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The Role of Core Needle Biopsy for Thyroid Nodules with Initially Indeterminate Results on Previous Fine-Needle Aspiration: A Systematic Review and Meta-Analysis

C.H. Suh, J.H. Baek, C. Park, Y.J. Choi, and J.H. Lee



ABSTRACT

BACKGROUND: Sonography-guided fine-needle aspiration leads to relatively frequent cases of indeterminate cytology for the diagnosis of thyroid nodules.

PURPOSE: Our aim was to evaluate the efficacy and safety of core needle biopsy for the examination of thyroid nodules with initially indeterminate results on fine-needle aspiration.

DATA SOURCES: A computerized search of the MEDLINE and Embase databases was performed to identify relevant original articles.

STUDY SELECTION: Studies investigating the use of core needle biopsy for thyroid nodules with initially indeterminate results on previous fine-needle aspiration were eligible for inclusion.

DATA ANALYSIS: The pooled proportions for nondiagnostic results, inconclusive results, malignancy on core needle biopsy, the ability of core needle biopsy to diagnose malignancy, and the related complications of the procedure were analyzed.

DATA SYNTHESIS: The meta-analytic pooling was based on a random-effects model. Nine eligible studies, involving 2240 patients with 2245 thyroid nodules, were included. The pooled proportion for nondiagnostic results was 1.8% (95% CI, 0.4%–3.2%), and the pooled proportion for inconclusive results was 25.1% (95% CI, 15.4%–34.9%). The pooled proportion for malignancy was 18.9% (95% CI, 8.4%–29.5%). With regard to the diagnostic performance for malignancy, the sensitivity of core needle biopsy varied, ranging from 44.7% to 85.0%, but the specificity was 100% in all cases. No major complications of core needle biopsy were observed.

LIMITATIONS: The relatively small number of included studies and retrospective nature were limitations.

CONCLUSIONS: Core needle biopsy has low nondiagnostic result rates and high specificity for the diagnosis of malignancy. It is a safe diagnostic technique with a higher diagnostic yield, especially when molecular testing is not available or fine-needle aspiration did not yield enough cells for molecular testing.

ABBREVIATIONS: AUS = atypia of undetermined significance; CNB = core needle biopsy; FLUS = follicular lesion of undetermined significance; FNA = fine-needle aspiration; US = ultrasound

Sonography (US)-guided fine-needle aspiration (FNA) is an accurate and safe technique for the diagnosis of thyroid nodules. However, FNA leads to relatively frequent indeterminate cytology.^{1,2} According to the 2015 American Thyroid Association Management Guidelines, repeat FNA or molecular testing may be used to supplement the malignancy risk assessment of thyroid nodules with cytology findings of atypia of undetermined significance (AUS)/follicular lesion of undetermined significance

(FLUS).³ Moreover, if repeat FNA or molecular testing findings are deemed inconclusive, either surveillance or a diagnostic operation may be performed, given certain clinical risk factors, US patterns, and patient preferences.³ Nevertheless, repeat FNA has reportedly high rates of nondiagnostic (6.9%–9.9%) or inconclusive results (19.2%–52.5%) in the examination of thyroid nodules with initially indeterminate results on previous FNA.^{4–8}

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Several recent studies have reported the advantages of using core needle biopsy (CNB) for the examination of thyroid nodules with initially indeterminate results on previous FNA.^{6–14} CNB has been reported to have low rates of nondiagnostic (0.5%–3.8%) and inconclusive (9.1%–45.3%) results compared with the inconclusive results of FNA (19.2%–52.5%).^{6,7,9,11,12,14} However, some physicians remain skeptical of the use of CNB for the examination of thyroid nodules with initially indeterminate results on previous FNA because most research has included observational or descriptive studies with small sample sizes. Furthermore, the American Thyroid Association guidelines do not recommend the routine use of CNB, possibly because of the high associated morbidity rates and the limited evidence elucidated thus far.³ Hence, it is essential to collect and review the currently available data regarding the prevalence of nondiagnostic results, diagnostic performance, and complications of CNB for the examination of thyroid nodules with initially indeterminate results on previous FNA.

To our knowledge, no studies have generated a comprehensive systematic summary of cases of thyroid nodules with initially indeterminate results on previous FNA. Accordingly, we aimed to systematically review the published literature and evaluate the prevalence of nondiagnostic results, diagnostic performance, and complications of CNB for thyroid nodules with initially indeterminate results on previous FNA, which could provide additional data to support standardized management of these lesions.

MATERIALS AND METHODS

Literature Search Strategy

A computerized search of the MEDLINE and Embase databases was performed to identify relevant original articles on the use of CNB for examining thyroid nodules with initially indeterminate results on previous FNA until May 15, 2016. We used the following search terms: (thyroid) AND (core-needle biopsy OR core needle biopsy OR CNB) AND (Bethesda category 3 OR atypia of undetermined significance OR AUS OR follicular lesion of undetermined significance OR FLUS OR indeterminate OR inconclusive). Our search was limited to English-language studies. The bibliographies of the selected articles were screened to identify other relevant articles.

Inclusion Criteria

Studies investigating the use of CNB for thyroid nodules with initially indeterminate results on previous FNA were eligible for inclusion. However, we included only studies that fulfilled all of the following criteria:

- 1) Population. Patients with thyroid nodules who underwent CNB evaluations following initially indeterminate results on previous FNA.
- 2) Reference Standard. Because the diagnostic criteria for CNB of thyroid nodules have not been standardized, the histologic results of CNB were grouped into the 6 categories of the Bethesda System^{6,9,15}: nondiagnostic results, benign, AUS or FLUS, follicular neoplasm or suspicious for follicular neoplasm, suspicious for malignancy, and malignant.¹⁶ We defined indeterminate results as those that at least fulfilled the criteria of thyroid nodules with Bethesda category 3 (AUS and FLUS), including cases with atypical cells that could not be

diagnosed as “suspicious for malignancy” or “malignancy,” or those with cellular follicular nodules that could not be diagnosed as “follicular neoplasm” or “suspicious for follicular neoplasm.” The malignant nodules were diagnosed after an operation or biopsy. In contrast, benign nodules were diagnosed after an operation, in cases in which at least 2 sets of benign findings were noted on FNA and/or CNB, or in cases in which benign cytology findings were noted on FNA or CNB and the nodule size remained stable after 1 year.

- 3) Outcomes. Results that were sufficiently detailed to evaluate the prevalence of nondiagnostic results, diagnostic performance, and complications of CNB.

Exclusion Criteria

The exclusion criteria were as follows: 1) case reports and case series with a sample size of <10; 2) review articles, editorials, letters, comments, and conference proceedings; 3) studies that did not focus on the use of CNB for thyroid nodules with initially indeterminate results on previous FNA; and 4) studies with partially overlapping patients and data. Two reviewers (C.H.S. and J.H.B.) independently selected the literature reports with a standardized form.

Data Extraction

These data were extracted from each of the following studies and entered into standardized data forms: 1) authors, year of publication, hospital or medical school, years of patient recruitment, study design, and sample size; 2) mean age, nodule size, and patient reference standards; 3) rates of nondiagnostic results, inconclusive results, and malignancy; 4) diagnostic performance of CNB for malignancy; and 5) complications, the size of the core needle, and patient anticoagulation status. One reviewer (C.H.S.) extracted the data from the studies, and the second reviewer (J.H.B.) confirmed the accuracy of the extracted data. There were a few disagreements, which were resolved by a unanimous decision.

Quality Assessment

The quality of the included studies was analyzed independently by 2 reviewers (C.H.S. and J.H.B.) with customized questionnaires based on the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria.¹⁷ Very few disagreements were noted, which were resolved by consensus.

Data Synthesis and Statistical Analysis

The pooled proportions for the nondiagnostic results, inconclusive results, and malignancy on CNB following initially indeterminate results on previous FNA were adopted as the primary indices. The meta-analytic pooling was based on the inverse variance method for calculating weights, and the pooled proportions and their 95% confidence intervals were determined by using the DerSimonian-Laird random-effects model.^{18–20} Heterogeneity among the studies was determined by using following methods: The Cochran Q-test was performed for the pooled estimates with $P < .05$ indicating heterogeneity. In addition, we performed the Higgins inconsistency index (I^2) test: 0%–40%, might not be important; 30%–60%, may represent moderate heterogeneity;

50%–90%, may represent substantial heterogeneity; and 75%–100%, may represent considerable heterogeneity.^{21,22} The publication biases were visually assessed by using funnel plots. Thereafter, publication bias–adjusted pooled estimates—that is, adjusted pooled proportions—were obtained by using the trim-and-fill method.²³ If the original unadjusted pooled proportions and the trim-and-fill–adjusted pooled proportions were in agreement, the results were regarded as robust for publication bias.

The secondary indices of this study included the diagnostic performance of CNB for malignancy and complications. We estimated the descriptive statistics for the diagnostic performance of CNB, including sensitivity, specificity, positive predictive value, and negative predictive value. All statistical analyses were performed by using R statistical and computing software, Version 3.0.2 (<http://www.r-project.org/>) with the “metafor” and “mada” packages.

RESULTS

Literature Search

The study selection process is illustrated in Fig 1. A literature search of the Ovid MEDLINE and Embase databases identified 105 articles; after we removed the duplicates, 77 articles were screened for eligibility. Of those, 64 were excluded after a review of their titles and abstracts, including 35 review articles; 12 case reports; 9 letters, editorials, or conference abstracts; and 8 articles not related to the topic of interest of this study. The full texts of the remaining 13 articles were reviewed; a search of their bibliographies found no additional eligible studies. Of these 13 articles, 4 were further excluded after reviewing their full texts, due to the presence of partially overlapping patient cohorts.^{24–27} Finally, 9

eligible studies, involving 2240 patients with 2245 thyroid nodules, were included in this meta-analysis.^{6–14}

Characteristics of the Included Studies

The detailed characteristics of the 9 included studies are summarized in the On-line Table. All the included studies were retrospective in nature. The mean patient age ranged from 46 to 54.1 years. Of the 9 studies, only CNB was performed for the thyroid nodules in 6,^{9–14} whereas both CNB and repeat FNA were performed in 3.^{6–8} Among the studies, 2 included patients who simultaneously underwent repeat FNA and CNB of each nodule, wherein repeat FNA was performed before CNB.^{6,7} In those studies, real-time US guidance was used to determine that the CNB and repeat FNA were focusing on the same nodule. In 8 studies, the size of the core needle was 18 ga; 1 study was not explicit.¹³

The inclusion of thyroid nodules was slightly heterogeneous among the studies. Five studies included thyroid nodules with initial AUS or FLUS results at previous FNA,^{6,7,9,12,14} whereas Jang et al¹¹ included nodules with initial AUS results at previous FNA. Moreover, Trimboli et al¹³ included nodules with initial AUS or FLUS or follicular neoplasm/suspicious for follicular neoplasm results at previous FNA. Hahn et al¹⁰ included nodules with initial inconclusive results at previous FNA, and Park et al⁸ included initially indeterminate nodules at previous FNA. Hence, we finally included 6 studies (1836 nodules) that examined nodules with initial AUS or FLUS results at previous FNA in the quantitative synthesis of our meta-analysis.^{6,7,9,11,12,14} Among these 6 studies, 4 (496 nodules) included assessments of the diagnostic performance of thyroid malignancy.^{6,7,9,14} Two studies were excluded due to the presence of insufficient data for creating the diagnostic 2-by-2 table for CNB.^{11,12} The quality of the included studies, as assessed by the QUADAS-2 tool, was moderate overall, with all the studies satisfying ≥ 5 of the 7 items (On-line Fig 1).¹⁷

Prevalence of Nondiagnostic Results, Inconclusive Results, and Malignancy of CNB

Among the 6 studies included, 1836 nodules with initial AUS or FLUS results at previous FNA were examined. The pooled proportions for nondiagnostic results, inconclusive results, and malignancy on CNB are summarized in the Table, and the corresponding forest plots are shown in Fig 2. The pooled proportion for nondiagnostic results was 1.8% (95% CI, 0.4%–3.2%), and the pooled proportion for inconclusive results was 25.1% (95% CI, 15.4%–34.9%). The pooled proportion for malignancy was 18.9% (95% CI, 8.4%–29.5%). Considerable heterogeneity was observed among the studies in terms of the pooled proportions on CNB ($I^2 = 94.6\%$ – 98.3%). The funnel plots showed a publication bias for the pooled proportion for nondiagnostic results and ma-

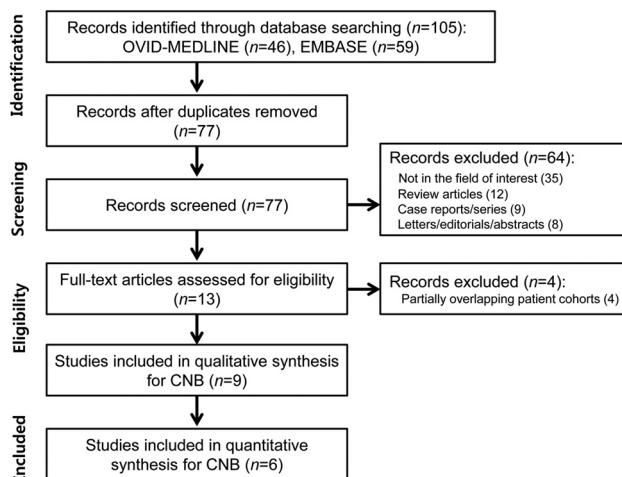


FIG 1. Flow diagram of the study selection process.

Summary of the meta-analytic pooled proportions for nondiagnostic results, inconclusive results, and malignancy on CNB

	No. of Studies	Total No. of Cases	Summary Estimate			Trim-and-Fill Estimate	
			Pooled Proportion (95% CI)	P Value for Heterogeneity ^a	I ^{2b}	No. of Missing Studies	Adjusted Pooled Proportion (95% CI)
Nondiagnostic results	6	1836	1.8% (0.4%–3.2%)	<.01	94.6%	2	0.8% (–0.8%–2.5%)
Inconclusive results	6	1836	25.1% (15.4%–34.9%)	<.01	95.8%	0	
Malignancy	6	1836	18.9% (8.4%–29.5%)	<.01	98.3%	1	15.6% (4.4%–26.8%)

^a P value by the Cochran Q method to test the heterogeneity of the pooled data, with $P < .05$ indicating substantial heterogeneity.

^b Higgins index for heterogeneity (0%–40%, might not be important; 30%–60%, may represent moderate heterogeneity; 50%–90%, may represent substantial heterogeneity; 75%–100%, may represent considerable heterogeneity).

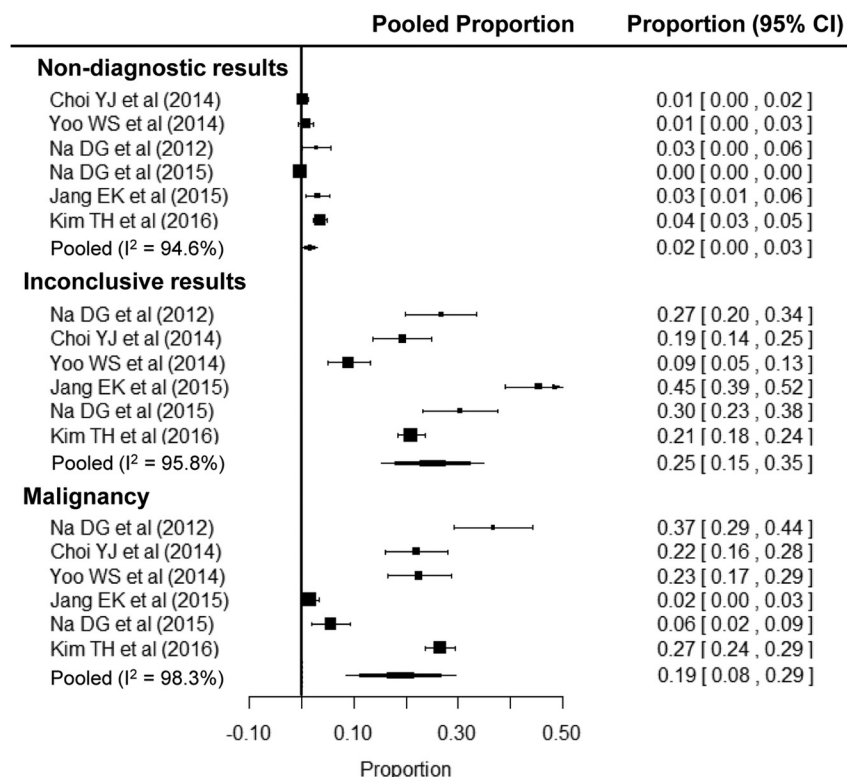


FIG 2. Forest plots for nondiagnostic results, inconclusive results, and malignancy of the CNB. Numbers are pooled estimates with 95% confidence intervals in parentheses. Horizontal lines indicate 95% CIs, and the black box on each line indicates the standardized mean difference for each study. The black diamond at the bottom of the plot shows the average effect size of the included studies.

lignancy on CNB (On-line Fig 2). After we adjusted for publication bias with the trim-and-fill approach, the adjusted pooled proportion for nondiagnostic results was 0.8% (95% CI, -0.8% – 2.5%) and the adjusted pooled proportion for malignancy was 15.6% (95% CI, 4.4% – 26.8%), which were in agreement with the unadjusted pooled estimates.

Diagnostic Performance of CNB for Malignancy

The diagnostic performance of CNB for malignancy was described in 4 studies involving 496 nodules. The diagnostic criteria for malignancy included a classification of Bethesda category 6 (malignancy). Pooling was not performed due to the relatively small number of studies included, the high risk of bias, and the inherent heterogeneity based on various study designs. The sensitivity varied from 44.7% to 85.0%; in fact, the lower margin of the 95% CI reached 25.2%. Nevertheless, the specificity was consistent, and all studies indicated a specificity of 100%; in fact, the lower margin of the 95% CI reached 89.1%. The positive predictive values were also consistent (100% in all 4 studies), whereas the negative predictive values varied (65.0%, 88.0%, 88.1%, and 94.0%).

Complications

Six of the 9 studies reported on the complications of CNB.^{6–10,12} In these 6 studies, no major complications, procedure-related deaths, or need for hospital admission or intervention was reported. One study reported a case (1/191) of neck swelling, pain, and perithyroid hematoma,⁹ whereas another study reported the

occurrence of minor complications, including small perithyroid hematomas in 8 patients (8/220) and mild transient parenchymal edema in 5 patients (5/220). All these patients had undergone simultaneous CNB and repeat FNA for each nodule in that study.⁶ They used 18-ga needles for CNB and 21-, 23-, or 25-ga needles for FNA. In case of patients receiving antiplatelet therapy, procedures were performed after discontinuing these medications for 1 week.

DISCUSSION

We performed a systematic review and meta-analysis to evaluate the efficacy and complications of CNB in the examination of thyroid nodules with initially indeterminate results on previous FNA. In the present study, we found that the pooled proportion for nondiagnostic results was 1.8% (95% CI, 0.4% – 3.2%); for inconclusive results, it was 25.1% (95% CI, 15.4% – 34.9%); and for malignancy, it was 18.9% (95% CI, 8.4% – 29.5%). With regard to the diagnostic performance for malignancy, the sensitivity of CNB varied from 44.7% to 85.0%, but the specificity was constant at 100%. There were no major compli-

cations associated with CNB. Considering these findings, CNB is a safe diagnostic technique with higher diagnostic yield, especially when molecular testing is not available or FNA does not yield enough cells for molecular testing.

Several studies have reported that CNB is useful for evaluating thyroid nodules with initial “nondiagnostic results” on previous FNA.^{15,28,29} A recent meta-analysis demonstrated that CNB may serve as a complementary diagnostic technique for thyroid nodules with initial nondiagnostic results on previous FNA, including 4 studies.³⁰ Currently, the definite diagnosis and management of thyroid nodules with initially “indeterminate results” on previous FNA are commonly encountered problems in daily clinical practice. Therefore, we performed this systematic review and meta-analysis of thyroid nodules with initially indeterminate FNA results, including 9 studies. In the present study, CNB demonstrated low nondiagnostic result rates (1.8%; 95% CI, 0.4% – 3.2%) and high specificities (100%) in the diagnosis of malignancy. The Korean Society of Thyroid Radiology guidelines mentioned that CNB might be useful for obtaining conclusive results in cases of thyroid nodules with initially indeterminate results on previous FNA.^{31,32} We believe that consistent evidence favoring the use of CNB, including the results of our systematic review with a meta-analysis, may be considered as a subsequent diagnostic approach for thyroid nodules with initially indeterminate results on previous FNA.

A gene-expression classifier is a molecular assay that was developed to improve surgical decision-making in cases of thyroid

nodules with initially indeterminate results on previous FNA. A previous prospective multicenter study reported on the ability of a gene-expression classifier to correctly identify indeterminate nodules (AUS/FLUS), with high sensitivity and negative predictive values (90% and 94%–95%, respectively) but low specificity (53%).³² In our present study, the specificities were 100% and the negative predictive values were variable, ranging from 65.0% to 94.0%. Moreover, a recent interinstitutional validation study showed that there were wide variations in the performance of the gene-expression classifier.³³ The cost of the gene-expression classifier is also high. Hence, although CNB shows slightly lower negative predictive values compared with those of the gene-expression classifier, CNB may serve as a better alternative method, with higher specificities and lower cost, in institutions in which the gene-expression classifier is not available.

CNB is reportedly more effective at obtaining large tissue samples, which enable molecular testing for the accurate diagnosis and assessment of the histologic architecture. Several recent articles have reported on molecular testing, which can be used for identification in CNB specimens of thyroid nodules with initially indeterminate results on previous FNA.^{11,12,24,27} Choi et al²⁴ revealed that the combination of *BRAF* V600E mutation analysis and CNB may add further value to the examination of thyroid nodules with initial AUS results on previous FNA. Furthermore, Kim et al¹² suggested a simple triage scheme involving US findings, CNB, or *BRAF* V600E mutation analysis, which can be used to identify a subpopulation of patients with a low or high likelihood of thyroid cancer among those with thyroid nodules with initial AUS/FLUS results on previous FNA. Jang et al¹¹ demonstrated that *NRAS* codon 61 mutation analysis along with CNB could be useful for achieving a clinical decision in cases of thyroid nodules with initial AUS results on previous FNA. Moreover, Trimboli et al²⁷ reported that galectin-3 and HBME-1 could improve the accuracy of CNB in cases of thyroid nodules with initially indeterminate results on previous FNA. Hence, it would be ideal for CNB to be integrated with radiologic, cytopathologic, or histologic approaches, along with certain patient factors, to optimize patient management. Moreover, further studies on long-term outcome data would help prove its clinical utility.

In our current systematic review, we did not observe any major complications of CNB. However, 1 case exhibited minor complications (1/191), including swelling, pain, and perithyroid hematomas after the CNB procedure.⁹ CNB is known to be a safe, well-tolerated method and is associated with a low complication rate.³⁴ Modern spring-activated biopsy needles (18–22 gauge) and US guidance can now be used to achieve high diagnostic accuracy and low complication rates. Despite such advances, CNB should be performed carefully under US guidance by experienced operators who are familiar with the US anatomy of the thyroid gland and perithyroid areas.^{30,31,35}

Our meta-analysis had several limitations of note. First, there were several inherent limitations of our study—that is, the relatively small number of included studies and its retrospective nature. Therefore, this meta-analysis should be interpreted cautiously if one wants to apply the findings. However, we used validated systematic review methods and reported results according to the standard reporting guidelines: the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses³⁶ and the guidelines of the *Handbook for Diagnostic Test Accuracy Reviews* published by the Cochrane Collaboration.³⁷ Second, our meta-analysis showed considerable heterogeneity in the pooled proportions. These heterogeneities were possibly due to the technical variation among the institutions or operators, the nodule characteristics, the number of passes, or the absence of standardized pathologic criteria for CNB. Third, a comparison of diagnostic performance between CNB and repeat FNA could not be performed. Repeat FNA also provides definitive categorization of indeterminate nodules.³⁸ Fourth, the prevalence of malignancy in patients with nondiagnostic/indeterminate thyroid nodules and the mortality of thyroid cancer remains low. Therefore, the clinical impact of the observed higher conclusive results of CNB compared with repeat FNA could be controversial.^{39,40}

CONCLUSIONS

This systematic review and meta-analysis indicate that CNB has low nondiagnostic result rates and high specificities for the diagnosis of malignancy. CNB is a safe diagnostic technique with higher diagnostic yield, especially when molecular testing is not available or FNA did not yield enough cells for molecular testing.

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