

In all, 20% of cases and 24% of controls had an AI missed on a previously CT performed more than two years ago ($p = 0.3$). In comparison, 24% of cases and 29% of controls had a CT with missed incidentaloma more than six months ago ($p = 0.3$). Among these, 33% and 47%, respectively, were identified at referral ($p = 1$). In conclusion, up to 13% ($(0.24 \times 0.67 \times 347)/347$) of case scans could have been avoided.

DISCUSSION

The NNTS strategy, sparing 53% of consultations, comes at the cost of not performing a physical examination, BP measurement and endocrine-focused medical history. The caveat is that some cases who are eligible for PHA screening are missed along with patients with mild autonomous cortisol secretion not sufficiently described with regards to the potentially negative effect of cortisol hypersecretion.

In the past decade, mild autonomous cortisol secretion has received an increased focus with a recent study indicating an increased mortality and morbidity risk [5], but with the cause-effect relationship remaining a subject of considerable debate and without consensus on the appropriate intervention. The transformation effect would be lower, although still significant, at centres choosing to enlist patients with mild autonomous cortisol secretion in a clinical follow-up regimen. Overall, hypercortisolism screening was comparable between cases and controls.

We screened for PHA only if the criteria for possible secondary hypertension were met. The decision not to evaluate all hypertensive patients was based on a proportionality principle considering that the prevalence of PHA in AI studies varies greatly (median 2% (95% CI: 1.5-10%)) [6, 7] and acknowledging that the prevalence does not exceed that reported in the general hypertensive population (overall 6% (95% CI: 2-13%)) [7]. Furthermore, patients with hypertension follow a control programme at their GP who may refer them to an endocrine unit if they meet the criteria of secondary hypertension. To increase the focus on the referral possibility, the GP received a discharge letter summarising the criteria for evaluation of PHA if the patient did not undergo PHA screening. A recent prospective AI study found that 3% (9/269) of patients had an elevated aldosterone-renin ratio. All these patients met the conventional criteria for secondary hypertension screening [6]. From an endocrinologist's point of view, measuring the aldosterone-renin ratio in all hypertensive patients may seem meticulous, but it comes at a significant financial cost and is resource intensive. Furthermore, measuring the aldosterone-renin ratio comes with the risk of causing anxiety for the patient and, in the worst case, unnecessary invasive testing and surgery. Extrapolating these findings to an AI cohort needs to consider that they have a ten-year higher median age than a PHA cohort. Lastly, the present study found the same prevalence of PHA in cases as in controls. Owing to the NNTS selection criteria, the lower prevalence of PHA screening within the NNTS group was expected. Screening rates did not differ between cases attending clinics and controls.

The combination of a surge of incidental findings and imaging being applied at a lower threshold of suspicion increases the risk of overdiagnosis. This is substantiated by studies reporting that 52% of all adrenalectomies have a benign histological diagnosis [4, 8]. Even in patients with extra-adrenal malignancies and adrenal tumours with imaging characteristics of adrenal metastasis, 35% of surgically removed adrenal tumours are benign [9]. We acknowledge that these estimates are prone to uncertainty with either the indication for or the mode of discovery being reported systematically.

A total of 19 cases (9%) deviated from the algorithm and were included in the NNTS group without meeting the criteria. Five additional cases (2%) continued the NNTS pathway although offered attendance at a clinic because the patient declined to see an endocrinologist. Among the 19 cases, five are of special interest as they had a HU > 20. In three of these cases, a senior endocrinologist took note of the HU > 20 but made a conscious decision to deviate from the algorithm. None of these tumours showed tumour growth at follow-up. Two cases were referred directly to surgery.

Our data suggest that 13% of CTs could have been avoided if previous scans had been evaluated before performing a new CT.

As indicated by Supplementary Figure 1, both patient information and medical chart text could be standardised, which would contribute to a more rapid workflow.

Limitations

A total of 16% of cases had extra-adrenal malignancy. We acknowledge that our cohort may not represent a true incidentaloma cohort although the cancer rates are lower than in most previous studies. Patients with extra-adrenal malignancy were included in the present quality study because they are often handled by the same outpatient clinic. Hence, the design represents the clinical setting in which the NNTS pathway is applied.

We acknowledge that PHA screening also relied on the general practitioners' referral if they suspected PHA according to the discharge letter.

The control group was historical and consisted of patients from only two of the four hospitals. We cannot exclude a time- or hospital-dependent difference in the attitude towards the management of AI, which may explain the different clinical pre-intervention characteristics between cases and controls. Individual

randomisation to control or NNTS pathways is prone to carry-over effects, and an optimal design would have been cluster randomisation of the involved hospitals. Finally, we acknowledge that the low prevalence of hormonal hypersecretion in incidentaloma patients entails a risk of type II error.

CONCLUSION

We provide evidence that the NNTS pathway is an efficient manner of handling the increased burden of incidental radiological findings, saving 53% of all attendance consultations while significantly reducing time to end of pathway for the NNTS group.

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Conflicts of interest none. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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