

# Computed Tomography-Guided Lung Biopsy for Molecular Tests: A Meta-Analysis

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## Research article

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# Abstract

## Background

To evaluate the potential clinical effectiveness of computed tomography (CT)-guided lung biopsy in the molecular tests.

## Materials and Methods

We searched the related studies from the PubMed, Embase, and Cochrane Library until July 2021. The endpoints included adequacy rates for molecular tests, positive rates of epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) translocation, and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations.

## Results

Initially, we were able to identify 1783 potentially relevant studies among which, only 12 were ultimately included in the present meta-analysis. All the studies were retrospective in nature. A total of 2559 patients underwent CT-guided lung biopsy and 1414 of them received molecular testing. We found that pooled adequacy rate for molecular tests, positive rate of EGFR mutations, and positive rate of ALK translocation were 95% (95% CI: 0.93–0.98), 49% (95% CI: 0.42–0.56), and 7% (95% CI: 0.04–0.09), respectively. Moreover, only 1 article reported the positive rate of KRAS mutation of 6% but a significant heterogeneity was detected in the endpoints of adequacy rate for molecular tests ( $I^2 = 86.2\%$ ,  $P < 0.001$ ) and positive rate of EGFR mutations ( $I^2 = 77.7\%$ ,  $P < 0.001$ ). While conducting a meta-regression analysis, we did not identify any variables that could significantly influence adequacy rate for molecular tests and positive rate of EGFR mutations. A high risk of publication bias was also found in the endpoint of adequacy rate for molecular tests (Egger test:  $P = 0.043$ ).

## Conclusions

CT-guided lung biopsy can serve as an effective method to provide sufficient lung cancer samples for molecular testing. EGFR gene was found to be the most frequently mutated during the analysis.

## Introduction

Computed tomography (CT)-guided lung biopsy, which includes both core needle biopsy (CNB) and fine needle aspiration biopsy (FNAB), have been widely used in diagnosis of lung nodules and masses with the diagnostic accuracy  $> 90\%$  [1–5].

In recent years, treatment modalities for lung cancer not only include conventional chemo- and radiotherapy, but also encompasses the application of individual molecular target therapies [6–8]. The common tested gene include epidermal growth factor receptor (EGFR) gene and anaplastic lymphoma kinase (ALK) fusion gene [6–8]. Tyrosine kinase inhibitor (TKI) gefitinib could be potentially used as the first-line treatment for patients with non-small-cell lung cancer that display EGFR gene mutation, and TKI gefitinib could effectively prolong the progression-free survival (9.2 vs. 6.3 months,  $P < 0.001$ ) when compared to the patients who received the conventional chemotherapy for treatment [9]. Therefore, CT-guided lung biopsy has been widely used for the molecular testing [10–21]. However, the adequacy rates for molecular test (83%-99%), positive rates of EGFR mutations (34%-72%) and ALK translocation (5%-9%) have been found to significantly vary from these studies [10–21]. These differences may be attributed possibly to the use of different types of needles (fine or core needles) or different lesion sizes. Therefore, a proper meta-analysis is needed to make an explicit conclusion for the clinical application of CT-guided biopsy in molecular tests.

In this meta-analysis, we aimed to evaluate the potential clinical effectiveness of CT-guided lung biopsy in the molecular tests.

## Methods

### Study selection

We explored the related studies from the PubMed, Embase, and Cochrane Library until July 2021. This meta-analysis was registered at <https://inplasy.com/> (Number: INPLASY202180059). The research strategy used was: (((((computed tomography[Title/Abstract] OR (CT[Title/Abstract])) AND ((lung[Title/Abstract] OR (pulmonary[Title/Abstract]))) AND (biopsy[Title/Abstract])) AND (((molecular[Title/Abstract] OR (gene[Title/Abstract])) OR (genic[Title/Abstract]))).

The inclusion criteria were as following: (a) the studies included the contents of CT-guided lung biopsy for molecular tests; and (b) the studies should contain at least one of the following endpoints: adequacy rates for molecular test, positive rates of EGFR mutations, ALK translocation, and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations. The excluded criteria were: (a) studies which did not report the type of needles used; (b) case reports; (c) animal studies; and (d) reviews.

### Quality assessment

All included studies were non-randomized controlled trials, which were assessed by at least two independent investigators with the Newcastle–Ottawa scale [22]. The 9-point Newcastle-Ottawa scale was assessed in the aspects of selection (4 points), comparability (2 points), and exposure (3 points), with assessments of high ( $\geq 7$ ), moderate (4–6), and low ( $< 4$ ) qualities.

### Data extraction

For this analysis, two investigators independently extracted data from these studies, and a third investigator was included to resolve any discrepancies. First authors, publication years, countries, sample sizes, gender distributions, age, and lesion size were regarded as the baseline data. The endpoints in this study included adequacy rates for molecular tests, positive rates of EGFR mutations, ALK translocation, and KRAS mutations. Among these, the adequacy rates for molecular testing was considered as the primary endpoint.

## **Statistical analyses**

Stata v12.0 was used to calculate the pooled adequacy rates for molecular test, positive rates of EGFR mutations, ALK translocation, and KRAS mutations. The random-effects model was generated. Heterogeneity was calculated by using the Q test and the  $I^2$  statistic, with  $I^2 > 50\%$  being indicative of significant heterogeneity. The sources of heterogeneity were detected by using the meta-regression, subgroup analysis, and sensitivity analysis. The subgroup analyses were performed based on the different needle types (fine or core needles) used, mean lesion sizes ( $<$  or  $\geq 4$  cm), and countries (Asian or Western). Additionally, Egger test was used to evaluate the potential risk of publication bias by Stata v12.0. A high risk of publication bias was considered if the P value was  $> 0.05$ .

## **Results**

### **Study characteristics**

Initially, we explored a total of 1783 studies that were potentially relevant to the present analysis. Thereafter, 282 duplicate studies were excluded from analysis. Based on the selection criteria, 15 articles were assessed for eligibility. Among these 15 articles, 3 studies were excluded because of lack of the data about endpoints ( $n = 2$ ) and insufficient information about the needle types used ( $n = 1$ ). Finally, 12 articles were included in this meta-analysis (Table 1, Fig. 1).

Table 1  
Characteristics of studies included in meta-analysis.

Studies	Year	Country	All patients number	Gender (male/female)	Patients with molecular test	Mean age (y)	Size of lesion (cm)	NOS
Zhuang [10]	2011	China	43	16/27	43	62	4	8
Cheung [11]	2010	Taiwan	47	24/23	47	64.6	4	8
Hou [12]	2013	China	40	29/11	40	32–81	3.3	8
Hsiao [13]	2013	Taiwan	332	199/153	134	65.3	4.9	8
Wang[14]	2013	China	228	93/135	228	62.1	3.4	8
Chen [15]	2014	China	353	228/125	236	59	4	8
Coley [16]	2015	USA	210	Not given	115	Not given	Not given	6
Florentine [17]	2015	USA	216	103/113	22	70	Not given	7
Lian [18]	2017	China	250	156/94	250	63	Not given	7
Tian [19]	2017	China	560	323/237	176	51.8	1.8	8
Beck [20]	2017	Korea	196	72/124	100	67.7	4.1	8
Porrello [21]	2019	Italy	42	Not given	23	Not given	Not given	6
NOS: Newcastle–Ottawa score.								

All articles included were retrospective studies. Moreover, 10 articles could be considered as of high quality [10–15, 17–20], while 2 articles were regarded belonging to moderate quality [16, 21]. A total of 2559 patients underwent CT-guided lung biopsy and 1414 of them received molecular testing.

Moreover, among the 12 articles, 9 articles were from Asia and 3 articles were from Western countries. Two articles used fine needles [10, 14], 7 articles used core needles [11–13, 15, 19–21], and 3 articles employed both fine and core needles [16–18]. The sizes of the needles ranged from 16G to 20G. Five articles only tested the EGFR mutations [10–14], 5 articles tested EGFR mutations and ALK translocation [15, 17–19, 21], and 2 articles tested EGFR mutations, ALK translocation, and KRAS mutations [16, 20] (Table 2).

Table 2  
Characteristics of CT-guided biopsy.

Studies	Types of needles	Size of needles	Contents of molecular tests	Adequacy for molecular test	Positive EGFR mutation	Positive ALK translocation	Positive KRAS mutation
Zhuang [10]	Fine	18 and 20G	EGFR	Not given	53%	-	-
Cheung [11]	Core	18 and 20G	EGFR	Not given	72%	-	-
Hou [12]	Core	18 and 20G	EGFR	Not given	38%	-	-
Hsiao [13]	Core	18 and 20G	EGFR	99%	60%	-	-
Wang[14]	Fine	18 and 20G	EGFR	96%	43%	-	-
Chen [15]	Core	16G	EGFR, ALK	99%	Not given	Not given	-
Coley [16]	Core, Fine	20 and 22G	EGFR, ALK, KRAS	96%	Not given	Not given	Not given
Florentine [17]	Core, Fine	20G	EGFR, ALK	95%	Not given	Not given	-
Lian [18]	Core, Fine	16-20G	EGFR, ALK	83%	50%	7%	-
Tian [19]	Core	18G	EGFR, ALK	95%	43%	8%	-
Beck [20]	Core	20G	EGFR, ALK, KRAS	96%	34%	5%	6%
Porrello [21]	Core	16-18G	EGFR, ALK	Not given	44%	9%	-

CT: computed tomography; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma receptor tyrosine kinase; KRAS: kirsten rat sarcoma viral oncogene homolog.

### Adequacy rate for molecular tests

It was found that eight articles with 1261 patients reported the adequacy rates for molecular test [13–20]. The pooled adequacy rate for molecular test was 95% (95% CI: 93%-98%, Fig. 2). A significant

heterogeneity was detected among these studies ( $I^2 = 86.2\%$ ,  $P < 0.001$ ). A high risk of publication bias was also found (Egger test:  $P = 0.043$ ).

The meta-regression analysis indicated that the adequacy rate for molecular test was not directly associated to the needle types used ( $P = 0.338$ , 95% CI: -0.25-0.11), lesion sizes ( $P = 0.729$ , 95% CI: -0.12-0.15), and countries ( $P = 0.452$ , 95% CI: -0.10-0.19).

The subgroup analyses have been shown in Table 3. The pooled adequacy rates for molecular test were 98%, 96%, and 91% based on the use of core needle, fine needle, or both types, retrospectively. A significant heterogeneity was only detected in the subgroup in which both types of needles were used ( $I^2 = 94.7\%$ ,  $P < 0.001$ ). The pooled adequacy rates for molecular test were 99%, 96%, and 91% based on the different mean lesion sizes ( $\geq 4$  cm,  $< 4$  cm, and unknown), retrospectively. A significant heterogeneity was only detected in the subgroup of unknown ( $I^2 = 94.7\%$ ,  $P < 0.001$ ). The pooled adequacy rates for molecular test were 96% and 96% based on patients belonging to Asian and Western countries, retrospectively, however a significant heterogeneity was only detected in the subgroup of patients in Asian countries ( $I^2 = 90\%$ ,  $P < 0.001$ ).

Table 3  
Subgroup analysis in adequacy for molecular test.

	Studies (n)	Pooled rates	95% confidential interval	Heterogeneity
Needle types				
Core	5	98%	0.98–0.99	$I^2 = 47.7\%$
Fine	1	96%	0.93–0.99	-
Both	2	91%	0.88–0.94	$I^2 = 94.7\%$
Mean lesion size				
$\geq 4$ cm	3	99%	0.98-1.00	$I^2 = 8.7\%$
$< 4$ cm	3	96%	0.94–0.98	$I^2 = 0.0\%$
Unknown	2	91%	0.88–0.94	$I^2 = 94.7\%$
Countries				
Asian	6	96%	0.97–0.99	$I^2 = 90.0\%$
Western	2	96%	0.93–0.99	$I^2 = 0.0\%$

The sensitivity analysis data showed that the significant heterogeneity disappeared ( $I^2 = 50\%$ ,  $P = 0.060$ ) when Lian et al. study [18] was removed.

### **Positive rates of EGFR mutations**

Nine articles with 971 patients reported positive rates of EGFR mutations [10–14, 18–21]. The pooled positive rate of EGFR mutation was 49% (95% CI: 42%-55%, Fig. 3) and a significant publication bias was found (Egger test:  $P = 0.727$ ).

The meta-regression analysis found that the positive rates of EGFR mutations were not associated with the needle types used ( $P = 0.655$ , 95% CI: -0.29-0.20), lesion size ( $P = 0.349$ , 95% CI: -0.13-0.31), and the countries ( $P = 0.590$ , 95% CI: -0.60-0.38).

The subgroup analyses have been shown in Table 4. The pooled positive rates of EGFR mutations were 49%, 47%, and 44% based on the application of core needle, fine needle, and both of them, retrospectively. A significant heterogeneity was only detected in the subgroup of core needle ( $I^2 = 87.8\%$ ,  $P < 0.001$ ). The pooled positive rates of EGFR mutation were 53%, 43%, and 49% based on the different mean lesion sizes ( $\geq 4$  cm,  $< 4$  cm, and unknown), retrospectively. A significant heterogeneity was only detected in the subgroup of lesion size  $\geq 4$  cm ( $I^2 = 88.4\%$ ,  $P < 0.001$ ). The pooled positive rates of EGFR mutations were 48% and 44% based on patients in Asian and Western countries, retrospectively. A significant heterogeneity was only detected in the subgroup of Asian countries ( $I^2 = 80.4\%$ ,  $P < 0.001$ ).

Table 4  
Subgroup analysis in positive rate of EGFR mutation.

	Studies (n)	Pooled rates	95% confidential interval	Heterogeneity
Needle types				
Core	5	49%	0.44–0.53	$I^2 = 87.8\%$
Fine	3	47%	0.42–0.51	$I^2 = 28.4\%$
Both	1	44%	0.24–0.64	-
Mean lesion size				
≥ 4 cm	4	53%	0.48–0.59	$I^2 = 88.4\%$
< 4 cm	3	43%	0.38–0.47	$I^2 = 0.0\%$
Unknown	2	49%	0.43–0.56	$I^2 = 0.0\%$
Countries				
Asian	8	48%	0.45–0.51	$I^2 = 80.4\%$
Western	1	44%	0.24–0.64	-
EGFR: epidermal growth factor receptor.				

The sensitivity analysis showed that a significant heterogeneity always existed after removing any of these included studies.

### Positive rates of ALK translocation

Four articles with 383 patients reported the positive rates of ALK translocation [18–21]. The pooled positive rate of ALK translocation was 7% (95% CI: 42%-55%, Fig. 4). However, no significant heterogeneity was detected among these studies ( $I^2 = 0\%$ ,  $P = 0.837$ ). A low risk of publication bias was found (Egger test:  $P = 0.576$ ) among the analyzed reports.

### Positive rates of KRAS mutation

Only 1 article reported the positive rate of KRAS mutation at 6% [20].

## Discussion

In this meta-analysis, we have systematically evaluated the potential clinical effectiveness of lung biopsy in the molecular tests. First of all, the pooled adequacy rate for molecular tests from CT-guided biopsy was observed to be 95%. This result indicated that CT-guided lung biopsy can serve as an effective

method for molecular tests. Kim et al. [23] have reported that no significant differences could be found in mutant EGFR detection rates (29.5% vs. 28.9%,  $P > 0.05$ ) between biopsy and resected samples. A study of surgical specimens and small tissue biopsies have revealed up to 80% agreement in gene mutation analyses data of lung cancer [24].

When we performed the subgroup analyses based on the different needle types used and lesion sizes, the pooled adequacy rates for molecular tests were all found to be greater than 90% in each group. The meta-regression also indicated that both FNAB and CNB were sufficient for conducting the molecular tests. Furthermore, the adequacy rate for molecular tests was also not significantly influenced by the lesion sizes or countries of origin.

However, a significant heterogeneity was detected ( $I^2 = 86.2\%$ ,  $P < 0.001$ ) for the endpoint of adequacy rate for molecular tests. Among these subgroups, a significant heterogeneity was detected in the subgroups of both the needle types used, unclear lesion size, and studies conducted in Asian countries. The sensitivity analysis showed that Lian's study [18] might be the source of potential heterogeneity. Among all included studies, only Lian et al. [18] reported the adequacy rate for molecular tests  $< 90\%$ . In Lian's study, both fine and core needles were used, and they did not report the mean size of the lesions detected [18]. Moreover, except for the needle types, lesion sizes, and countries, the other factors which might possibly influence the adequacy for molecular tests include operators' experience, pathologists' experience, quality of samples, and the condition of contamination by the presence of non-cancer cells [10]. Further prospective studies are still needed to evaluate the exact contribution of these additional factors.

The EGFR is over-expressed in 40%-80% of patients with non-small cell lung cancer (NSCLC), especially in the Asian patients [10]. It has been reported that targeted therapy using EGFR inhibitors has shown greater clinical response rates in the subgroup of patients with the following characteristics: women, non-smokers, adenocarcinoma, and East Asian origin [10, 11]. Thus, EGFR mutations have been commonly tested for patients with NSCLC.

In this meta-analysis, the pooled positive rate of EGFR mutations was 49%, which indicated that almost half of the NSCLC patients might potentially benefit from the use of EGFR inhibitor therapy. The meta-regression and subgroup analyses showed that positive rates of EGFR mutations was not associated with the needle types used, lesion sizes, and countries of origin. However, a significant heterogeneity was detected ( $I^2 = 77.7\%$ ,  $P < 0.001$ ). Although the subgroup analysis found that a significant heterogeneity was detected in the groups of core needle, mean lesion  $\geq 4$  cm, and Asian countries, the sensitivity analysis did not precisely indicate about the particular study, which was the main source of heterogeneity. Moreover, in addition to the factors mentioned above, the EGFR mutations may be also attributed to the gender, smoking condition, histological types and tumor stages [18].

ALK fusion gene is another driver gene implicated in the pathogenesis of NSCLC [18]. Overall response rate of crizotinib in the phase I clinical trial treatment of ALK positive NSCLC patients was reported to be

approximately 64% [25]. In this meta-analysis, the pooled positive rate of ALK translocation was 7% without exhibiting any significant heterogeneity ( $I^2 = 0\%$ ,  $P = 0.837$ ). The low heterogeneity might be attributed to the following factors: (a) the number of included studies for determining this endpoint was relatively small; and (b) the range of the positive rates of ALK translocation was possibly small (5–9%). Lian et al. [18] also found that the rates of positive ALK were comparable between FNAB and CNB groups (6.5% vs. 4%,  $P > 0.05$ ). It has been previously reported that stage IV NSCLC patients were found to be associated with a higher rate of ALK translocation [18].

KRAS mutation rate was only reported in 1 included study [20]. The most frequent of KRAS mutation are detected in pancreatic cancer [26]. Further studies regarding the status of KRAS mutations in NSCLC are needed.

This meta-analysis has some major limitations. First, all included studies were retrospective in nature with high heterogeneity in adequacy rate for molecular testing and EGFR mutations. Although some subgroup analyses have been performed, several other important factors (such as gender, age, operator experience, tumor stage, and pathological types) which also could significantly influence the results were not included for subgroup analyses because we could not stratify the data based on these factors from the included studies. Second, a significant publication bias was found in the endpoint of adequacy rate for molecular tests. It also needs to be highlighted that during the course of this study period (2010–2020) there have been several new developments related to biopsy procedures and techniques of molecular tests. Third, there was no control group included in this meta-analysis, and therefore, we could not precisely compare the CT-guided lung biopsy to other approaches that have been adopted in molecular tests.

## Conclusion

In conclusion, the findings of our meta-analysis revealed that CT-guided lung biopsy can serve as an effective method to provide sufficient lung cancer samples for molecular tests. EGFR gene was found to be the most frequent mutated and can contribute to lung cancer progression.

## List Of Abbreviations

ALK  
anaplastic lymphoma kinase;  
CT  
computed tomography;  
CNB  
core needle biopsy;  
EGFR  
epidermal growth factor receptor;  
KRAS

kirsten rat sarcoma viral oncogene homolog;  
TKI  
tyrosine kinase inhibitor.

## Declarations

**Ethics approval and consent to participate:** This is a meta-analysis and ethics approval and consent to participate are not required.

**Consent for publication:** This is a meta-analysis and consent for publication is not required.

**Availability of data and materials:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Competing interests:** None.

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**Authors' contributions:** YL designed this work. YBS and YFF searched the articles. FFX, XSY, and YL performed the data extraction and statistical analyses. JHZ wrote this article. Final manuscript was approved by all authors.

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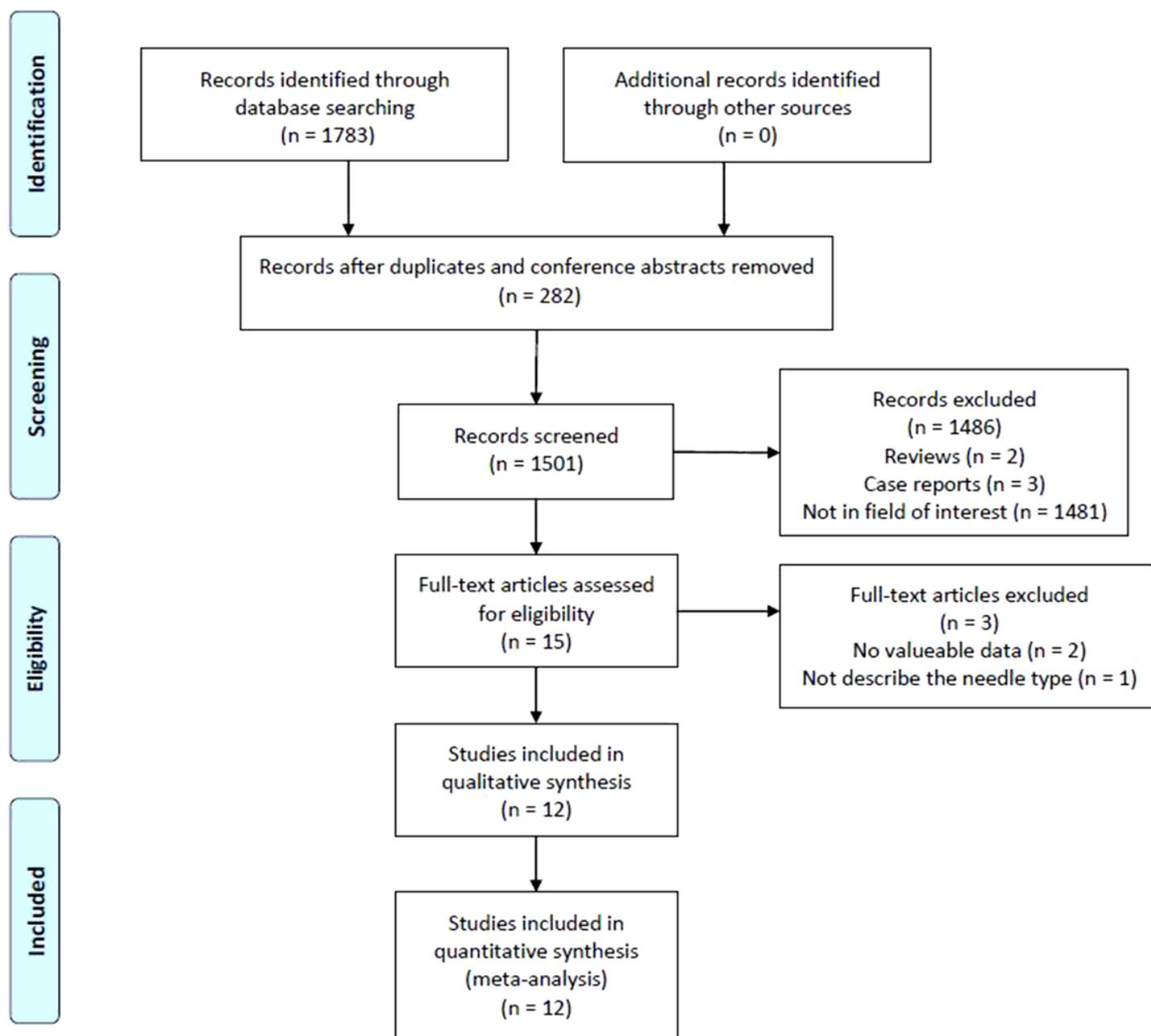
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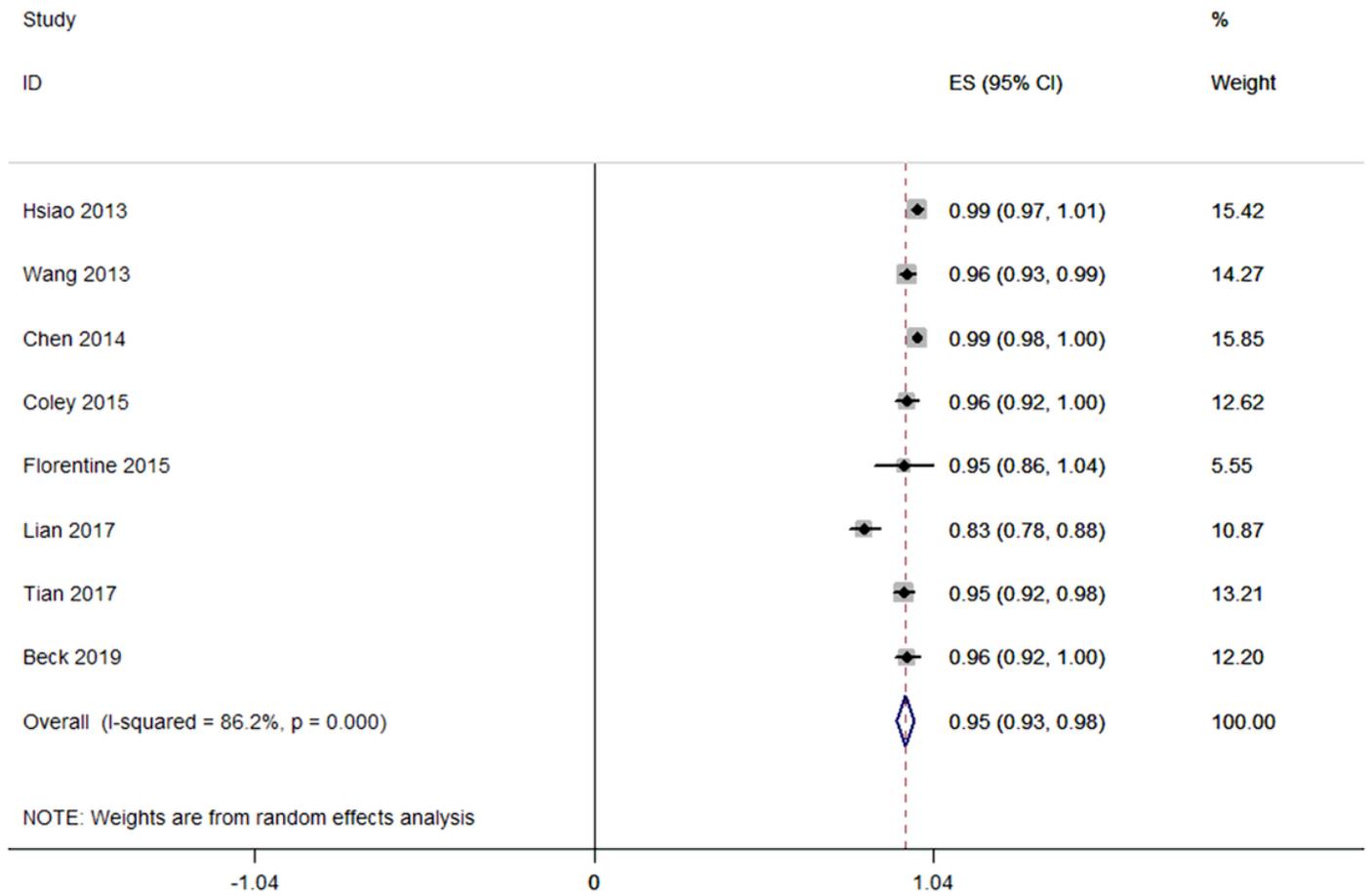
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## Figures



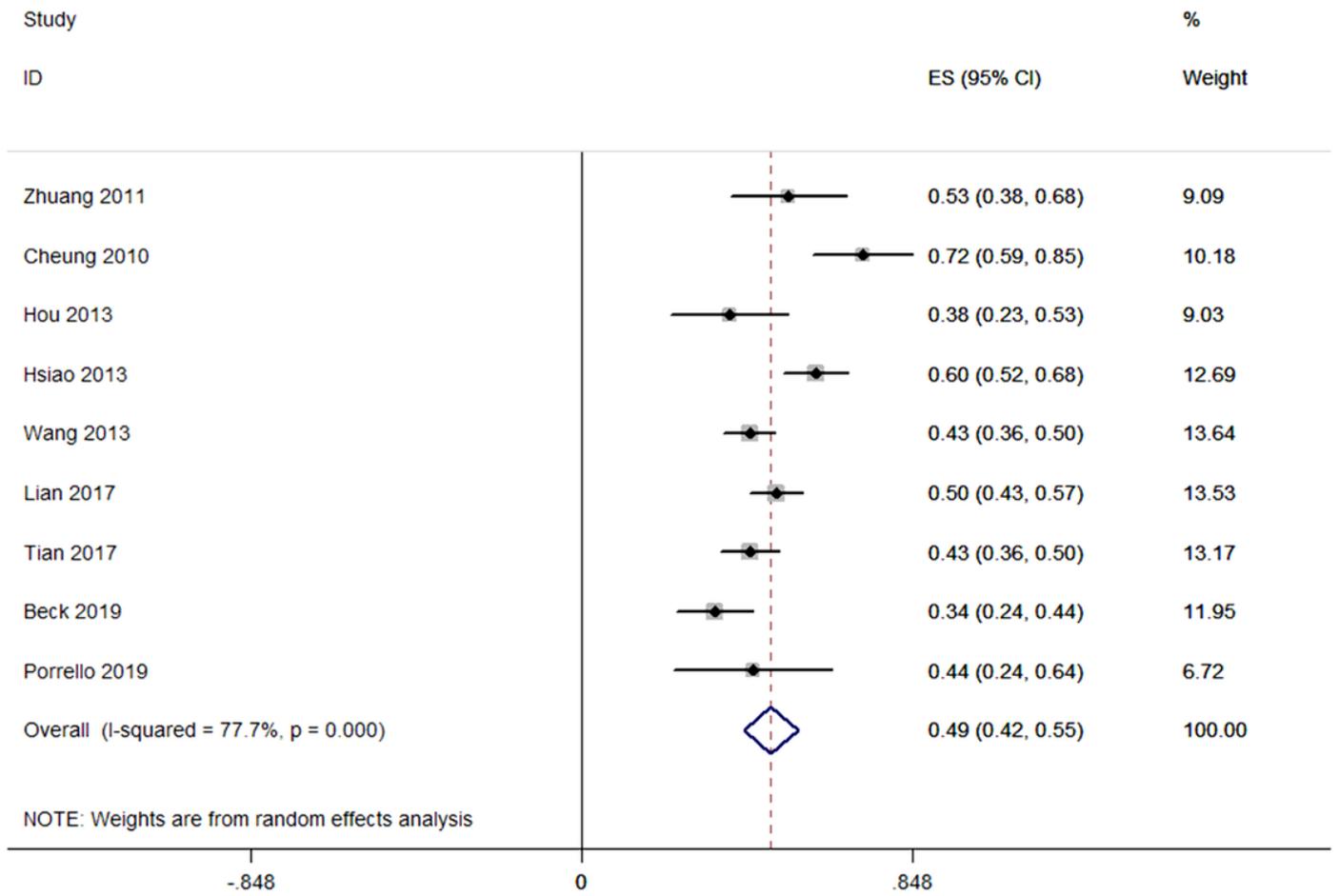
**Figure 1**

The flowchart of this meta-analysis.



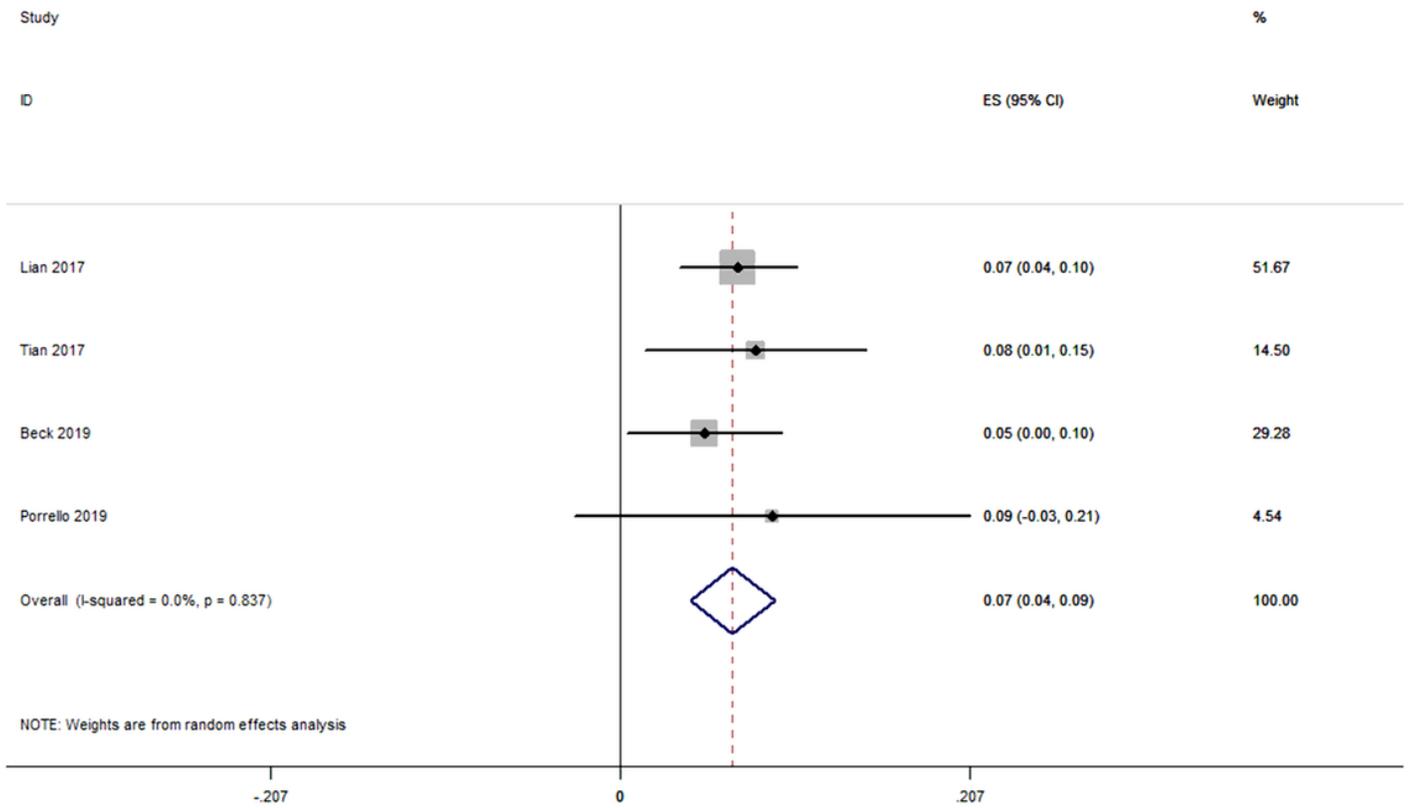
**Figure 2**

The forest plots of the adequacy rate for molecular tests.



**Figure 3**

The forest plots of the positive rates of EGFR mutation.



**Figure 4**

The forest plots of the positive rates of ALK translocation.