

Prevalence of Thyroid Cancer In Patients With Nodular Goiter and an Initial Benign Fine-Needle Aspiration Biopsy*

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ABSTRACT

Introduction: Nodular goiter is a common condition, with fine-needle aspiration biopsy (FNAB) being a fundamental tool for diagnosis. Although false negatives in cytology are very low (less than 3%), we suggest ongoing monitoring of nodules via ultrasound and potential repeat biopsy. This study aims to estimate the prevalence of thyroid cancer in patients with initially benign FNAB.

Materials and Methods: Retrospective observational cohort study. Patients over 18 years old evaluated at the outpatient clinics of the Endocrinology and Nuclear Medicine Service of a private community hospital in the City of Buenos Aires were included. They had thyroid nodules with initially benign fineneedle aspiration biopsy performed between 1/2/2008 and 31/2012 and underwent repeat biopsy during a follow-up period of more than one year. All patients who underwent surgery during the followup period were recorded (reason for surgery and histology).

Results: A total of 536 patients (383 women) with a mean age of 64.5 ± 12.5 years were included. There were 160 (29.85%) solitary nodules, measuring 19.9 ± 9.2 mm, with 203 (37.8%) patients exhibiting a cystic component. Forty-six patients underwent surgery, with 25 due to a second malignancy or suspicious finding on biopsy, 16 due to nodule size, three due to hyperthyroidism, and two due to concurrent hyperparathyroidism. We found thyroid cancer in 16 patients, with 11 occurring in the biopsied nodules and five discovered incidentally during surgery for other reasons. The prevalence of malignancy by biopsy (11/536) was 2% (95% CI 1-4%), while the overall malignancy prevalence was 3% (95% CI 2-5%). Among the 11 patients with false negatives from the initial biopsy, 7 underwent repeat biopsy due to increased size or suspicious features, and 4 for surveillance purposes. All had low stages and favorable outcomes, except for one patient who presented with papillary carcinoma, a high cell variant. The five patients with carcinomas found during surgery had papillary microcarcinomas.

Conclusion: In our population, we found a low prevalence of false negatives in biopsy results among patients with nodular goiter. Key words: nodular goiter, thyroid, thyroid cancer, fine needle puncture.

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Prevalencia de cáncer de tiroides en pacientes con bocio nodular con punción inicial benigna*

RESUMEN

Introducción: el bocio nodular es una patología frecuente y la punción aspirativa con aguja fina (PAAF) constituye una herramienta fundamental para el diagnóstico. Si bien los falsos negativos de la citología

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son muy bajos (menores del 3%), se sugiere el control evolutivo de los nódulos mediante ecografía y eventual repetición de la punción. El objetivo de este estudio es estimar la prevalencia de cáncer de tiroides en pacientes con PAAF inicial benigna.

Material y métodos: estudio observacional de cohorte retrospectivo. Se incluyeron pacientes mayores de 18 años evaluados por consultorios externos del Servicio de Endocrinología y Medicina Nuclear de un hospital privado de comunidad de la Ciudad de Buenos Aires, con nódulos tiroideos con punción inicial benigna realizada entre 2/1/2008 y 31/12/2012, y repetición de la punción en un seguimiento mayor de 1 año. Se consignaron todos los pacientes operados en el seguimiento (motivo de cirugía e histología).

Resultados: se incluyeron 536 pacientes (383 mujeres) de 64,5±12,5 años. Fueron 160 (29,85%) nódulos únicos, de 19,9 ± 9,2 mm y en 203 (37,8%) pacientes con componente quístico. Se operaron 46 pacientes, 25 por segunda punción maligna o sospechosa, 16 por tamaño, 3 por hipertiroidismo y 2 por hiperparatiroidismo concomitante. En 16 se halló cáncer de tiroides, 11 fueron en el nódulo punzado y 5 fueron hallazgos en pacientes operados por otros motivos. La prevalencia de malignidad por punción (11/536) fue 2% (IC 95: 1-4%), la prevalencia global de malignidad fue 3% (IC 95: 2-5%). De los 11 pacientes con falsos negativos de la primera punción, 7 fueron punzados nuevamente por aumento de tamaño o características de sospecha y 4 por control. Todos tuvieron estadios bajos y buena evolución, excepto 1 paciente que presentó un carcinoma papilar subtipo células altas. Los carcinomas hallados en la cirugía de 5 pacientes fueron microcarcinomas papilares.

Conclusión: en nuestra población encontramos una baja prevalencia de falsos negativos de la punción en pacientes con bocio nodular.

Palabras clave: bocio nodular, tiroides, cáncer de tiroides, punción con aguja fina

INTRODUCTION

The widespread increased use of thyroid ultrasound in clinical evaluation and health screening has led to a higher prevalence of asymptomatic thyroid nodules, making them one of the most common pathologies in clinical practice^{1,2}. Although the prevalence of nodular goiter detected by palpation is 5 to 11%, ultrasound screening studies have reported a much higher prevalence, between 33 and 68%¹. However, it is worth noting that 90% of these nodules are benign.

In this context, fine-needle aspiration (FNA) biopsy is crucial to confirm benignity in most cases and to identify those that require surgical resection^{1,3}. Although false negatives in cytology are less than 3%, we recommend ultrasound follow-up at 12 to 24 months after cytology and repeating the puncture of nodules in case of a significant increase in size or the appearance of suspicious ultrasound signs of malignancy¹. However, the increase in the use of thyroid ultrasound and the performance of FNA biopsies entails an increase in healthcare expenses, which poses additional challenges in managing resources within the health system. On the other hand, since the majority of patients with thyroid cancer detected by this method have shown a low mortality rate due to the disease, in recent years, there has been a shift in the treatment of thyroid cancer towards less extensive surgical approaches, more limited use of I¹³¹, and the possibility of active surveillance instead of opting for immediate interventions in small, localized tumors. Hence, the discussion arises regarding the appropriate follow-up of thyroid nodules with benign puncture.

In this study, our objective is to estimate the prevalence of thyroid cancer in patients with nodular goiter and initially benign FNA biopsy and to describe the characteristics of these tumors.

MATERIAL AND METHODS

We designed a retrospective cohort study for consecutive adult patients with thyroid nodules. We included adults over 18 years old who had thyroid nodules with an initially benign puncture performed between 1/2/2008 and 31/12/2012, treated in outpatient clinics by the Endocrinology and Nuclear Medicine Service of a private community hospital in the city of Buenos Aires, with at least one year of ultrasound follow-up, and who also had an additional puncture of the initially evaluated nodule (rFNA). Those with an initial FNA with insufficient sample, cyst, follicular proliferation (suspicious of malignancy or malignant), or according to the current Bethesda criteria categories I, III, IV, V, or VI were excluded; patients with nodules with a predominantly cystic component (> 50% cystic component on ultrasound) and a history of thyroid surgery or previous FNA were also excluded. The protocol was approved by the local Ethics Committee, protocol number 2478.

We considered a diagnosis of thyroid cancer with the histological confirmation of primary thyroid cancer in those patients with an initially benign FNA who had undergone surgery during their follow-up.

The hospital has a computerized clinical records system that centralizes all clinical, surgical, and diagnostic

interventions of patients at the institution. We searched for patients with an initially benign puncture and who had at least one new puncture during their follow-up. Records review and data collection were performed by endocrinologists participating in the study. We recorded the anthropometric data, thyroid function, ultrasound records, and FNA cytology results in a standardized form.

We considered the cytology to be benign when it was presented as nodular hyperplasia, nodular goiter, or lymphocytic thyroiditis for punctures performed before 2009 and as Bethesda II from 2009 onwards (the year we started to apply the Bethesda category reporting method systematically in our institution). We recorded the punctures performed during follow-up and the reasons for their performance (nodule size increase, suspicious ultrasound characteristics, or routine check). Follow-up cytology was considered suspicious based on the suspected report of papillary carcinoma, follicular proliferation, or Bethesda categories IV, V, and VI. We defined benign cytology according to the mentioned criteria. Bethesda category III was considered indeterminate, and if Bethesda III persisted in a new puncture, it was included in the suspicious category.

We recorded the baseline ultrasound scans and, at the time of the new punctures, we entered the number of nodules (single or multiple), the size of the primary nodules, the presence of cystic component (50%), the presence of ultrasound features of suspected malignancy (microcalcifications, irregular borders, nodule more or narrower than wide, hypoechogenicity, predominantly central vascularization, or predominantly central vascularization). We recorded the presence of suspicious ultrasound characteristics of malignancy (microcalcifications, irregular borders, nodule wider than wide, hypoechogenicity, predominantly central vascularization, or suggestion of puncture in the ultrasound report), ultrasound changes (increase in size or appearance of new suspicious characteristics of malignancy) in ultrasound before the new puncture and in the last ultrasound performed in subsequent controls.

The performance of surgery was recorded in the included population, noting the reason (puncture suspicious for malignancy, nodule size, hyperthyroidism, associated primary hyperparathyroidism, or other cause), as well as the results of the definitive pathological anatomy.

In the Endocrinology Service, the usual approach to a thyroid nodule with an initially benign puncture is ultrasound control at 12 months and a new puncture of the nodules if there is an increase in size, suspicious ultrasound characteristics, or the appearance of new nodules with puncture criteria, or for control in some cases. In all cases, a physician from the Anatomic Pathology Service specialized in thyroid pathology (A.M.J.) interpreted the cytology and histology.

We performed ultrasound scans and clinical controls by various sonographers and endocrinologists from the Diagnostic Imaging Service and the Hospital's Endocrinology and Nuclear Medicine Service. We

evaluated 929 patients with an initially benign puncture performed between 1/2/2008 and 31/12/2012 and one new puncture (rFNA) during follow-up. We excluded 393 patients due to a nodule with a predominantly cystic component, an initial puncture insufficient for diagnosis, a history of thyroid surgery, or previous FNA; we included 536 patients. See flowchart (Fig. 1). The patients' follow-up time was 54.35 months (range 12 to 131.8 months).

Sampling and Statistical Analysis

The sampling was consecutive of all patients with a first FNA with a benign result who met the selection criteria. The prevalence of cancer in patients with an initially negative FNA was estimated (percentage with its 95% confidence interval). We described continuous variables with mean and standard deviation or median and interquartile range depending on the observed distribution. We described categorical variables as proportions. Time to event (surgery) and disease-free time as median and interquartile range; disease-free time for each histologic subtype appears graphically with a box plot. Categorical variables were compared with chi2 or Fisher as appropriate, and $p < 0.05$ was considered statistically significant. We used the State version 13® software.

RESULTS

Anthropometric data and functionality

Ninety percent were women ($n=483$), with a mean age of 64.5 ± 12.5 years, and almost 80% of the patients were euthyroid (Table 1).

Thyroid Ultrasound and Puncture

Most patients had more than one nodule on ultrasound ($n: 376; 70\%$), and 37.9% ($n: 203$) had a less than 50% cystic component. The size of the main nodule punctured was $19.9 + 9.2$ mm in the initial puncture and $21.8 + 10.1$ mm in the new puncture (see Table 1).

We punctured 717 nodules in 536 patients (362 patients had one nodule needled, 167 patients had two nodules, and seven patients had more than two nodules). In 464 patients, we performed a single new puncture of the nodules, and in 72 patients, two or more punctures were performed in the follow-up.

Regarding suspicious ultrasound characteristics for malignancy, only 18% ($n: 97$) presented suspicious ultrasound signs at the first FNA, and 23.5% ($n: 102$) at the second FNA.

The most frequent reasons for new puncture were, in 59.8%, control, in 33.4%, increased size in 2.2%, the appearance of ultrasound signs suspicious of malignancy, and in 2%, due to an increase in size plus a change in ultrasound characteristics. In the second puncture, we verified a cytological change that motivated a change in management in 5.4% ($n: 29$) of the patients: in 58.6% ($n: 17$), follicular proliferation or Bethesda IV, and in 41.4% ($n: 12$), suspicion of papillary carcinoma, papillary carcinoma, or Bethesda V or VI. There was no case with a Bethesda III puncture. In 2 patients, cytological changes occurred in the third puncture performed.

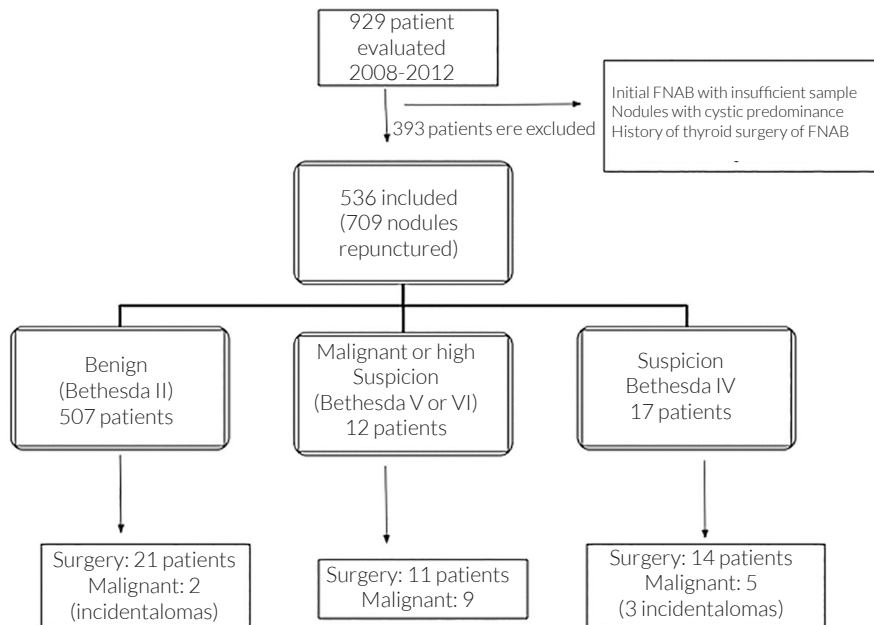


Figure 1. Patient inclusion and global results.

Table 1. Population characteristics

Age, Years	64.5+12.5
Women n° (%)	483(90%)
Body Mass Index (BMI)	27.2+4.9
TSH mIU/L (milli-international units per liter)	1.9+ 2.8
Thyroid Functional Status	
Euthyroid	423(78.9%)
Hypothyroid with T4	68(12.6%)
Hyperthyroid	25(4.6%)
Hypothyroid	17(3.17%)
Measurement of anti-TPO	342
anti-TPO positive (positive for thyroid peroxidase antibodies)	75/342(21.9%)
Size of nodule punctured (mm)	19.9+9.2
Size of 2nd nodule punctured (mm)	14.8+6.5
Ultrasound characteristics of malignancy 1st a FNAB	97 (18%)
Ultrasound characteristics of malignancy 2nd a FNAB	102 (23.5%)

THYROID SURGERY: 46 patients underwent surgery, 54.3% (n: 25) due to malignant or suspicious puncture, 34.7% (n: 16) due to large size, 6.5% (n: 3) due to hyperthyroidism, and 4.3% (n: 2) due to concomitant hyperparathyroidism. We found thyroid cancer in 34.8% of the patients (n: 16), of which 68.7% (n: 11) was in the punctured nodule (see Fig. 1 and Table 2) and in 31.3% (n: 5), it was a finding in patients operated for other reasons (see Fig. 1 and Table 3).

The median follow-up between the initial FNA and the histological confirmation of thyroid cancer was 39.4 (18.6-56.3) months. The prevalence of thyroid cancer detected by repeating the puncture was 2% (n: 11; 95% CI: 1-4%), and the overall prevalence of thyroid cancer was 3% (n: 16, 95% CI: 2-5%). In 65.2% (n: 30) of the operated patients, the result was benign (60% nodular hyperplasia, 36.7% follicular adenoma, and 0.3% lymphocytic thyroiditis).

Table 2. Clinical characteristics of patients with initial benign FNA, second puncture in follow-up with suspected malignancy, and histological confirmation of thyroid cancer

P	Sex	Age	Reason for second puncture	Tumor histopathology (mm)	Size (8th edition)	TNM
1	F	75	Control	Classic papillary carcinoma	10	T1a NOMO
2	F	63	Increase in size	Encapsulated follicular variant of papillary carcinoma	20	T1a NOMO
3	F	65	Increase in size	Papillary carcinoma FV	20	T2 NOMO
4	M	68	Suspicious characteristics	Classic papillary carcinoma	7	T1a NOMO
5	M	46	Control	Papillary carcinoma FV	17	T1b NOMO
6	F	50	Control	Papillary carcinoma FV	15	T1b NOMO
7	F	63	Control	Encapsulated follicular variant of papillary carcinoma	15	T3 NOMO
8	F	51	Increase in size	Papillary carcinoma FV	10	T1a NOMO
9	F	36	Suspicious characteristics	Classic papillary carcinoma	10	T1a NOMO
10	F	84	Increase in size	Papillary tall cell carcinoma	80	T4aNxMo
11	F	77	Suspicious characteristics	Oncocytic variant of papillary carcinoma	8	T1NOMo

VF: variedad folicular.

Table 3. Clinical characteristics of patients with benign FNA and thyroid cancer found at surgery (incidentaloma)

Sex	Age	Reason for surgery (months)	Histopatology	Time to diagnosis	Tumor size mm	TNM
F	43	Suspicious puncture of another nodule	Encapsulated follicular variant of papillary carcinoma	54	5	T1a NOMO
F	73	Suspicious puncture of another nodule	Papillary microcarcinoma	76	7	T1a NOMO
F	59	Suspicious puncture of another nodule	Papillary microcarcinoma	27	3	T1a NOMO
M	71	Increase in size	Papillary microcarcinoma	20	5	T1a NOMO
M	78	Increase in size	Encapsulated follicular variant of papillary carcinoma	23	9	T1a NOMO

Of the 11 patients with false negatives (see Table 2) from the first puncture, 63.6% (n: 7) were punctured again due to an increase in size or suspicious characteristics, and 36.4% (n: 4) for control. When evaluating the suspicious ultrasound characteristics or the increase in size in patients with a second benign puncture and those with a second suspicious or malignant puncture confirmed by histology, we did not verify significant differences. All patients with a diagnosis of thyroid cancer by puncture

presented with low stages, the median (P25-75) follow-up of the cohort was 37.9 (26.3-49.6) months, ten patients remained disease-free, and only one died from thyroid cancer (it was a patient with a high-cell subtype of cancer associated with a worse prognosis). Figure 2 shows the median follow-up by histological subtype. The papillary microcarcinomas found in the surgery of 5 patients evolved disease-free with a median follow-up of 24 months (12-52).

DISCUSSION

In our cohort study of 536 patients with nodular goiter and initially benign cytology, we verified 16 patients with a diagnosis of thyroid carcinoma: 11 of them were false negatives from the initial puncture, and 5 were surgical findings in nodules initially without puncture criteria (incidentalomas).

The prevalence of malignancy through the repetition of the puncture was 2% (95% CI: 1-4%), and the overall prevalence of thyroid cancer, including surgical incidentalomas, was 3% (95% CI: 2-5%). These results are similar to those reported by Ospina et al.⁴, who referred malignancy rates of 1.2 to 4.1%, by Orlandi et al.⁵, who obtained 1.3% of papillary carcinoma, and by other authors⁶⁻⁸. Given the low frequency of false negatives, we agree with the recommendations of the ATA (American Thyroid Association) that the control of possible false negatives is not an indication to repeat the FNA, suggesting the repetition of this in those nodules with ultrasound characteristics of malignancy or with an increase in size.

Monitoring the benign thyroid nodules involves ultrasound to detect malignant nodules not diagnosed in the initial puncture or to monitor nodule growth. Ultrasound patterns associated with malignancy include the presence of microcalcifications, irregular borders, a nodule that is taller than wide, hypoechogenicity, and predominantly central vascularization; the sensitivity and specificity of these characteristics vary, and none by itself identifies malignant nodules; moreover, there is high intraobserver and interobserver variability^{1,3}. Rosario et al.⁹ observed suspicious ultrasound characteristics as the main factor associated with malignancy in nodular

goiter. Angell et al.¹⁰ observed a different growth pattern in malignant nodules; in their study, a growth of more than 2 mm per year is a malignancy predictor. As our study was retrospective, it did not have a single criterion or time frame for the second puncture, with nodule control being the reason for repeating the study in almost 60% of cases. Patients with false negatives from the puncture had nodules with increased size or suspicious characteristics in 63.6% of cases, but this was not a statistically significant difference. The ultrasound scans performed by different operators could not accurately record the presence or absence of all suspicious ultrasound characteristics in all studies;

Nor were ultrasound-based risk stratification systems (Thyroid Imaging Reporting and Data System or TIRADS) used, which correlate with the risk of malignancy^{3,11}. The strength of our work rests on the high number of patients included and the evaluation by a single specialized pathologist of both the thyroid cytology and histology. In the new puncture, we verified a cytological change that motivated a change in management in 5.4% of the patients. Of the 11 patients diagnosed with thyroid cancer from the repetition of the study, ten evolved disease-free, two were encapsulated follicular variants of papillary carcinoma, which are associated with an excellent prognosis, and 5 were papillary microcarcinomas, which nowadays would probably be suitable for active surveillance, but that was not the usual practice at the time of patient evaluation.

Only one patient had a poor outcome, presenting with a high-cell subtype of papillary carcinoma that initially indicated surgery due to clinical characteristics and growth, but the patient underwent surgery after cytological confirmation; the patient developed distant

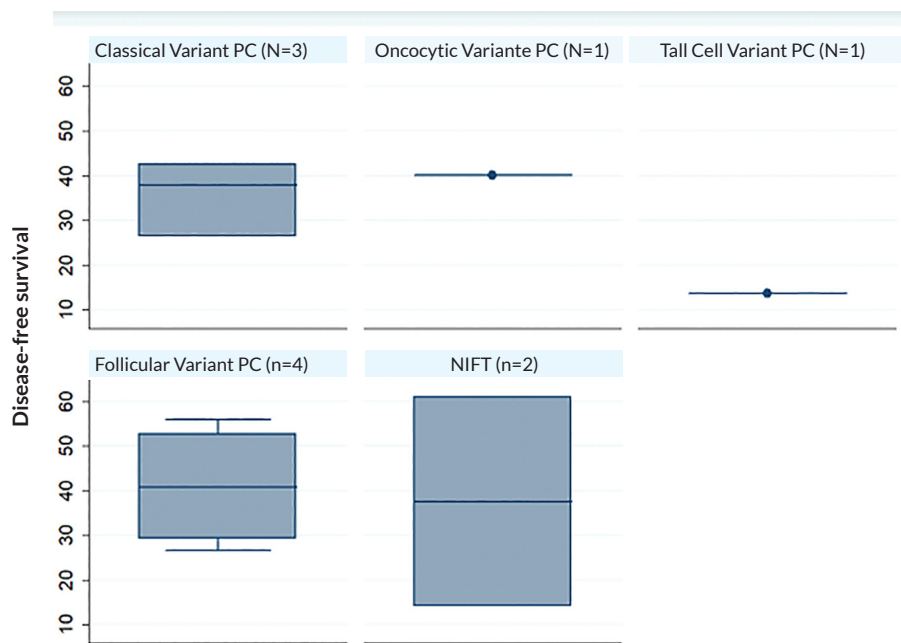


Figure 2. Disease-free survival in patients with initial benign FNA, second puncture in follow-up with suspected malignancy, and histological confirmation of thyroid cancer (initial FNA false negatives), according to histological subtypes.

metastases and died from thyroid carcinoma. Of the five patients with cancer findings in surgery had papillary microcarcinomas, two of them encapsulated follicular variants of papillary carcinoma, recently included in the category of low-risk neoplasia in the 5th WHO classification¹², with which the vast majority of patients with thyroid cancer in our cohort had an indolent evolution. Our work has a mean follow-up time of 4.5 years, but other authors have shown good evolution of benign nodules over a longer time. Ng et al.¹⁸ have reported long-term follow-up (13.9 years) of a cohort of 2,207 patients with nodular goiter, of whom only 3.4% presented a diagnosis of thyroid cancer during follow-up and 1.8% microcarcinoma, diagnosed at 3.4 years of follow-up; none of these patients died from thyroid cancer. Nou et al.¹⁴ reported similar results with an average of 8.5 years of follow-up.

CONCLUSION

The prevalence of thyroid cancer in patients with an initially benign puncture is very low, 3% if we consider all patients with a diagnosis of thyroid cancer and 2% if we exclude surgical findings; the majority of these patients show an excellent evolution. Such results confirm the utility of puncture in the initial diagnostic study of patients with thyroid nodules without the need for routine repetition or control in cases of benignity.

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Conflict of Interests: The authors declare no conflicts of interest.

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