

# Advancements in the diagnosis and treatment of sub-centimeter lung cancer in the era of precision medicine (Review)

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**Abstract.** Lung cancer is the malignancy with the highest global mortality rate and imposes a substantial burden on society. The increasing popularity of lung cancer screening has led to increasing number of patients being diagnosed with pulmonary nodules due to their potential for malignancy, causing considerable distress in the affected population. However, the diagnosis and treatment of sub-centimeter grade pulmonary nodules remain controversial. The evolution of genetic detection technology and the development of targeted drugs have positioned the diagnosis and treatment of lung cancer in the precision medicine era, leading to a marked

improvement in the survival rate of patients with lung cancer. It has been established that lung cancer driver genes serve a key role in the development and progression of sub-centimeter lung cancer. The present review aimed to consolidate the findings on genes associated with sub-centimeter lung cancer, with the intent of serving as a reference for future studies and the personalized management of sub-centimeter lung cancer through genetic testing.

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## 1. Introduction

Lung cancer remains the leading cause of cancer-related deaths, with 2.3 million newly diagnosed cases worldwide in 2020 according to the International Association of Research on Cancer (1-3). It ranks second in terms of incidence and first in terms of mortality among malignant tumors (4,5). The World Health Organization classifies primary lung cancer as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) based on histological criteria. NSCLC accounts for >80% of lung cancer cases, and is mainly divided into adenocarcinoma, squamous cell carcinoma and large cell carcinoma (6). Imaging examination is used to determine the primary tumor site, histopathological examination to verify the tumor type and molecular pathology examination to formulate treatment plans. Patients with early-stage lung cancer are often asymptomatic and are commonly identified through routine medical examinations, such as chest computed tomography (CT) examinations (7,8). Symptoms tend to manifest in medium and advanced stages, leading to missed

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**Abbreviations:** AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma *in situ*; ALK, anaplastic lymphoma kinase; BRAF, V-raf murine sarcoma viral oncogene homolog B1; CALGB, cancer and leukemia group B; CTR, consolidation-to-tumor ratio; EGFR, epidermal growth factor receptor; FISH, fluorescence *in situ* hybridization; GGN, ground glass nodules; IAC, invasive adenocarcinoma; KRAS, Kirsten rat sarcoma viral oncogene homolog; LCSG, Lung Cancer Study Group; mGGN, mixed GGN; MET, mesenchymal-epithelial transition factor; NCCN, National Comprehensive Cancer Network; OS, overall survival; pGGN, pure GGN; RATS, robot-associated thoracic surgery; RET, rearranged during transfection proto-oncogene; ROS1, ROS proto-oncogene 1 receptor tyrosine kinase; SCLC, small cell lung cancer; SN, solid nodules; VATS, video-associated thoracic surgery; VDT, volume doubling time

**Key words:** sub-centimeter lung cancer, gene mutation, pulmonary nodules, genetic testing

opportunities for surgical intervention, resulting in a 5-year overall survival (OS) rate of 39% on average for patients with lung cancer (9,10).

The popularization of medical examination and low-dose CT technology has led to an increase in the proportion of patients with early-stage lung cancer. This benefits numerous patients with lung cancer by enabling detection and treatment at an earlier stage, thereby improving the survival rate of those affected (8). However, this has also resulted in the identification of a significant number of sub-centimeter lung lesions. Traditional qualitative diagnostic methods are of limited value in these cases, which has led to an inconsistency in the diagnostic protocols (11). Furthermore, a large number of studies in previous years have established an association between gene mutations and tumor development, leading to the emergence of targeted drugs based on gene mutations in the era of precision medicine for lung cancer treatment (12-14). Despite these advancements, the diagnostic and therapeutic options for sub-centimeter lung lesions remain controversial (15-18). Determining the best target and timing of drug treatment for patients with sub-centimeter lung cancer continues to be a matter of debate (19-21). The objective of the present review was to summarize the current status of the diagnosis and treatment of sub-centimeter lung cancer and to provide novel ideas and a scientific basis for improving the diagnosis and treatment strategies for this condition.

## 2. Sub-centimeter pulmonary nodules

Recently, a large number of pulmonary nodules, especially those with a small diameter, have been detected in patients, raising concerns about pulmonary health (8,22,23). Notably, pulmonary nodules are identified in ~1.6 million patients annually in the USA, and the cases in China exceed 100 million (24). A sub-centimeter pulmonary nodule, defined as a small growth in the lung with a diameter of <1 cm, can be observed on a CT scan (25). The solid component of a nodule is the area that completely covers the bronchus and blood vessels (26). Based on the proportion of solid components, sub-centimeter pulmonary nodules can be classified as pure ground glass nodules (pGGN), subsolid nodules or mixed ground glass nodules (mGGN), and solid nodules (SN) (27). Since the vast majority of sub-centimeter pulmonary nodules are benign or cannot be unequivocally diagnosed as lung cancer, regular review is a safer option, particularly for patients diagnosed for the first time. The National Comprehensive Cancer Network (NCCN) and the Fleischner Society have recently published a follow-up strategy for the first discovered solitary sub-centimeter pulmonary nodules, as presented in Table I. However, discrepancies exist in the guidelines due to differences in national conditions and epidemiological characteristics. For example, the British Thoracic Society has set the mGGN distinction limit at 5 mm (28). Furthermore, with regard to screening age, the American College of Chest Physicians and NCCN recommend 55 years (29,30), while the Chinese Medical Association recommends 45 years (31).

Assessment of the malignant probability of pulmonary nodules detected by chest CT is mainly based on the diameter, consolidation-to-tumor ratio (CTR), imaging signs and volume doubling time (VDT). The CTR is defined as the ratio of the

maximum consolidation diameter to the overall maximum diameter of the nodule (32). Nodules with a small diameter and few solid components are often associated with low malignancy, typically associated with early clinical stage malignancy. The imaging signs of pulmonary nodules mainly include lobulation, burr, vacuolation, pleural indentation, vascular collection, spinous processes and inflatable bronchi (33-36). Additionally, imaging signs of nodule malignancy are harder to detect in comparison with large nodules. The VDT, defined as the time required to double the three-dimensional volume of the lung nodule (37), is also considered as an indicator. Due to the small basic size of sub-centimeter lung nodules, the changes in diameter reflected on the images are difficult to capture when their volume is doubled and 3D imaging techniques are required for evaluation when necessary (37).

## 3. Sub-centimeter lung cancer

Either the imaging or the pathological size of pulmonary lesions is always an essential element to assess the stage of lung cancer development. The tumor-node-metastasis stage, developed by the Union for International Cancer Control and the American Joint Committee on Cancer, represents the primary tumor extent, the degree of regional lymph node involvement and the extent of distant metastasis (38). Sub-centimeter lung cancer mainly appears at the early stage and is commonly determined to be no later than pT1aN0M0. Nevertheless, there are still limited data in surgical and pathological reports regarding early pulmonary lesions classified as pT1N0M0, especially those ≤1 cm in size, which are defined as sub-centimeter lung cancer with no sign of nodal involvement and metastasis (39). There is emerging evidence revealing that sub-centimeter lung cancer exhibits distinctive characteristics. Patients with sub-centimeter lung cancer are found to have a younger median age in the lung cancer population. Furthermore, the pathological type is mostly proved as adenocarcinoma, among them, the incidence of atypical adenomatous hyperplasia (AAH), adenocarcinoma *in situ* (AIS), and minimally invasive adenocarcinoma (MIA) is generally high (27,40). However, it is still possible that they may evolve into invasive adenocarcinoma (IAC), invade the pleura and develop into lymph node metastasis (33,34). Independent risk factors for the progression of invasive lung cancer include tobacco use, tumor history, mGGN or SN and tumor diameter >5 mm (11-13,27). There are numerous predictive models for pulmonary nodules; however, their diagnostic accuracy remains limited in sub-centimeter lung nodules, especially for lesions with a diameter of 1-5 mm (34-36,41).

Surgical resection is the gold standard for sub-centimeter lung cancer treatment. In 1995, the Lung Cancer Study Group (LCSG) identified in the LCSG821 clinical trial that lobectomy was the standard surgical mode; however, the definite conclusion about the optimal mode of surgery remains unknown (42). Jiang *et al* (43) and Bai *et al* (44) found that among patients with stage IA1 sub-centimeter lung cancer, patients who underwent sub-lobar resection, including anatomical segmentectomy and wedge resection, had a similar 5-year OS compared with patients who underwent lobectomy. Sub-lobar resection is expected to be a novel standard surgical procedure for stage IA lung cancer that meets specific requirements, based

Table I. Follow-up strategy for sub-centimeter pulmonary nodules.

| Characteristics<br>Type    | National comprehensive cancer network |                   |                          | Fleischner society              |             |                   |
|----------------------------|---------------------------------------|-------------------|--------------------------|---------------------------------|-------------|-------------------|
|                            | Maximum diameter                      |                   |                          |                                 |             |                   |
|                            | <6 mm                                 | 6-8 mm            | >8 mm                    | <6 mm                           | 6-8 mm      | >8 mm             |
| Solid nodules              | 1 year                                | 6 months          | 3 month or PET-CT        | No follow-up required or 1 year | 6-12 months | 3 month or PET-CT |
| Mixed ground glass nodules | 6 months                              | 3 month or PET-CT | Enhancement CT or PET-CT | No follow-up required           | 3-6 months  | 3-6 months        |
| Pure ground glass nodules  | 1 year                                | 1 year            | 1 year                   | No follow-up required           | 6-12 months | 6-12 months       |

PET-CT, positron emission tomography-computed tomography.

on the release of the outcomes of clinical trials designed by the Japan Clinical Oncology Group, West Japan Oncology Group, and Cancer and Leukemia Group B (CALGB). Minimally invasive surgery, such as video-associated thoracic surgery (VATS), has replaced the traditional thoracotomy surgery and is currently the mainstream surgical method (32,45,46). In recent years, Da Vinci system robot-associated thoracic surgery (RATS) has developed rapidly. Compared with VATS, RATS offers superior imaging quality, a hand fibrillation filtration system, and increased flexibility and freedom. The advantages are particularly evident in intricate procedures like lymph node sampling and lung sleeve resection (47-49). In addition, thermal ablation therapy has received increasing attention as one of the supplements for patients with inoperable sub-centimeter lung cancer.

#### 4. Gene mutation and targeted therapy in sub-centimeter lung cancer

The most representative lung cancer-related gene mutations, including epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), V-raf murine sarcoma viral oncogene homolog B1 (*BRAF*), mesenchymal-epithelial transition factor (*MET*), ROS proto-oncogene 1 receptor tyrosine kinase (*ROS1*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), rearranged during transfection proto-oncogene (*RET*) and *TP53* mutations, have led to the development of constantly updated treatment means for advanced lung cancer through the identification of driver genes and the advance of targeted therapies. However, the lack of clinical trials for targeted therapy for patients with sub-centimeter lung cancer remains a challenge. Most sub-centimeter lung cancers, due to being in early clinical stages, are not included in studies, which undermines the specificity of the results for sub-centimeter lung cancer.

*EGFR* is a member of the tyrosine kinase receptor family, situated in the short arm of chromosome 7 and considered to be the most pivotal driver gene in patients with NSCLC (50-52). Previous studies have demonstrated that the incidence of *EGFR* mutation is higher in Asian non-smoking women and mutations are predominantly found in adenocarcinoma (53-55).

Targeted medicines, such as osimertinib, gefitinib, almonertinib and afatinib, known as *EGFR* tyrosine kinase inhibitors, are recommended for patients at an advanced clinical stage who are *EGFR* mutation-positive (56-61). In the case of brain metastases, osimertinib is the recommended treatment, given that a clinical study has demonstrated its capability to reduce the risk of brain metastasis by 82% (62). For non-classical *EGFR* mutations, afatinib is the preferred option (56).

*ALK* is located in the short arm of chromosome 2, crucial in neural development and associated with neuroblastoma (54,63). The typical *ALK* mutation, the fusion of echinoderm microtubule associated protein like 4 and *ALK*, is caused by chromosome translocation. In cases where the fusion gene is identified during chemotherapy, guidelines suggest targeted therapy with alectinib, ensartinib or crizotinib (64,65). In a randomized clinical trial, ensartinib was associated with superior progression-free survival and efficacy compared with crizotinib, thereby becoming a novel first-line treatment option for *ALK*-positive patients with NSCLC (66).

*BRAF* is positioned in the long arm of chromosome 7 and is the driver gene for various tumors, including melanoma, thyroid cancer and lung cancer (15,67-69). The most common *BRAF* mutation is the V600E point mutation, with an approximate mutation rate of 3% in lung adenocarcinoma (16). For patients with the *BRAF* V600E point mutation, the current preferred treatment is dabrafenib plus trametinib, which exhibits marked antitumor activity and a manageable safety profile (70-74).

*MET* is known as the hepatocyte growth factor receptor and is located at the long arm of chromosome 7 (75). *MET* contributes to nerve and muscle formation and is involved in embryogenesis and wound healing. *MET* mutations lead to tumor cell proliferation and angiogenesis. Savolitinib has been demonstrated to be an effective targeted medicine with an acceptable safety profile (76).

*ROS1* is rarely mutated in NSCLC, is situated in the long arm of chromosome 6 and tends to form a fusion gene (54,69,71). Crizotinib is the only targeted medicine unanimously approved for patients with *ROS1* mutations (16,77).

*KRAS* is located at the short arm of chromosome 12 and mutations are predominantly found in exons 1 and 2, leading

to uncontrolled cell proliferation. A total of ~20% of all *KRAS* mutations occur in patients with lung cancer (22,78,79). It has been observed that patients with resistance to *EGFR* tyrosine kinase inhibitors are prone to *KRAS* gene mutations (71,80,81).

*RET* is present in the long arm of chromosome 10, and mutations typically occur in the form of fusion genes (82,83). Although novel *RET* inhibitors are under development, there is still a gap in the efficacy of *RET* fusion-targeted therapy compared with other gene mutation types (83).

*TP53* is a tumor suppressor gene regulating the cell cycle, associated with patients who are smokers, and predominantly linked to squamous cell carcinoma and SCLC (84-86). There are currently no available targeted therapies for *TP53* mutations in patients with lung cancer.

## 5. Genomic characterization of sub-centimeter lung cancer

Throughout the entire life of humans, genomic instability is serving a crucial role in carcinogenesis (87,88). Studies on the genomics of lung cancer have made marked progress over the decades. This encompasses genomic variation that includes, but is not limited to, gene mutations, gene amplifications, gene deletions and gene rearrangements. Most current research has focused on genetic mutations in lung cancer, making it the focal point of discussion. Mutated genes, such as *EGFR*, *BRAF*, *KRAS*, *ALK* and *TP53*, have a higher incidence rate in sub-centimeter lung cancer. Early lung cancer progression to the advanced stage relies on the impact of several oncogenes, including *EGFR*, *KRAS* and *TP53* (89-92). A number of studies have demonstrated an association between the mutated gene *KRAS* and the solid components and diameter of the tumor (93,94). Furthermore, gene mutations, such as *ALK* mutations, suggest a poor prognosis of patients (95-97). In addition, mutated genes in lung cancer are associated with various factors, such as the living area (98,99), age (100), sex (101) and smoking history (102) of patients. In sub-centimeter lung cancer, *BRAF* mutation is classified as a special subtype, potentially serving a specific role in the early stages of lung cancer. Research has revealed that *BRAF* has a higher mutation frequency and clonal index in sub-centimeter lung cancer and is mostly present in AAH and AIS (102,103) and is potentially related to the overall low malignancy of sub-centimeter lung cancer. It has been demonstrated that *BRAF* mutation could stimulate proliferation and induce hyperplasia but is rarely associated with the development of malignancy, unlike *EGFR*, *TP53* and *KRAS* mutations, which indicate malignant transition (102). There is also evidence of mutual exclusivity between *BRAF* and *KRAS* mutations (103).

Supporting the theory of genome evolution, Hu *et al* (90) hypothesized that lung cancer develops from the early stage to IAC. Sub-centimeter lung cancer, known for its small diameter, is evaluated based on the CTR, which serves as a crucial imaging reference index for determining its malignancy. Chen *et al* (94) revealed a lower tumor mutation burden in pGGN compared with mGGN, suggesting that the former exist in a balanced state with a less active metabolism and immune environment, leading to their identification as inert nodules. Additionally, Li *et al* (26) confirmed that mGGN exhibited a lower somatic mutation count, genomic alteration count and intratumor heterogeneity compared with SN. Furthermore,

research has demonstrated that, as the GGN solid component increases, the mutation frequency of *EGFR*, *KRAS* and *TP53* increases (93). Notably, *KRAS* mutations are associated with a higher rate of CD8<sup>+</sup> T cell infiltration, stronger proliferative and immunosuppressive signals (92,102,104). *ALK* mutations are more frequently observed in young adults and are mainly diagnosed at an advanced tumor stage (100,105,106). It is worth mentioning that *ALK* mutation is associated with *EGFR* mutation, suggesting an increased malignant potential leading to decreased OS of patients (105). Supporting this notion, Campbell *et al* (107) found that *ALK* was more detectable in SN.

## 6. Genetic testing technology and its application

Genetic testing is recommended for patients with sub-centimeter lung cancer with clinical stage IB or above, in accordance with the current clinical consensus (16,95). The mostly adopted methods for lung cancer genetic testing at present are fluorescence *in situ* hybridization (FISH), PCR, microarray technology and DNA sequencing technology (108-110). FISH is the gold standard for detecting *ALK* and *ROS1* gene rearrangements in lung adenocarcinoma, as it is capable of obtaining chromosome information that cannot be detected by conventional techniques (69). It is a technique that hybridizes fluorescein-labeled probes to cellular nucleic acid. PCR technology, characterized by high sensitivity, high specificity and high yield, can amplify small amounts of DNA fragments in large quantities (111). Real-time PCR technology, also known as quantitative PCR technology, can dynamically monitor the number of products in the reaction process, eliminating the interference of product accumulation in the quantitative analysis, and effectively detecting gene mutation and the expression of oncogenes. Microarray technology is particularly suitable for the analysis of gene expression differences in separate tissues, with the advantage of low sample size requirement and the disadvantage of inferior specificity (108,110). DNA sequencing technology aims to determine the order of the four bases in a stretch of DNA molecule (111). High-throughput DNA sequencing technology, also referred to as next-generation sequencing technology, is commonly used (108). The specimen for genetic testing comes from the tumor tissue resected during the operation, and the results are more accurate than those obtained using other methods such as detection in peripheral blood (54). Additionally, the concentration of DNA extracted from the specimen continuously decreased over time, indicating biased results and potential under-detection of mutated genes with lower mutational abundances if the testing is not performed in a timely manner. Therefore, timely genetic testing for patients who require subsequent treatment is recommended, as taking targeted medicines in conjunction with timely follow-up can reduce the risk of recurrence and avoid delaying the treatment.

Gene mutations in primary and metastatic lung cancer are often discrepant (96). Currently, the preoperative application of genetic testing technology is principally used to determine the source of the tumor and to provide guidance for subsequent treatment (67,111,112). Determination of the distinctive tumor gene mutations can help identify the source of the tumor and contribute to selecting suitable adjuvant therapy. Neoadjuvant

therapy refers to a novel clinical treatment approach for patients with potential operative indication (16,95). It aims at reducing the size of the tumor bed, removing small lesions in the circulatory system and reducing the clinical stage to ultimately achieve improved surgical efficacy. Targeted medicines can specifically block the biological functions generated by driver genes, inhibiting or even blocking the growth and metastasis of malignant tumors at the molecular level (69,113). The current commonly used techniques for obtaining tissue specimens include transthoracic wall lung puncture, bronchoscopy and transbronchial needle aspiration. Sepesi *et al* (114) conducted a clinical trial of neoadjuvant therapy with nivolumab in 44 patients with early lung cancer and the results indicated that neoadjuvant therapy was generally safe and effective, with postoperative morbidity and mortality comparable with those of untreated patients. Genetic testing can distinguish driver gene-positive patients from driver gene-negative patients, thus contributing to selecting suitable adjuvant therapy. Currently, neoadjuvant therapy is mostly used in patients with stage III lung cancer; however, to the best of our knowledge, its optimal treatment mode has not been established.

Genetic testing can detect the lung cancer-related genes expressed in patients with advanced lung cancer in order to evaluate whether targeted medicines are required (78,115). The continuous emergence of novel targeted medicines with improved efficiency and tolerable toxicity is prolonging the survival time of patients detected to be lung cancer driver genes-positive, thus highlighting the importance of genetic testing in targeted drug therapy for non-surgical treatment of lung cancer (69,113). Tsutani *et al* (116) performed a clinical study based on *EGFR* gene mutations in 475 patients with stage I high-risk NSCLC. The results suggested a clear advantage of adjuvant chemotherapy for patients who were *EGFR* mutation-negative or unknown, but not for patients who were *EGFR* mutation-positive. This trial also demonstrated that genetic testing should be individualized, enabling each patient to get the optimal treatment option.

Tissue specimens are obtained by needle biopsy and other techniques for patients with advanced sub-centimeter lung cancer and drug treatment based on this is the preferred treatment plan. However, the guidelines do not routinely recommend genetic testing and adjuvant targeted therapy for the vast majority of patients with postoperative sub-centimeter lung cancer in stage I, which is not consistent with the current clinical practice. Patients with pathological risk factors, including low differentiation, vascular invasion, dirty layer pleural invasion and air cavity dissemination, have a worse OS and need more radical treatment, with lobectomy as the standard surgery. The need for postoperative adjuvant treatment requires further exploration in the future.

## 7. Discussion and outlook

Lung cancer poses a significant threat to human health due to factors such as environmental pollution, smoking, dust, respiratory infections and genetic mutations (69,74,81). Intercepting the progression of lung cancer at an early stage is critical. In order to improve the relapse-free survival rate for patients developing IAC at the sub-centimeter level, it is urgent to conduct clinical trials with a larger sample size to determine

the independent risk factors and guide early clinical management (12). The prediction model of sub-centimeter lung cancer based on clinical data requires continuous improvement (2). Therefore, different countries and regions can make efforts to develop guidelines that align with their actual epidemiological situation. Future guidelines should include a reasonable follow-up time, precise reexamination content and detailed treatment measures, to effectively address the challenges associated with lung cancer (117-119).

As aforementioned, the mutations of *EGFR*, *TP53* and *KRAS* could be one of the explanations for the positive associations between the solid ingredients and the malignancy degree in pulmonary nodules. Exploration of genomics aims to identify the deep mechanism underlying the progression of sub-centimeter lung cancer (15). *BRAF* mostly appeared in AAH and AIS and it may serve an extraordinary role in the early stage of lung cancer development. Existing findings require further confirmation as genetic mutations vary in diverse regions, sexes and lung cancer types. In addition, *ALK* mutation might be a sign of suboptimal prognosis. The potential relationship of antagonism and synergy between different genes suggests that studies should not be limited to a certain class of oncogenes but should be designed to examine a variety of oncogenes (15).

Despite the fact that postoperative genetic testing and adjuvant targeted therapy are not typically recommended for sub-centimeter lung cancer without cut-end failure, it is worth noting that the 5-year disease-free survival of patients with stage IA lung cancer was 64.1% even after lobar resection according to the results from CALGB140503 (46). This unexpected finding suggests the need to include patients with stage IA NSCLC in future trials on postoperative adjuvant targeted therapy, especially with the increasing proportion of patients with sub-centimeter lung cancer. By incorporating patients with stage IA NSCLC, future research efforts could help reduce the recurrence rate of patients with risk factors associated with recurrence and metastasis, ultimately contributing to an improved prognosis. This is important, since the majority of clinical trials on these aspects do not typically include patients with stage IA NSCLC, despite the potential benefit. The combination of genetic testing technology and targeted therapy has greatly improved the prognosis of patients with middle and advanced lung cancer, highlighting the potential impact of including patients with stage IA NSCLC in future research on postoperative adjuvant targeted therapy.

Increasing novel gene alterations are being identified by researchers, in addition to the well-studied genetic mutations (120-122). The future research focus is the development of effective targeted medicines for rare gene mutations and polygene mutations. Some mutations previously recognized to exist only in other malignancies might also be future directions of research in lung cancer. High applicability and low toxicity are aims in the generation of novel targeted medicines.

Genetic testing technologies have the potential to add unique value to the accurate diagnosis and treatment of sub-centimeter pulmonary nodules when combined with imaging methods, given the high incidence of such nodules. This combination can improve the diagnosis quality of sub-centimeter lung cancer and aid in identifying nodules

with a high risk of recurrence. The refinement of prediction models resulting from genetic testing can provide suggestions for surgical method selection, prognosis prediction and the need for subsequent treatment. It is anticipated that future research will focus on increasing the sensitivity of gene detection techniques, exploring the molecular mechanism and raising awareness of the importance of a comprehensive evaluation approach for sub-centimeter pulmonary nodules. The increasing popularity and advancement of genetic testing technology can lead to the integrated management of diagnosis and treatment methods for patients with sub-centimeter lung cancer, incorporating gene testing and targeted therapy.

## 8. Conclusion

Over the years, the number of patients with sub-centimeter lung nodules has increased. Qualitative diagnostic and treatment strategies for these nodules, which may develop into lung cancer, pose significant challenges in clinical practice. In the era of precision medicine, genetic detection technology and targeted therapy for genetic alterations are increasingly crucial in the diagnosis and treatment of lung cancer. Genomic studies have continuously unraveled the molecular mechanisms contributing to the malignancy progression of sub-centimeter lung cancer. It is anticipated that, in the future, combining genetic information with other clinical data will lead to the development of a comprehensive evaluation system for sub-centimeter pulmonary nodules.

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XW wrote the manuscript. JS and ZL provided study materials and revised the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

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## Competing interests

The authors declare that they have no competing interests.

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