Advances in the Basic Sciences in Thoracic Oncology in the Last 20 Years and Their Translational Impact

Michele Carbone, MD, PhD,[a,b,*] Christopher Amos, PhD,[c] Richard L. Attanoos, MD,[d] Mattia Boeri, PhD,[e] Raphael Bueno, MD,[f] Paul A. Bunn, MD,[g] Lucian R. Chirieac, MD,[h] Benjamin Cooper, MD,[i] Dean Fennell, MD, PhD,[j] Francoise Galateau-Salle, MD,[k] Lydia Giannakou, MD,[a] Chandra V. Goparaju, PhD,[l] Raffit Hassan, MD,[m] Paul Hofman, MD, PhD,[n] Mark G. Kris, MD,[o] Weimin Mao, MD,[p] Michael Minaai, MS,[a] Tsetsuya Mitsudomi, MD, PhD,[q] Thierry J. Molina,[r] Luis M. Montuenga, PhD,[s] Kazuki Nabeshima, MD, PhD,[t] Antonio Passaro, MD, PhD,[u] Solange Peters, MD, PhD,[v] Arun Rajan, MD,[m] David B. Richardson, PhD,[w] Hilary Robbins, PhD,[x] Christian Rolfo, MD, PhD,[y] Charles M. Rudin, MD, PhD,[z] Jonathan M. Samet, MD, MS,[aa] Arnaud Scherpereel, MD, PhD,[ab] David S. Schrump, MD, MBA,[ac] Gabriella Sozzi, PhD,[ad] Emanuela Taioli, MD, PhD,[ae] Silvia D. Visonà,[af] Haining Yang, MD, PhD,[a] Yoshie Yoshikawa, PhD,[a] An Zhao,[ag] Harvey I. Pass, MD[l]

[a]*Thoracic Oncology Program, University of Hawaii Cancer Center, Honolulu, Hawaii*
[b]*Università Magna Græcia, Scuola di Medicina, Anatomia Patologica, Catanzaro, Italy*
[c]*University of New Mexico, New Mexico, Albuquerque*
[d]*Department of Cellular Pathology, University Hospital of Wales and School of Medicine, Cardiff University, Wales, United Kingdom*
[e]*Unit of Epigenomics & Biomarkers of Solid Tumors, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[f]*Division of Thoracic Surgery, Lung Center and International Mesothelioma Program, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts*
[g]*Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado*
[h]*Department of Pathology, Mount Sinai Hospital, New York, New York*
[i]*Department of Radiation Oncology, NYU Langone Health, New York, New York*
[j]*University of Leicester & University Hospitals of Leicester NHS Trust, Leicester, United Kingdom*
[k]*College MESOPATH, Paris, France*
[l]*Department of Cardiothoracic Surgery, NYU Langone Health, New York, New York*
[m]*Thoracic and GI Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland*
[n]*Laboratoire de Pathologie Clinique et expérimentale CHU, Nice, IHU RespirERA Université côte d'Azur Nice, Nice, France*
[o]*Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, and Weill Cornell Medical College, New York, New York*
[p]*Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou, Zhejiang, People's Republic of China*
[q]*Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, Osaka-Sayama, Japan*
[r]*Department of Pathology, Hôpitaux Universitaires Robert Debré et Necker Enfants-Malades, AP-HP, Université Paris Cité, Paris, France*
[s]*Solid Tumors Program, Clínica Universidad de Navarra Cancer Center and CIMA, University of Navarra, Pamplona, Spain; IdisNa, Pamplona, Spain; CIBERONC, Madrid, Spain*

***Corresponding author.**

Address for correspondence: Michele Carbone, MD, PhD, Thoracic Oncology Program, University of Hawaii Cancer Center, 701 Ilalo Street, Building A-4R, Room 450, Honolulu, Hawaii 96813. E-mail: mcarbone@cc.hawaii.edu

Cite this article as: Carbone M, Amos C, Attanoos RL, et al. Advances in the basic sciences in thoracic oncology in the last 20 years and their translational impact. *J Thorac Oncol*. 2026;21:41-76.

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2025.11.002

[t]Department of Diagnostic Pathology, Pathological Diagnosis Center, Fukuoka Tokushukai Hospital Fukuoka University, Fukuoka Prefecture, Japan
[u]European Institute of Oncology IRCCS, Milan, Italy
[v]Department of Oncology, University Hospital CHUV, Lausanne, Switzerland
[w]UC Irvine Joe C. Wen School of Population & Public Health, Irvine, California
[x]Genomic Epidemiology Branch, International Agency for Research on Cancer, Lyon, France
[y]Department of Internal Medicine, Division of Medical Oncology, The Arthur G. James Comprehensive Cancer Center, Columbus, Ohio
[z]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York
[aa]Colorado School of Public Health, Aurora, Colorado
[ab]Service de Pneumologie et d'Oncologie Thoracique CHU de Lille - Hôpital Albert Calmette, Lille, France
[ac]Thoracic Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland
[ad]Unit of Epigenomics & Biomarkers of Solid Tumors, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[ae]Institute for Translational Epidemiology and Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York
[af]Department of Public Health, Experimental and Forensic Medicine, Unit of Legal Medicine and Forensic Sciences, University of Pavia, Pavia, Italy
[ag]Zhejiang Cancer Institute, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou, Zhejiang, People's Republic of China

Received 13 October 2025; revised 3 November 2025; accepted 4 November 2025
Available online - 8 January 2026

ABSTRACT

In this article, we summarize the progress made in lung cancer, mesothelioma, and thymic epithelial malignancy during the period 2005–2025. We enlisted multidisciplinary thoracic oncologic experts to tackle this task. The main focus of the article concerns how basic science with translational impact has improved the diagnosis, prognosis, and therapy of these cancers. During the past 20 years, we have come to the realization that "lung cancer" is a name that encompasses tumors with vast histologic, immune, and genomic differences that in turn influence prognosis and response to therapy. For example, programmed death-ligand 1 levels are being used as an immune signature which guides the use of immunotherapy. There is an 85% higher risk for developing lung cancer among first-degree relatives of patients with lung cancer. Accordingly, an increasing number of lung cancers are being identified in carriers of predisposing germline pathogenic inactivating mutations, suggesting that screening programs for early lung cancer detection may benefit family members. Underscoring the role of genetics, and the importance of germline testing, a different variant of mesothelioma has been identified developing in carriers of inactivating heterozygous germline mutations of *BAP1* and of other tumor suppressor genes, including a new variant of mesothelioma caused by fusion genes. These variants of mesothelioma are characterized by specific histologic and molecular genetic alterations. These patients benefit from screening programs as they are at risk of multiple malignancies, their tumors are usually much less aggressive, and they are more responsive to therapy compared with sporadic, asbestos-induced mesotheliomas. Thus, the tailored therapeutic approach that is described here for lung cancer may extend to patients with mesothelioma, rather than the previous "one therapy fits all" approach. Progress in the rare thymic epithelial tumors has been less marked; however, recent insights into the biology of thymic tumors have resulted in the development of clinically relevant interventions.

Keywords: Genetic predisposition; Lung cancer; Mesothelioma; Thymic malignancies

Introduction

During the past 20 years, medical research has led to a significant improvement in both prevention and therapy for thoracic malignancies. To summarize all of these landmark contributions by innumerable scientists and clinicians all over the world is, in essence, an impossible task, and some initiatives may be absent, for which we apologize but in no way consider less important. The point is really that the International Association for the Study of Lung Cancer (IASLC) has been instrumental in helping us move forward with thoracic oncology and with either presenting these accomplishments in meetings or publishing in the *Journal of Thoracic Oncology*, among other high-profile journals. This manuscript has attempted to divide this evolution into discrete sections, but we all know that the lines are blurred with that type of segmentation.

In the past two decades, lung cancer (LC) care has been transformed by initiatives and innovations that span prevention, diagnostics, and therapy. Furthermore, both globally and in the United States, cigarette smoking has markedly declined. Worldwide, the WHO's most recent trend report reveals a sustained fall in adult tobacco

use since 2000,[1] and in the United States, the adult smoking rate fell from 20.9% in 2005 to 11.5% to below 11.5% in 2022.[2]

Population-level early LC detection became an established practice using low-dose computed tomography (LDCT) screening: the U.S. National Lung Screening Trial demonstrated a 20% reduction in LC mortality versus chest radiography, establishing CT screening as a life-saving intervention,[3] later corroborated by Europe's NELSON trial using volume CT and nodule growth rate assessment.[4] These trials resulted in national and international screening guidelines, defining eligibility criteria and shifting stage at diagnosis toward curability.

Concurrently, precision oncology personalized the treatment of NSCLC with international guidelines directing the use of routine molecular profiling with tumor sequencing.[5,6] Targeted therapies using highly active oral therapies for oncogenic drivers, such as EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, RET, NTRK, HER2, and KRAS G12C, have improved both survival and quality of life.[7] The integration of liquid biopsy (cell-free DNA [cfDNA]) has further accelerated care by providing rapid, minimally invasive genotyping at diagnosis and progression; Food and Drug Administration (FDA)–approved assays and trial data (i.e., AURA3[8]) demonstrated strong concordance with tissue testing and actionable guidance—particularly for resistance mutations such as EGFR T790M—and led to improved outcomes as adjuvant therapy for resected NSCLC.[9]

Immuno-oncology has been equally transformative. In advanced NSCLC, programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors displaced chemotherapy as first-line therapy for biomarker-selected patients (e.g., pembrolizumab in PD-L1 $\geq$ 50%) and improved survival after platinum failure (e.g., nivolumab versus docetaxel).[10,11] Immune checkpoint blockade then moved to combined therapy: consolidation durvalumab after chemoradiation for unresectable stage III disease (PACIFIC) significantly prolonged progression-free survival (PFS) and overall survival (OS) and became a new standard of care, a benefit now reproduced in real-world cohorts.[12] In resectable disease, neoadjuvant chemoimmunotherapy (CheckMate-816) increased pathologic complete response and event-free survival (EFS).[13]

For surgery, limited resection of stage I LC has become a standard of practice,[14] as well as the increasing use of robotics for diagnosis[15] and resection.[16] Radiation oncology advanced in parallel. Stereotactic body radiation therapy (SBRT) matured from an experimental technique to a curative modality for medically inoperable stage I NSCLC, achieving durable local control and favorable survival with limited toxicity, thereby expanding curative options beyond surgery.[17]

Together, these innovations have redefined LC from a uniformly lethal disease to one where earlier detection, biologically tailored treatment, and durable control have become the norm instead of the exception. Figure 1 reveals a timeline of the main discoveries in LC during the past 20 years.

The more rare mesotheliomas and thymic malignancies have found a limited development of novel therapies because these are Orphan diseases, and, therefore, the rarity of these diseases creates challenges in generating preclinical data and conducting clinical trials, and industry support has been limited. Progress for these rare malignancies has been entirely dependent on limited grant funding and donations. On the positive side, thanks to the measures taken in the Western World in the 80s and 90s to drastically reduce exposure to asbestos, during the past 20 years we have found a decline in the incidence of mesothelioma in the USA, Australia, etc.[35–37] Asbestos remains, however, the main cause of pleural mesothelioma (PM).[38] Presently, peritoneal mesotheliomas are rarely linked to asbestos exposure,[39,40] because these mesotheliomas historically developed in patients exposed to high amounts of asbestos, exposures that presently are rarely found in our society.[35–37] The discovery that a fraction of mesotheliomas estimated at 12% to 15% caused by genetic mutations of BAP1 and of other genes are a different and much less aggressive disease compared with asbestos-induced mesothelioma is having a major positive impact in the life of these patients and their families.[41] Instead, there has been limited improvement in the therapy of sporadic, often asbestos-induced mesothelioma. The addition of bevacizumab to chemotherapy[42] improved median survival for epithelioid mesothelioma to approximately 18 months. More recently, immunotherapy has also improved mesothelioma median survival of a few months mostly in patients with the sarcomatoid variant. However, the possible benefit of immunotherapy for patients with the epithelioid variant of mesothelioma remains controversial, and this issue was debated in two recent articles in *JTO*. We refer the reader to those articles.[43,44] In 2008, Flores et al.[45] demonstrated that pleurectomy provided an overall better outcome compared with extrapleural pneumectomy; this manuscript radically changed the surgical approach to mesothelioma worldwide. However, in 2011, a phase 3 clinical trial[46] called into question whether surgery provided any benefit to patients with mesothelioma and a more recent phase 3 clinical trial concluded that surgery does more harm than good to these patients.[47] These trials have been discussed in detail in a recent perspective in *JTO* by surgeons who are in favor and against the use of surgery for this mesothelioma, and we refer the readers to this article.[48] The

Figure 1. Key References for Lung Cancer Timeline (2000–2025).
Screening • National Lung Screening Trial Research Team. N Engl J Med 2011;365:395–409.[18] • de Koning HJ et al. N Engl J Med 2020;382:503–513 (NELSON).[4] • USPSTF Recommendation Statement. JAMA 2021;325:962–970.[19] Surgery • McKenna RJ Jr. Ann Thorac Surg 2006;81:421–425 (VATS outcomes).[20] • Saji H et al. JCOG0802/WJOG4607L. NEJM 2022;386:1257–1267 (segmentectomy vs lobectomy)[21] • Cerfolio RJ et.al. J Thorac Cardiovasc Surg 2016 Oct;152(4):991-997 (robotic thoracic surgery)[22] • Altorki N et al: N Engl J Med. 2023 Feb 9;388(6):489-498 (wedge and segmentectomy vs lobectomy).[14] Radiation Therapy • Timmerman R et al. JAMA 2010;303:1070–1076 (SBRT in inoperable early-stage).[23] • Chang JY et al. Lancet Oncol 2015;16:630–637 (SBRT vs lobectomy pooled).[24] • Antonia SJ et al. N Engl J Med 2017;377:1919–1929 (PACIFIC).[25] • Kleber T, et al. International Journal of Radiation Oncology Biology Physics. 2025;123(1):S119. (STARS 10-yr update).[26]

Table 1. Milestones in Mesothelioma Research Timeline (2000–2025)

Year	Key Findings/Discoveries	References
2001	First evidence that, in some families, susceptibility to mesothelioma is transmitted in a Mendelian fashion (autosomal dominant)	Roushdy-Hammady et al.[49]
2003	The combination of cisplatin and pemetrexed improves median survival by 11.5 wk	Vogelzang et al.[50]
2008	Pleurectomy revealed to be superior to extrapleural pneumonectomy	Flores et al.[45]
2011	Identification of *BAP1* as the gene responsible for mesothelioma in some families	Testa et al.[51]
2015	Elucidation of BAP1 immunohistochemistry and its value in the differential diagnosis of mesothelioma. Identification of *BAP1* as the most frequent acquired (somatic) inactivating mutation in mesothelioma	Nasu et al.[52]
2015	Germline *BAP1* mutations linked to 7+ y median survival in mesothelioma	Baumann et al.[53]
2015	NGS analyses reveal the most frequently acquired (somatic) mutations in mesothelioma	Guo et al.[54]; Iacono et al.[55]
2016	Identification of the mechanism responsible for somatic BAP1 alterations and why NGS misses 50% of them	Yoshikawa et al.[56]
2016	First comprehensive genomic analyses of somatic alterations in mesothelioma	Bueno et al.[57]
2016	Identification of the first fusion gene (*ALK*) driving the growth of peritoneal mesothelioma in an adolescent	Loharamtaweethong et al.[58]
2017	Elucidation of key mechanisms of *BAP1* tumor-suppressor activity	Bononi et al.[59]
2021	Identification of a shared pathway of carcinogenesis mediated by HMGB1 caused by *BAP1* inactivation and/or asbestos	Novelli et al.[60]
2021	First clinical trial proposing that immunotherapy benefits patients with mesothelioma	Baas et al.[61]
2024	*BARD1* mutations linked to familial mesothelioma and elucidation of the underlying mechanisms	Novelli et al.[62]
2024	Randomized clinical trial revealing that surgery for mesothelioma does not help and may harm patients	Lim E et al.[47]
2025	Demonstration that mesothelioma in carriers of germline *BAP1* mutations is a different, much less aggressive disease than asbestos-induced mesothelioma and that these patients benefit from screening programs for early cancer detection	Carbone et al,[41]; Xu et al.[63]

NGS, next-generation sequencing.

main discoveries in mesothelioma during the first quarter of this century are outlined in Table 1.

The incidence of thymic epithelial tumors (TETs) is increasing due to early (incidental) detection via imaging and improvements in pathology classification.[64,65] True regional differences may also contribute to the increase. Survival for TETs (especially thymoma) has improved modestly in the past couple of decades. Several factors likely contribute to these observations and include earlier detection, advances in surgical techniques resulting in a greater proportion of patients achieving a complete surgical resection, and an improvement in the management of paraneoplastic autoimmune diseases.[66] It is hoped that advances in an understanding of the biology of these diseases, including comprehensive genomic profiling, interrogation of tumor immunology, and correlative findings from recent studies of tyrosine kinase inhibitors (TKIs) and immunotherapy,[67] will result in identification of a larger number of druggable targets in the near future. The main discoveries in TETs during the first quarter of this century are outlined in Figure 2.

Epidemiology

Lung Cancer

LC rates have been declining over time. Changes in smoking habits have changed the epidemiology of the disease to more females, never smokers, with adenocarcinoma. The introduction of LDCT screening has shifted stage to earlier, more curable disease.[68] Molecular markers have allowed a more personalized treatment. Immunotherapy has changed the landscape of late-stage disease to a more treatable condition.[69]

Medical Oncology • Shaw AT et al. N Engl J Med 2013;368:2385–2394 (crizotinib ALK+).[27] • Brahmer J et al. N Engl J Med 2015;373:123–135 (nivolumab vs docetaxel).[28] • Reck M et al. N Engl J Med 2016;375:1823–1833 (KEYNOTE 024).[10] • Antonia SJ et al. N Engl J Med 2017;377:1919–1929 (PACIFIC).[25] • Soria JC et al. N Engl J Med 2018;378:113–125 (FLAURA).[29] • Wu YL et al. N Engl J Med 2020;383:1711–1723 (ADAURA).[30] • Forde PM et al. N Engl J Med 2022;386:1973–1985 (CheckMate 816).[13] • Spicer J et al. Lancet 2023;401:1777–1790 (KEYNOTE 671).[31] • Planchard D et al: N Engl J Med. 2023 Nov 23;389(21):1935-1948 (FLAURA2).[32] Multidisciplinary / Guidelines • NCCN Clinical Practice Guidelines in Oncology: Non Small Cell Lung Cancer (Versions 1.2010–2025).[5] • ASTRO/ESTRO SBRT Guidelines. Pract Radiat Oncol 2017;7:295–301.[33] • ESMO Guidelines Committee. Ann Oncol. 2025;36(11): 1245-1262. Early and locally advanced non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.[34]

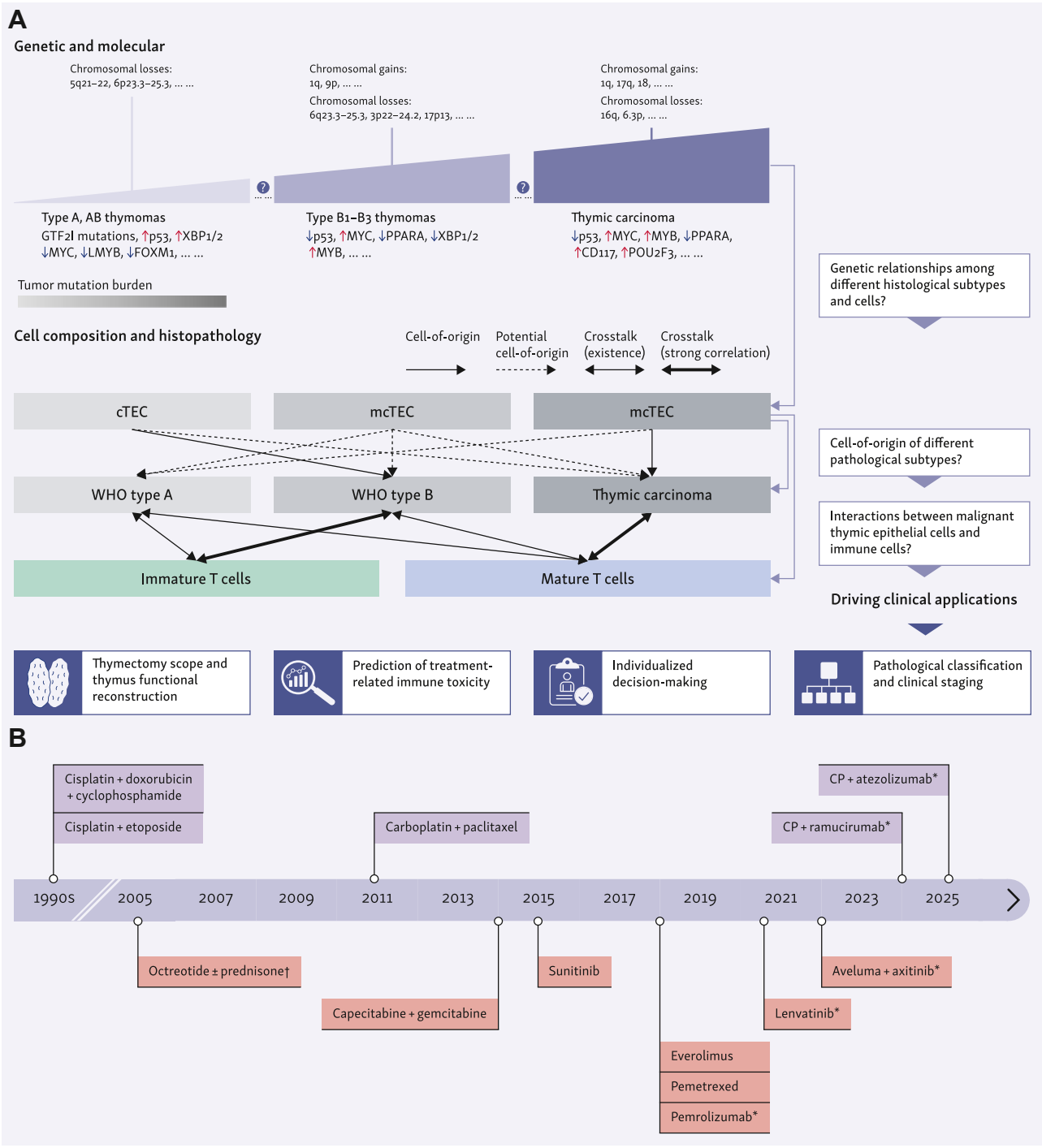

Figure 2. (*A*) Basic science knowledge of TETs. Recent advances in unraveling the cellular, genomic, and immunologic composition of TETs have the potential to drive clinical applications related to diagnosis and treatment. Genomic aberrations and the cell-of-origin of TET WHO subtypes are outlined. Interactions between the malignant epithelial cells and resident immune cells need further investigation. Knowledge of these interactions has the potential to contribute to the understanding of thymoma-associated autoimmune diseases and facilitate the development of TET-directed therapies. (*B*) Evolution of systemic therapy for TETs. A timeline of clinical trials that have influenced the medical management of advanced thymoma and thymic carcinoma during the past 20 years. Purple boxes include recommendations for first-line therapy. Pink boxes include recommendations for subsequent systemic therapy. CP, carboplatin plus paclitaxel; TET, thymic epithelial tumor; † indicated for thymoma if tumor uptake is observed on an octreotide scan or a dotatate positron emission tomography scan; * indicated for thymic carcinoma.

Lung-sparing surgery has decreased complications and expanded the number of patients candidates for surgery in early-stage disease to include those with comorbidities and high body mass index.

Mesothelioma

Mesothelioma remains a rare cancer globally, ranking 32nd in incidence and 26th in mortality (GLOBOCAN 2022 summary data)[70,71]; rates reveal a modest decline in the past 30 years in some high-income countries, reflecting reduced asbestos exposure, but global rates stay significant due to long latency and continued asbestos exposure in lower-income settings. Past history of clearly documented asbestos occupational exposure is less frequently observed in high-income countries, and many mesothelioma cases develop in patients with exposures that are difficult to identify and detect.[36] An increase in mesothelioma in females might be indicative of an increased environmental exposure to mineral fibers, past history of radiation therapy, underlying genetic causes, etc. (reviewed in Carbone et al.[38]). Familial cases of mesothelioma developing in carriers of inactivating germline mutations of *BAP1* and of other tumor suppressor genes, as well as those mesothelioma—mostly peritoneal mesotheliomas in young women—caused by gene fusions, present profound biologic, histologic, and clinical differences that require a tailored clinical approach.

Thymic Epithelial Tumors

We observe an increase in the incidence of TETs over time, especially in the rates of thymic carcinoma. The proportion of TETs diagnosed at early stages has also increased over time, and it has been accompanied by an improvement in survival. Improvements in the histologic and molecular aspects of these cancers, standardization of nomenclature, staging, and advancements in surgery, radiation therapy, and the availability of a greater number of systemic therapies, including the application of immunotherapy for thymic carcinomas, together contributed to an improvement in survival.[72]

Lung Cancer

The Environment and Lung Cancer

At the 20th anniversary of the *Journal of Thoracic Oncology*, there is certainty as to the centrality of the environment in causing LC. The dominance of environmental factors in causing LC reflects the lung's interface with the atmosphere; its surface area of 70 square meters is bathed with contaminants from the inhalation of approximately 10,000 L of air daily. Exposures to toxins, and carcinogens specifically, even if present at low concentrations in air, cumulate over time increasing cancer risk.

Smoking tobacco products remains the predominant cause of LC globally with more than 1 billion tobacco smokers worldwide. The mutagenic effects of exposure to tobacco smoke are supported by genomic analyses that reveal distinct patterns of mutations in LCs in smokers compared with never smokers, with cancers in smokers having far more mutations.[73]

Outdoor air pollution has been confirmed as causing LC, not surprisingly because the air pollution mixture includes known carcinogens. In 2013, the International Agency for Research on Cancer designated ambient air pollution and airborne particulate matter as known causes of LC.[74] The mutagenic effects of outdoor air pollutants are supported by genomic analyses that reveal different mutational spectra in LCs among never smokers depending on exposure to air pollution.[75]

Radon, through its radioactive progeny, is an established cause of LC and a ubiquitous exposure in indoor environments. Models for its risk that guide mitigation policies have been based on epidemiologic studies of radon-exposed underground miners, recently updated and replicated in the large international Pooled Uranium Miner Analysis (PUMA).[76]

In 2025, what is the burden of LC attributable to the environment? Figure 3 provides a global estimate of the number of LC deaths from various causes, spanning from 1990 to 2021. The tragic dominance of smoking remains.

Genetic Predisposition of Lung Cancer

Although tobacco smoke or environmental exposures are major causes of LC, genetics also play a significant role. An extensive, systematic review found an 85% higher risk for developing LC among first-degree relatives of patients with LC.[78] Segregation[79–82] and linkage analyses[83,84] provided evidence of genes with a large effect on risk. Very high risks for LC development are associated with rare germline mutations in *TP53*[85] and retinoblastoma (*RB1*).[86] Evaluation of cases of familial LC with *EGFR* mutations who were resistant to targeted therapy identified inherited mutation of the *EGFR* T790M variant.[87] This variant confers a particularly elevated risk among nonsmokers.[88] In addition, very rare variants increasing LC risk have been reported in *HER2*,[89] *MET*[90] *MAST1*,[91] and selected surfactant proteins (*SFTA*, *SFTC*).[92–94] Sequencing in high-risk families identified several rare variants with moderate-to-large effect on LC risk (Fig. 4), such as *PRKN* (also known as *PARK2*),[95,96] *ATM*,[97] *FGF5*,[98] and *APOE*.[99]

Genome-wide association studies (GWAS) using population-based cases have detected a large number of single-nucleotide polymorphism (SNP) variants that

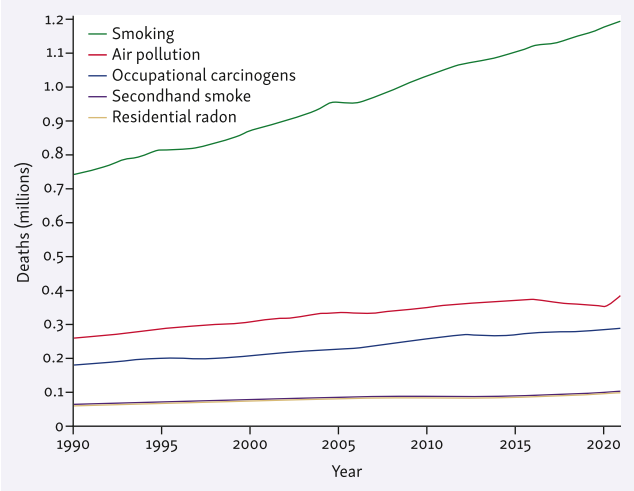

Figure 3. Number of deaths worldwide from lung cancer by risk factor and calendar year, both sexes, all ages, from 1990 to 2021.[77]

contribute to LC risk. The design of these studies is most effective in identifying common variants that usually convey little risk per variant toward disease risk. However, the common SNPs in *CHRNA5* and *CYP2A6* having the largest impact on LC risk also influence smoking behavior. These variants of *CHRNA5* and *CYP2A6* also impede smoking cessation. Several clinical studies and trials revealed that individuals with these variants benefit most from pharmacologic interventions with varenicline or bupropion compared with individuals not carrying these variants.[100–104] GWAS studies provide novel information about the pathways that contribute to LC risk and highlight the roles of telomere maintenance,[105–109] DNA repair,[97,110] immune surveillance,[111–113] and nicotine metabolism.[114–119]

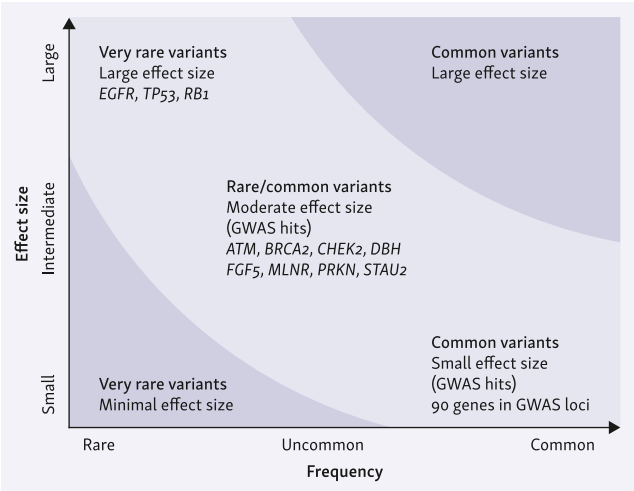

Figure 4. Genetic predisposition and architecture of LC. The inverse relationship between allelic frequency and effect size for LC genetic risk factors. LC, lung cancer.

The public health impact of any single variant is limited, but their identification can lead to improved screening, prevention, and treatment strategies targeted specifically at highest risk individuals.[120–124] LDCT for LC is among the few screening paradigms for cancer that lead to reduced overall mortality along with reduced cause-specific mortality.[18] Although LDCT reduces overall mortality, the best approach for selecting high-risk populations who would benefit most from screening is an area of ongoing research.[125] Individuals who have inherited high-risk variants predisposing to LC development are a special population that should be targeted for screening to improve the sensitivity of cancer detection. Inherited TP53 mutations that cause Li-Fraumeni syndrome substantially elevate risks for LC, particularly among smokers.[85] Individuals with inherited *RB1* mutations also have greatly increased risks for small cell LC[86] However, both inherited *RB1* and *TP53* mutations confer susceptibility to ionizing radiation, and a targeted prevention strategy using MRI is encouraged[126] for *TP53* mutation carriers. As noted previously, individuals with risk variants that increase smoking behavior respond most effectively to pharmacologic along with behavioral intervention. Finally, polygenic risk scores, which combine information from many SNPs, could be used to refine thresholds for selecting individuals for LDCT[127] in particular by modifying that age at which individuals become eligible for screening based on their risk.

Screening for Lung Cancer

From 2005 to 2010, enthusiasm for LDCT was tempered by concerns about false positives, overdiagnosis, and radiation exposure. The field pivoted decisively in 2011 with the National Lung Screening Trial (NLST), a 53,000-participant U.S. randomized trial revealing a 20% reduction in LC mortality (and almost equal to 7% reduction in all-cause mortality) with annual LDCT compared with chest radiography among heavy smokers aged 55 to 74 years with more than or equal to 30 pack-years who currently smoked or quit within 15 years.[3]

That result dramatically changed U.S. policy. In 2013, the U.S. Preventive Services Task Force (USPSTF) issued a "B" recommendation for annual LDCT in adults aged 55 to 80 years with more than or equal to 30 pack-years who currently smoke or quit within 15 years—explicitly mirroring NLST-like risk.[128] Medicare followed with national coverage in 2015, aligning payment with the USPSTF framework and standardizing shared decision-making and program requirements.[129] To improve

consistency and reduce unnecessary follow-up, the American College of Radiology introduced Lung-RADS in 2014 (updated in 2019 and again in 2022) to standardize reporting and management; the 2022 version update refined management for cystic, juxtapleural/airway-centered, and infectious-appearing nodules, helping reduce false-positive rates and streamline follow-up.[4,130]

International confirmation arrived with the Dutch–Belgian NELSON trial (reporting in 2020), which revealed larger LC mortality reductions—approximately 24% in men and almost equal to 33% in women—using a volume-based LDCT protocol and nodule-management strategy.[4] NELSON strengthened external validity beyond the United States and informed subsequent guideline expansions.

In 2021, the USPSTF broadened eligibility to ages 50 to 80 years with more than or equal to 20 pack-years (still limiting to current smokers or those who quit within 15 y). Modeling and evidence syntheses supporting the change emphasized greater mortality benefit, improved equity (capturing more women and Black adults who tend to develop LC at lower pack-years), and acceptable harms with contemporary LDCT protocols.[19] Medicare expanded coverage accordingly in 2022—lowering the starting age and pack-years, and simplifying several program requirements—facilitating nationwide implementation under the new criteria.[131]

Professional-society guidance continued to evolve. In November 2023, the American Cancer Society (ACS) updated its guideline to recommend annual LDCT for adults aged 50 to 80 years with more than or equal to 20 pack-years who currently or formerly smoked—and notably removed the 15-year quit-time limitation, citing evidence that elevated risk persists beyond 15 years after cessation.[132] Although insurance coverage typically follows USPSTF, the ACS update signals momentum toward broader eligibility.

Despite strong trial evidence of mortality reduction from NLST and NELSON, real-world uptake has lagged. A nationwide, state-representative analysis of 2022 BRFSS data found only approximately 18% of eligible U.S. adults were up-to-date with screening, with wide geographic and demographic disparities—highlighting the ongoing need to expand access, optimize shared decision-making, and integrate tobacco-cessation services within screening programs.

In summary, 2005–2025 saw LDCT screening move from controversy to consensus: NLST demonstrated a 20% mortality reduction[3]; NELSON reinforced and extended benefits[4]; USPSTF (2013-2021) and CMS (2015-2022) progressively expanded and operationalized eligibility[2,3,7,8]; ACR Lung-RADS (2014, 2019, 2022) standardized practice[4,130]; and ACS (2023) recommended even broader inclusion.[133] The remaining challenge is implementation—ensuring that evidence-based screening reaches those at risk while maintaining high-quality, low-harm programs that continually integrate advances in nodule management and risk assessment.[4,130] The other challenge is how to use screening and other biomarkers in the future for high-risk nonsmokers defined either as exposed passively or in cohorts such as nonsmoking Asian women with high incidence of EGFR mutations in their families.

Genomics and Targeted Therapies for Lung Cancers

Translating advances in molecular and cell biology to treatments has transformed LC care. The discovery of oncogenes[134] and recognition of oncogene addiction[135] as one determinant of cancer growth established protein products of those genes as therapeutic targets.[136–138] Drugs that inhibit the effects of these oncoproteins take advantage of this vulnerability of the cancer cell to maximize anticancer benefit and minimize effects on normal tissues that lead to toxicities.[139] Potentially actionable oncogenic drivers have been identified in 64% of lung adenocarcinoma specimens.[140] As drug development accelerated, molecular pathologists created robust genomic testing platforms using DNA and RNA extracted from tumors and blood to uncover oncogenic drivers to match to targeted treatments.[141,142] The benefits of this multiplex approach led to its adoption as a standard of care for the simultaneous testing of blood and tumor biopsy specimens from all patients with lung adenocarcinomas at diagnosis.[5] In the last two decades, this worldwide effort identified an array of oncogenic drivers in LCs (mutations in *EGFR*, *KRAS*, *BRAF*, *MET*, and *HER2*; fusions in *ALK*, *RET*, ROS1, *NTRK*, and *NRG1*; and amplifications in *HER2* and *MET*) with 41 approved targeted therapies (Fig. 5).

The LC Mutation Consortium (LCMC) was instrumental in the understanding of oncogenic drivers in lung adenocarcinoma by operationalizing multi-institutional, multiplex genotyping linked to treatment and outcomes. In its seminal LCMC1 study (14 U.S. sites; enrollment 2009–2012), LCMC demonstrated that actionable drivers are common—identified in 64% of fully genotyped tumors—and that matched targeted therapy was associated with longer survival (median 3.5 versus 2.4 y; adjusted hazard ratio [HR], 0.69).[140] The program standardized testing for ten drivers (including EGFR, ALK, KRAS, ERBB2/HER2, BRAF) and directly connected results to therapy selection and trial enrollment, making routine multiplexed testing practical in real-world care.[140] LCMC then broadened its scientific scope. A comprehensive multi-institutional analysis

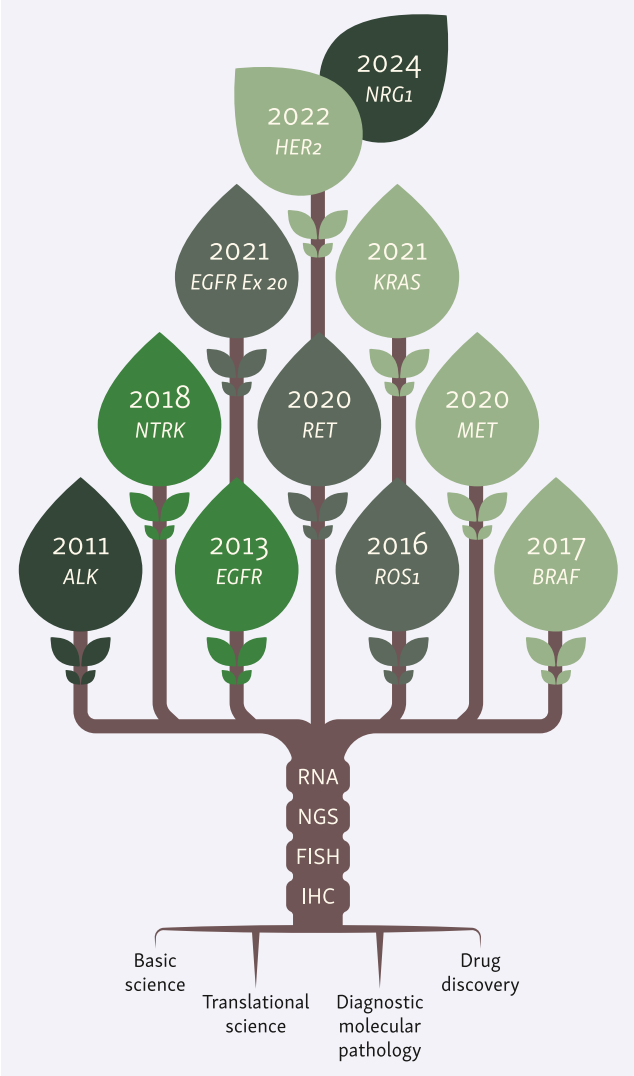

Figure 5. Two decades of progress discovering oncogenic drivers, creating drugs targeting oncoproteins, developing accurate and scalable methods to test patient samples for the presence of oncogenic drivers, and the validation of agent effectiveness in patients with lung adenocarcinomas. The years are for the first approval of a drug for that target. There is one branch for each target. Each leaf signifies a drug approved for that target (branch).

detailed driver frequencies and co-alterations across participating centers, establishing a durable baseline for U.S. practice and research.[143] LCMC2 expanded profiling (including RET and ROS1) and used the larger data set to probe questions beyond prevalence—such as how tobacco exposure and TP53 status interact with targetable drivers—revealing that smoking history and TP53 mutations modulate clinical behavior among genomically defined subsets.[144] The consortium also produced mutation-specific cohorts that clarified clinicopathologic features and outcomes for BRAF-mutant disease[145] and HER2-mutant adenocarcinoma,[146] helping catalyze subsequent targeted therapy development and trial design. Importantly, LCMC evaluated equity and biology together, reporting race-associated differences in driver prevalence and outcomes, thereby informing testing and access priorities.[147] Finally, LCMC characterized metastatic KRAS-mutant adenocarcinoma—historically a "nontargetable" group—providing outcomes benchmarks that later enabled evaluation of KRAS-directed strategies.[148] Collectively, LCMC's contributions—prospective, multicenter genomics tied to treatment; rigorous driver-specific cohorts; and equity-aware analyses—underpinned today's expectation that every advanced lung adenocarcinoma should undergo broad molecular testing, with therapy matched to the detected driver whenever possible.

In patients with stage IV disease and one of these molecular alterations, these targeted agents produce high response rates with limited off-target toxicities of cytotoxic chemotherapies and immunotherapies.[29,149–153]

The EGFR Evolution and Development of TKIs

The *EGFR*-mutant adenocarcinomas paved the way for therapeutic success, and in the past two decades, the treatment of EGFR-mutated lung adenocarcinoma has evolved from targeted proof-of-concept to an integrated, multimodal strategy spanning metastatic, locally advanced, and surgically resectable disease. Early development (2005–2012) established the predictive value of activating EGFR mutations (exon 19 deletions and L858R). Initial unselected trials yielded modest benefits, but subsequent analyses confirmed that mutation-positive tumors derived marked benefit from first-generation TKIs. The IPASS[154] trial demonstrated gefitinib's superiority over chemotherapy in mutation-positive disease, whereas WJTOG3405,[155] OPTIMAL[156] and EURTAC[157] established first-line gefitinib or erlotinib as the standard of care. Discovery of the T790M mutation as a dominant resistance mechanism defined the need for new generations of inhibitors.[158]

Second-generation TKIs (2013–2017), notably afatinib and dacomitinib, offered broader EGFR inhibition and improved PFS over chemotherapy or gefitinib (LUX-Lung 3/6, ARCHER 1050), though at a cost of increased toxicity.[159,160]

Third-generation TKIs (2015–2020) transformed management. Osimertinib,[8,161] designed to target both sensitizing and T790M mutations with enhanced central nervous system (CNS) penetration, improved PFS versus chemotherapy in T790M-positive patients (AURA3)[8] and became the first-line standard after the FLAURA trial,[29] which demonstrated superior PFS, OS, and CNS control compared with first-generation TKIs.

Combination regimens such as erlotinib plus ramucirumab (RELAY)[162] and gefitinib plus platinum–pemetrexed (NEJ009)[163] further extended PFS and OS.

In the 2020s, osimertinib expanded beyond metastatic disease. The LAURA[164] trial established consolidation osimertinib after chemoradiation as the standard for unresectable stage III EGFR-mutant NSCLC, whereas FLAURA2[32] confirmed that adding chemotherapy to first-line osimertinib improved PFS and emerging OS. Recent data from MARIPOSA[165] revealed that amivantamab plus lazertinib surpassed osimertinib in PFS and OS, introducing a bispecific antibody–TKI combination as an alternative first-line option.

Third-generation TKIs also achieved unmatched intracranial control, addressing the historical challenge of CNS metastases. Treatment of uncommon EGFR mutations (G719X, L861Q, S768I) favored afatinib, whereas exon 20 insertions—previously resistant—now respond to amivantamab plus chemotherapy per the PAPILLON study.[166]

EGFR TKI trials have also been performed in surgically resectable disease. Perioperative integration began with adjuvant trials of first-generation TKIs. ADJUVANT-CTONG1104[167] and EVAN[168,169] revealed improved disease-free survival (DFS) and tolerability over chemotherapy, though OS advantages were inconsistent.

Osimertinib revolutionized the adjuvant paradigm. The phase 3 ADAURA trial confirmed dramatic DFS benefit[30] and, subsequently, an OS advantage[9] with adjuvant osimertinib for stage IB to IIIA disease, cementing its adoption as the global standard.

Parallel neoadjuvant studies further advanced the field. EMERGING-CTONG1103[170] demonstrated higher response and nodal downstaging with erlotinib compared with chemotherapy in stage IIIA-N2 disease. The pivotal NeoADAURA phase 3 trial (ASCO 2025)[171] revealed that neoadjuvant osimertinib with or without chemotherapy achieved superior major pathologic response and downstaging versus chemotherapy alone, with high resection rates and maturing EFS. Together, ADAURA and NeoADAURA define a perioperative continuum in which osimertinib improves outcomes both before and after surgery, integrating molecular targeting into curative-intent management.

The problem, however, is that these kinase inhibitors are not curative and development of resistance is inevitable. Resistance mechanisms are variable, but repeated molecular testing reveals acquired targetable alterations in tumors of many patients.[172,173] Discovery of these resistance alterations led to development of new agents targeted to treat patients with tumors refractory to initial treatments.[8] Success in treating LCs with oncogenic drivers in individuals with stage IV disease prompted the use of targeted agents as neoadjuvant therapy.[171] Adjuvant trials after complete resections revealed superior survival also for *ALK* fusions.[30,174] In unresectable stage III lung adenocarcinomas, concurrent chemotherapy and radiotherapy followed by mutation specific kinase inhibitors improved survival with several agents.[164,175] These approaches have revealed that targeted agents used with local therapies lengthen survival and increase curability.

Radiation Oncology Advances in NSCLC

The modern era in lung radiation oncology began with SBRT for medically inoperable stage I NSCLC. The multicenter phase II RTOG 0236 established ablative SBRT (54 Gy/3 fractions) as highly effective, reporting excellent primary-tumor control with acceptable toxicity; long-term updates confirmed durable outcomes at 5+ years[17,23,176] Crucially, randomized evidence then demonstrated superiority of SBRT over conventionally fractionated radiotherapy: the phase III TROG 09.02 CHISEL trial revealed significantly less local failure and better survival with stereotactic ablative radiotherapy versus standard radiotherapy in inoperable stage I disease, cementing SBRT as standard of care.[177]

For unresectable stage III NSCLC, three advances shaped practice. First, dose escalation was tested and disproven by RTOG 0617: standard-dose 60 Gy concurrent chemoradiation outperformed 74 Gy, with higher doses associated with worse survival—redirecting the field toward quality and normal-tissue sparing rather than more dose.[178] Longer-term RTOG 0617 analyses linked cardiopulmonary exposure to outcomes and, prospectively within the trial, intensity-modulated radiotherapy (IMRT) reduced severe pneumonitis and lowered heart doses versus 3D-CRT, supporting IMRT as the preferred technique when delivering concurrent chemoradiation.[179]

Second, image-guided target definition matured from concept to randomized evidence. The multicenter PET-Plan trial demonstrated that FDG-PET–based, reduced target volumes during dose-escalated chemoradiation were noninferior to conventional volumes and did not increase toxicity, validating routine PET-integrated planning and selective nodal coverage in stage II to III NSCLC.[180]

Third—and practice-defining—the phase III PACIFIC trial established consolidation durvalumab after definitive concurrent chemoradiation as the standard for unresectable stage III disease. The original report revealed significant improvement in PFS with anti–PD-L1 therapy versus placebo,[180] followed by a definitive OS advantage and sustained 5-year survival benefits on extended follow-up.[12,25,181] PACIFIC unified radiation and immunotherapy into a peri-radiation standard, making optimization of chemoradiation delivery (e.g., heart/lung sparing via IMRT and PET-guided fields) clinically pivotal as a platform for immunotherapy.

Together, these trials defined 2005–2025 progress: SBRT replaced conventional RT for inoperable stage I disease (RTOG 0236; CHISEL); in stage III, the field shifted from "more dose" to "better delivery" (RTOG 0617 + IMRT benefits) while embracing PET-guided precision (PET-Plan); and PACIFIC added life-prolonging consolidation immunotherapy after well-executed concurrent chemoradiation.

SCLC

The approach to treatment of small cell LC remained fairly static, except for technical improvements in radiation delivery and in supportive measures, in the first decade of *JTO*'s existence. Cis- or carboplatin together with etoposide was the standard therapy for first-line treatment of patients with extensive-stage disease, and topotecan was the only drug approved for treatment of recurrent disease. Limited stage was approached with the same platinum doublet together with thoracic radiation. Prophylactic cranial irradiation was used to reduce the risk of primary progression in the brain. The first substantial change to the standard of care established in the 1990s was the advent of chemoimmunotherapy redefining the first-line therapy for patients with extensive-stage disease, adding either atezolizumab,[182] or durvalumab[183] to the chemotherapy doublet and as maintenance therapy (Supplementary Fig. 1). Although the immune checkpoint blockers extended median survival only modestly, they led for the first time to durable responses—including a small percentage of patients evidently cured of metastatic disease: a critical milestone. Immunotherapy subsequently changed the standard of care improving survival for patients with limited-stage disease as well, with maintenance durvalumab after definitive chemoradiotherapy.[184] The alkylating agent lurbinectedin was granted accelerated FDA approval for treatment of recurrent disease, primarily on the basis of improved toxicity relative to historical topotecan data,[185] and the addition of lurbinectedin to maintenance atezolizumab for extensive-stage disease recently demonstrated an improvement in survival as well.[186] Finally, the DLL3-directed T-cell engager tarlatamab was granted accelerated approval for treatment of recurrent disease[187] and has demonstrated a substantial improvement in survival over chemotherapy.[188] Multiple new and promising agents are now in active clinical development for patients with small cell LC, with notably exciting initial results found in trials of antibody-drug conjugates (ADCs) and other novel classes of targeted therapies.

Immunotherapy Science and Lung Cancer

In the mid-2000s, the idea that immune checkpoint inhibition could be effective in thoracic malignancies was speculative.[189–191]

NSCLC. The first breakthrough came when randomized trials revealed PD-1/PD-L1 blockade was superior to chemotherapy in previously treated NSCLC.[11,28,192] Soon after, strong evidence in the first-line setting among patients with high PD-L1 expression established PD-1/PD-L1 inhibitors as a new standard.[10,193,194] Combination regimens with chemotherapy then extended benefit across histologies, regardless of PD-L1 status.[195–198] In locally advanced NSCLC, adding PD-L1 blockade after completion of chemo-radiotherapy (CT-RT) created a new benchmark and paved the way for earlier-stage interventions.[25] Later, in resectable disease, neoadjuvant chemoimmunotherapy, adjuvant PD-1/PD-L1 inhibition, and perioperative strategies have consistently improved efficacy end points such as pathologic response (e.g., pCR and MPR), DFS, EFS, and OS. Although benefit is greater in PD-L1–positive tumors, meaningful outcomes are also observed in biomarker-negative tumors, demonstrating broad applicability across wild-type disease.[13,199–201]

However, challenges persist. In oncogene-driven NSCLC, responses to immune checkpoint inhibitors (ICIs) are modest, and in patients without a smoking history, the risk of early progression is higher, requiring careful patient selection. Advances such as single-cell and spatial profiling and circulating tumor DNA (ctDNA)–based minimal residual disease (MRD) monitoring are refining patient stratification, revealing mechanisms of resistance, and guiding rational combinations and treatment duration.[202,203]

By 2026, immunotherapy is firmly embedded across the NSCLC continuum, with future progress focused on integrating it with ADCs, targeted therapies, and next-generation immunomodulators to optimize outcomes in molecularly defined subsets.[204,205]

SCLC. In extensive-stage SCLC (ES-SCLC), adding an anti–PD-L1 antibody to platinum-based chemotherapy has, for the first time in decades, provided a statistically significant but modest improvement in OS, establishing a new standard of care. Despite this progress, most patients relapse quickly, reinforcing the urgency of novel approaches including maintenance strategies. Bispecific T-cell engagers (BiTEs) have recently demonstrated randomized evidence of benefit in the second-line setting and are also being explored as maintenance therapy after frontline chemo-immunotherapy to prolong response and delay progression, including as part of frontline combinations.

In limited-stage small cell LC (LS-SCLC), anti–PD-L1 checkpoint inhibition as consolidation after CRT has recently demonstrated a clinically meaningful improvement in survival, mirroring the paradigm previously established in locally advanced NSCLC.

By 2026, the focus in SCLC is on extending the durability of responses and integrating next-generation immunotherapies to improve outcomes in this historically aggressive and treatment-resistant disease (Supplementary Fig. 2).

Circulating Biomarkers in Lung Cancer

Cell-Free DNA and Other Circulating Biomarkers in Lung Cancer

In the last two decades, liquid biopsy (LB) has emerged as a powerful tool in thoracic oncology for tumor genotyping[206] and promises to revolutionize tumor early detection and therapeutic monitoring (Supplementary Fig. 3).

Among the potential biomarkers that can be assessed through LB, ctDNA has proven to be the most promising. Its levels vary according to tumor stage, making the clinical utility of ctDNA-based LB highly context dependent.[207]

In 2006, the first report of detection of EGFR mutation in ctDNA was published.[208] Since that, ctDNA analyses emerged as a minimally invasive source for biomarker testing, moving from EGFR mutation detection either at baseline or after acquired resistance to an alternative or complementary tool for tissue for tumor genotyping.[209–212] An important milestone in this field was in 2016 when the FDA approved the first plasma-based companion diagnostic, the Cobas EGFR Mutation Test v.2, followed in 2020 by two plasma next-generation sequencing (NGS) assays, Guardant360 CDx and Foundation One Liquid CDx. The NILE study revealed the noninferiority of plasma NGS compared with tissue testing, paving the way to the plasma-first approach.[213] Upfront use of LB in patients with suspected advanced LC before pathologic confirmation was then evaluated with the goal of shortening the time to treatment start.[214]

Many patients with LC relapse even after curative-intent treatment due to MRD. Detecting MRD, however, has been technically challenging because of its low abundance. In 2017, tumor-informed assays demonstrated that ctDNA could predict recurrence early,[215,216] and a growing body of evidence has demonstrated the prognostic value of ctDNA, highlighting its potential role in defining patient outcomes. Nevertheless, LB still faces sensitivity challenges even in metastatic disease and ctDNA-guided prospective clinical trials remain necessary to validate its clinical utility and to define evidence-based escalation or de-escalation approaches in the adjuvant setting.[217]

Beyond plasma, different alternative sources for ctDNA have been explored, including serum, cerebrospinal fluid, urine, pleural effusion, or bronchoalveolar lavage, albeit further validation studies are still required before clinical implementation of these strategies.[218,219]

In addition to ctDNA, other blood components including circulating tumor cells, ctRNA, extracellular vesicles, or tumor-educated platelets have been actively explored for clinical applications, albeit their widespread use for clinical purposes is still far.

Circulating Biomarkers for Lung Cancer Early Detection, Diagnosis, and Prognosis

The field of circulating biomarkers for LC early detection has evolved considerably in the last two decades,[220] with multiple opportunities to improve clinical management before and during screening,[221] on detection of incidental pulmonary nodules,[222] including at and after LC diagnosis (Table 2).

Initial proof-of-concept studies demonstrated that cfDNA and tumor-derived molecular alterations can be detected in the blood,[223] but progress was limited by small sample sizes and suboptimal technologies.[224] The advent of LDCT screening provided a paradigm shift, expanding the scope from strictly tumor-derived signals to include biomarkers reflecting host and immune responses.[3,225,226] Autoantibodies,[227] circulating microRNAs,[228] and proteins,[229,230] emerged as promising tools for risk stratification and early detection in prospective LDCT cohorts (Supplementary Fig. 4).

The EarlyCDT-Lung autoantibody test was the first evaluated in a randomized trial, but the design did not allow to distinguish biomarker benefit from that of LDCT.[231] The BioMILD trial confirmed that blood-based microRNA signatures can stratify risk and inform follow-up particularly in participants with suspicious LDCT findings.[232,233] The INTEGRAL program has assembled international resources of prediagnostic samples to develop protein panels for both prescreening risk stratification and nodule management.[234,235]

Recently, multi-cancer early detection (MCED) tests based on the methylome and fragmentome analyses of cfDNA have entered large-scale trials.[236,237] Although their sensitivity for screening detected early-stage LC remains modest, they may hold prognostic utility and contribute to multimodal risk models.[238,239] Looking ahead, integrating circulating biomarkers with LDCT radiomics and clinical risk models in prospective trials is expected to refine early detection and personalize screening strategies.[240]

Evolution of the Diagnosis of Lung Cancer

In the past two decades, molecular pathology has fundamentally transformed the understanding, diagnosis, and management of lung carcinoma. Early in the 2000s, LC classification relied primarily on morphology

Table 2. Clinical Applications of Circulating Biomarkers for Early Lung Cancer Detection

Time Point	Clinical Application
Before initiating LDCT screening	Improve risk assessment to better target screening to high-risk individuals; increase engagement of eligible but unscreened people
After a negative LDCT scan result	Refine risk assessment to allow longer screening intervals for the lowest risk individuals
After identification of a nodule on LDCT screening	Improve prediction of nodule malignancy to better target invasive diagnostic procedures to high-risk nodules
After detection of an incidental pulmonary nodule	Improve nodule malignancy prediction to guide diagnostic procedures
After onset of potential lung cancer symptoms	Fast-track individuals likely to have lung cancer to appropriate imaging and follow-up
During investigations for screen-detected lung cancer	Reduce overdiagnosis by identifying indolent tumors; improve diagnostic performance of invasive procedures such as bronchoscopy
At diagnosis of lung cancer, before treatment initiation	Improve prognostic assessment and guide treatment planning
During follow-up	Intercept second primaries

LDCT, low-dose computed tomography.

and immunohistochemistry (IHC) distinguishing SCLC from NSCLC with subtyping into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The role of IHC was essential for refining diagnoses when morphology was ambiguous. Specific subtyping for the grading of lung adenocarcinoma was published by the Pathology Committee of IASLC in 2020.[241] In 2011,[242,243] the IASLC, American Thoracic Society (ATS), and European Respiratory Society (ERS) lung adenocarcinoma classification was one of the first evidence-based guidelines to recommend molecular testing since the discovery of *EGFR* mutations and *ALK* rearrangements that marked a paradigm shift toward genotype-driven therapy. These molecular alterations clarified oncogenic mechanisms and paved the way to targeted treatments that dramatically improved patient outcomes. Subsequent discoveries of actionable driver mutations, including *ROS1*, *RET*, *MET exon 14 skipping*, *BRAF V600E*, *NTRK*, *HER2*, and *KRAS G12C*, expanded the scope of precision medicine and established NGS as the cornerstone of modern diagnostic workflows. The 2015[244] and 2021[245] WHO classifications of thoracic tumors formally integrated molecular features into diagnostic criteria, emphasizing combined histologic and molecular reporting. In parallel, the rise of immunotherapy introduced PD-L1 IHC and tumor mutational burden as critical predictive biomarkers, broadening the pathologist's role in guiding therapy.[246]

More recently, LB using ctDNA has emerged in patients with advanced LC as a minimally invasive alternative or a complementary approach for detecting actionable mutations and monitoring resistance mechanisms, notably in patients treated by TKIs.[206,247] Moreover, LB use reveals new open room for assessing the MRD in the preoperative LC setting, which could lead to postoperative escalation or de-escalation treatment.[248,249] More recently, new technologies demonstrated promising future opportunities for early LC detection using LB.[250] Advances in digital pathology, multiplex immunofluorescence, and spatial transcriptomics now enable deeper insights into tumor heterogeneity and the tumor microenvironment. This is an important perspective because recently the proportion of patients with NSCLC diagnosed at an early stage is continuously increasing. Recent study revealed the role of B-cell receptor (BCR) and T-cell receptor (TCR) repertoire analysis demonstrating more BCR/TCR clonotypes and increased BCR clonality in tumor than in non-neoplastic samples. Five histologic subtypes of adenocarcinoma demonstrated that higher histologic pattern complexity was associated with higher immune infiltration and low TCR clonality in the tumor-proximal regions associated with prognostic values in early-stage NSCLCs.[251]

Collectively, these innovations have redefined lung carcinoma as a molecularly heterogeneous disease that demands integrated, multidisciplinary testing strategies. Molecular pathology today is not limited to diagnostics but also plays a crucial role in real-time therapeutic decision-making.

Evolution of Surgery for Lung Cancer

From 2005 onward, LC staging underwent two major overhauls driven by the IASLC staging project. The seventh edition (2009) refined T-size cutoffs and stage groupings using a large international database and introduced harmonization with a new, precise mediastinal lymph node map to reconcile the historical Naruke and Mountain-Dresler systems.[252–254] The eighth edition (implemented globally in 2017; the United States in 2018) further subdivided T1/T2 by 1-cm increments up

to 5 cm, clarified separate tumor nodules/adenocarcinoma in situ/minimally invasive adenocarcinoma, and split M1 into single versus multiple extrathoracic metastases (M1b versus M1c), improving prognostic granularity and trial stratification.[255] The ninth edition (effective January 1, 2025) introduces additional refinements to T/N/M and stage groups to align with contemporary outcomes; early summaries emphasize more granular N-subclassification and refined M categories.[256]

Concurrently, preoperative staging integrated ^{18}F-FDG PET/CT as standard to reduce futile thoracotomies by detecting unsuspected nodal/distant disease and to assist radiotherapy planning.[257] The decisive procedural shift, however, was the rise of endosonographic needle techniques. Between 2007 and 2014, evidence syntheses and guidelines moved endobronchial and/or esophageal ultrasound–guided needle aspiration (EBUS/EUS-FNA) to the frontline for mediastinal assessment in potentially operable NSCLC, reserving surgical staging for negative/indeterminate results or specific nodal stations.[257,258] Contemporary CHEST guidance underscores EBUS-TBNA as the initial invasive test given high sensitivity/NPV and tissue adequacy for molecular testing—critical in the immuno-oncology era.[259]

Within the operating room, the following three themes dominated: (1) the extent of nodal surgery, (2) the move to minimally invasive anatomic resection (VATS → uniportal VATS → robotic), and (3) parenchyma-sparing resections validated by randomized trials.

First, the ACOSOG Z0030 randomized trial revealed no OS advantage for routine complete mediastinal lymph node dissection versus rigorous systematic sampling in clinically N0/selected N1 early stage tumors, supporting a quality-assured sampling strategy when preoperative staging is negative.[260] Later analyses and meta-analyses continue to debate survival effects in broader settings, but most guidelines prioritize completeness and nodal-station coverage over "dissection vs sampling" labels per se.[261]

Second, VATS lobectomy—established in the mid-2000s—consistently reduced pain, complications, and length of stay versus thoracotomy, with comparable long-term survival in pooled analyses.[262] The technique evolved to uniportal VATS in 2010 to 2011, enabled by articulating instruments and novel exposure strategies, and disseminated widely thereafter.[263,264] Robotic-assisted thoracic surgery (RATS) expanded in the late 2010s, offering enhanced dexterity and visualization; contemporary comparative studies and meta-analyses suggest similar oncologic quality to VATS with differences in conversion and perioperative profiles that vary by center experience.[265,266] Recent randomized-evidence meta-analyses of VATS versus open lobectomy even suggest an OS advantage for VATS, reflecting cumulative gains in technique and perioperative care.[267]

Third—and practice-changing—two modern randomized trials validated sublobar strategies. The Japanese JCOG0802/WJOG4607L trial (≤2 cm peripheral cT1a-bN0) found segmentectomy improved OS versus lobectomy at the cost of higher local relapse, arguing for segmentectomy as standard in this cohort.[21] The North American CALGB 140503 (Alliance) trial revealed noninferior DFS for sublobar (segmentectomy/wedge, with margins and node assessment) versus lobectomy in peripheral less than or equal to 2 cm cT1aN0 NSCLC, with similar OS, supporting broader parenchyma-sparing adoption within oncologic principles.[14,268] Together, these trials cemented anatomic segmentectomy for small peripheral tumors, especially when coupled with meticulous margin control and nodal evaluation.

Technological adjuncts accelerated precision resection. Indocyanine-green fluorescence (ICG-FI) methods—described in thoracic segmentectomy[269] and refined in the 2010s to 2020s—improved delineation of intersegmental planes and aided complex segmentectomy planning when combined with 3-D CT reconstructions and modern localization techniques.[270]

Finally, the modern perioperative paradigm in resectable NSCLC was catalyzed by CheckMate-816, where neoadjuvant nivolumab plus platinum-doublet chemotherapy significantly increased pathologic complete response and improved EFS versus chemotherapy and approximately 10% absolute 5-year OS gain, establishing durable benefit for neoadjuvant chemo-IO.[271] Parallel development of perioperative pembrolizumab in KEYNOTE-671 demonstrated superior EFS and, subsequently, OS benefit when pembrolizumab was given both before and after surgery compared with neoadjuvant chemotherapy and surgery alone, supporting a "sandwich" strategy across stage II to IIIB disease.[31] A third pillar, AEGEAN, revealed that perioperative durvalumab (neoadjuvant chemo-IO followed by adjuvant durvalumab) significantly improved EFS and pathologic complete response[272] with an emerging—though not yet definitive—OS signal on updated analyses.

Concurrently, adjuvant-only immunotherapy matured. IMpower010 established DFS benefit for atezolizumab after adjuvant chemotherapy in resected stage II to IIIA NSCLC—most pronounced in PD-L1–positive tumors—with long-term updates reinforcing durability and refining PD-L1–driven expectations.[273] PEARLS/KEYNOTE-091 demonstrated a DFS advantage for adjuvant pembrolizumab in an all-comer population after resection (with or without prior adjuvant chemotherapy), broadening

utility beyond PD-L1–restricted subgroups and revealing sustained benefit on later analyses.[200]

Mesothelioma

The Environment and Mesothelioma: Asbestos Carcinogenesis

Occupational asbestos exposure is strongly associated with the development of mesothelioma, LC, laryngeal cancer, and other intrathoracic malignancies.[38,274–279] Advances in understanding the carcinogenic potential of asbestos fibers have led to the implementation of policies to reduce or ban asbestos use in most of the developed countries. They also allowed for regulations in areas with high environmental exposure to asbestos or other carcinogenic mineral fibers (such as erionite) to reduce mesothelioma incidence.[280–283] Inhaled asbestos fibers that deposit in the pleural space can promote carcinogenesis through chronic inflammation, generation of reactive oxygen species (ROS) and DNA damage, and ferroptosis[284–286] (Fig. 6). The chronic inflammatory processes that drive mesothelial cell transformation have been directly linked to the action of high mobility group box 1 (HMGB1) and the NLRP3 inflammasome.[287–289] In asbestos-exposed mesothelial cells, HMGB1 translocates from the nucleus to the cytoplasm where it induces

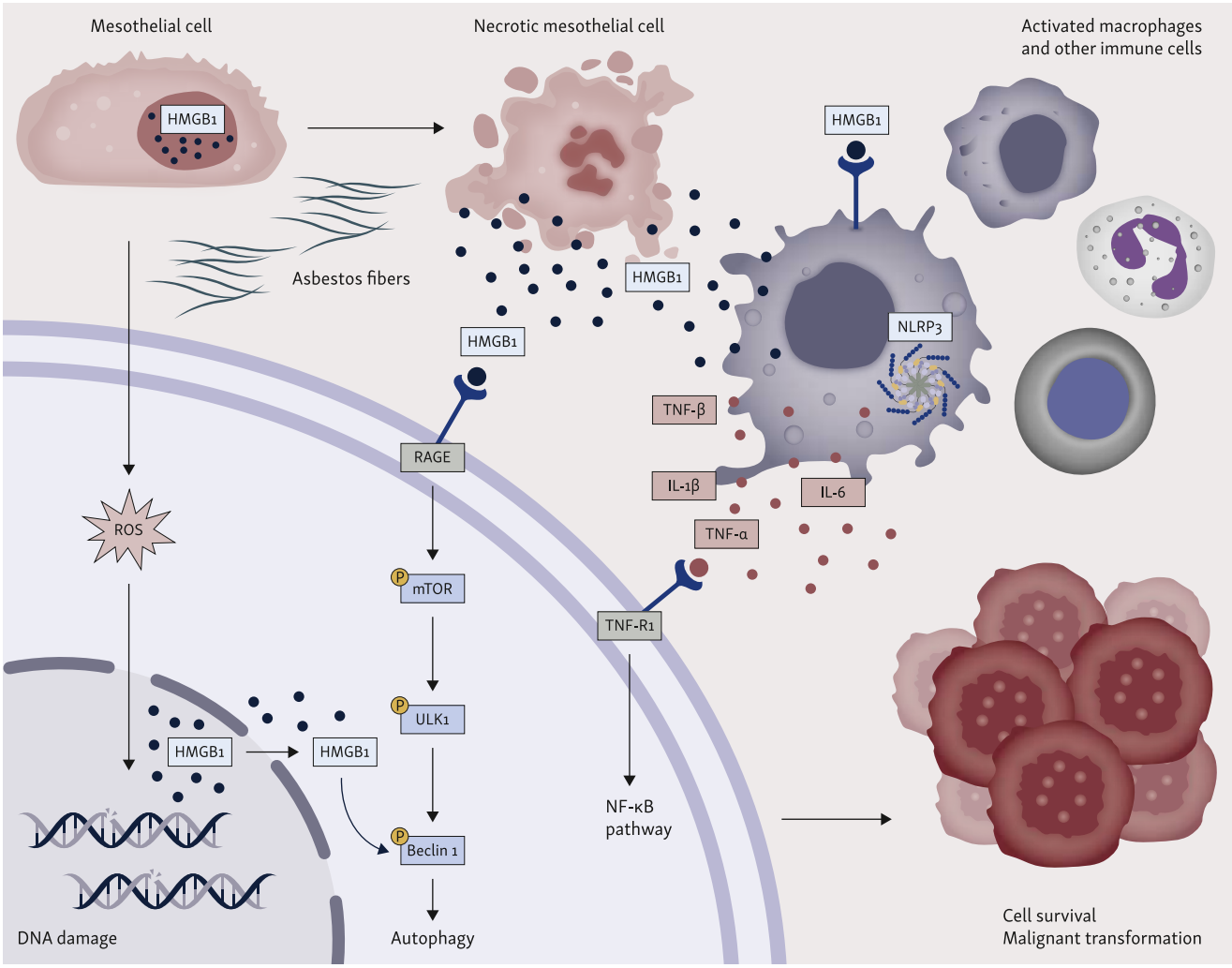

Figure 6. Mechanisms of asbestos carcinogenesis. Asbestos exposure induces reactive oxygen species (ROS) production, leading to DNA damage and necrosis. Necrotic mesothelial cells release high mobility group box 1 protein (HMGB1) into the extracellular space, where it acts as a damage-associated molecular pattern (DAMP). HMGB1 binds to its receptors on macrophages and other immune cells, activating the NLRP3 inflammasome and inducing the secretion of proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, and TGF-β, thereby establishing a chronic inflammatory microenvironment. In parallel, HMGB1 engages the receptor for advanced glycation end products (RAGE) on surviving mesothelial cells, activating the mTOR-ULK1-Beclin1 signaling cascade to promote autophagy. HMGB1 also directly interacts with Beclin1 in the cytoplasm to induce autophagy, supporting mesothelial cell survival under stress conditions. TNF-α, acting through TNF-R1, stimulates the NF-κB pathway, further sustaining cell survival. The combination of persistent ROS production, chronic inflammation, and enhanced pro-survival signaling promotes mesothelial cell hyperplasia and malignant transformation.

autophagy by binding to Beclin1 and activates the mTOR autophagy pathway by binding to its membrane receptor, RAGE.[290] HMGB1 is also released from necrotic mesothelial cells, following asbestos exposure, into the extracellular space, where it functions as a damage-associated molecular pattern (DAMP), initiating the inflammatory response and activating the NLRP3 inflammasome, which induce the release of cytokines, such as TNF-α and IL-1β, from macrophages and other surrounding cells. This, in turn, activates the NF-κB signaling cascade and survival pathways.[287,291–294] The induced chronic inflammatory reaction enhances DNA damage in surviving mesothelial cells, promoting mesothelial hyperplasia and malignant transformation.[295] Moreover, in individuals carrying heterozygous germline *BAP1* mutations, who are predisposed to the development of mesothelioma, HMGB1 serves as a key mediator of the gene-environment interaction and the increased inflammation and DNA damage of cells exposed to asbestos.[60] These findings highlight the important role of HMGB1 in asbestos carcinogenesis and mesothelioma pathogenesis, offering a promising target for therapeutic intervention.

Mesothelioma

Research during the past two decades has elucidated the once-enigmatic mechanisms of asbestos—and of other mineral fibers—carcinogenesis that has been linked mainly to HMGB1.[287] HMGB1 is reviewed in Carbone and Yang[296] and in other parts of this article. Aspirin and other anti-inflammatory drugs that interfere with HMGB1-induced inflammation were found to reduce asbestos carcinogenesis in mice, suggesting a possible preventive therapeutic strategy.[297] Additional experimental approaches to interfere with asbestos carcinogenesis have also demonstrated promising results by targeting the ERK1 and ERK2 pathways.[298]

The past 20 years have also revealed an increasing number of manuscripts confirming the relationship between therapeutic radiation and mesothelioma, which usually occur several years after completing radiation therapy (reviewed in Carbone et al.[38]).

Following studies in three Cappadocian Villages (Turkey) which revealed that susceptibility to mesothelioma was transmitted in a Mendelian fashion,[221] these researchers identified the first gene, BAP1, which when heterozygous mutated in the germline ($BAP1^{+/-}$) predisposes carriers to mesothelioma, uveal melanomas, and other cancers whose tumor cell contain biallelic BAP1 inactivation, $BAP1^{-/-}$, an evidence of pathogenicity.[49,51] Note that although BAP1 means "BRCA1-associated protein 1," this is a misnomer, as BAP1 does not bind BRCA1; it binds BARD1, a tumor suppressor that can bind both BRCA1 and BAP1.[62] Thus, immunoprecipitations for BRCA1 will bring down both BARD1 bound to BRCA1 and BAP1, bound to BARD1, which led to the initial confusion. This new hereditary medical condition has been named the "BAP1 cancer syndrome," and it is characterized by multiple malignancies that develop approximately 20 years earlier than their sporadic counterparts. Mesothelioma is the most common malignancy. In-depth studies of mesothelioma developing in $BAP1^{+/-}$ carriers, including a surgical clinical trial conducted at the U.S. National Cancer Institute, revealed that these mesotheliomas have unique histologic, biological, and clinical characteristics and these tumors have been named low-grade–BAP1-associated mesotheliomas (L-BAMs).[41,299] L-BAMs are characterized by superficial spreading, intrapleural growth and minimal invasion, usually limited to the submesothelial adipose tissue. Because these lesions invade the adipose tissue, they have been diagnosed as malignant mesothelioma, and because this is often a tricavitary disease, until very recently, these patients were often diagnosed with metastatic mesothelioma and treated very aggressively. Instead genetically related mesotheliomas are less aggressive,[7] median survival is estimated at approximately 7+ years, compared with the dismal 6 to 18 months median survival of asbestos-induced sporadic mesotheliomas.[41,53,300–303] Following resection, most patients may have prolonged survival, some have been cured and died at old age of other diseases.[41] L-BAM may also be susceptible to immunotherapy: the interim analysis of the clinical trial NCT04940637 which uses the combination of Niraparib, a PARP inhibitor, with Dostarlimab, a PD-1 inhibitor revealed a significant benefit in patients with mesothelioma carrying germline $BAP1^{+/-}$ and $BAP1^{-/-}$ in the tumor cells, compared with a lack of antitumor activity in patients with mesothelioma with germline wild-type $BAP1^{+/+}$ and somatic $BAP1^{-/-}$ inactivation in the tumor cells.[304]

The challenge to researchers in the coming years is to discover why carriers of germline *BAP1* mutations can survive many years with mesotheliomas and other cancers.

Additional germline mutations predisposing to mesothelioma have been identified lately.[53,62,301,305,306] Mechanistically, *BAP1*, *BARD1*, and other genes that cause or predispose to mesothelioma are for the most part involved in mechanisms that regulate DNA repair, intracellular calcium metabolism, cell death, and for BAP1, the stabilization of HIF-1a.[59,62,307,308] The high incidence of mesothelioma in germline $BAP1^{+/-}$ carrier mutations may be caused by the regulatory effect of BAP1 on HMGB1 cellular localization: loss of BAP1 leads to similar effect as asbestos exposure, releasing HMGB1 from the nucleus to the cytoplasm and extracellularly.[60]

Experimental evidence in vitro and in mice suggests that patients carrying germline inactivating mutations of DNA repair genes are at higher risk of developing mesothelioma when exposed to asbestos or to other carcinogenic fibers (gene × environment interaction). Reviewed in Carbone et al.,[300] BAP1 and asbestos regulate different mechanisms of cell death.[309] Recent experimental studies revealed that co-targeting two proteins in the Bcl-2 pathway—which modulates cell death—reduces chemotherapy resistance to mesothelioma.[310] This novel approach might benefit all patients, regardless of the cause of their mesothelioma.

Mesothelioma Genomics

Genomic analyses of mesothelioma tumor DNA revealed that mesotheliomas are characterized by a relatively low number of nucleotide level inactivating mutations and lack common activating mutations (with the exception of certain fusion genes, see subsequent discussion), and by a large number of copy number alterations and aneuploidy.[54–57] The most frequently somatically mutated genes (i.e., somatic mutations are acquired mutations present only in the tumor cells, these mutations must be distinguished from germline mutations that instead are present in all cell types in a given individual), in order of frequency, are *BAP1*, *CDKN2A*, and *NF2*.[54–57] BAP1 is somatically biallelic inactivated in 60% to 70% of mesotheliomas, and this can be easily detected by IHC revealing lack of BAP1 nuclear staining.[52] This stain proved very useful to distinguish mesotheliomas—BAP1 negative—from an array of reactive benign conditions that can mimic mesotheliomas but that have positive BAP1 stain.[52]

The 3p21 region, in addition of BAP1 mutations, often contains inactivating mutations of SETD2, PBRM1, and SMARCC1.[239] Because deletions are often not contiguous but rather are alternating with DNA segments having oscillating copy number changes, it appears likely that chromotripsis[239] triggered by chromosome mis-segregation during mitosis leads to the vast aneuploidy found in mesothelioma.[56,57,311] The presence of specific mutations does not significantly seem to affect the prognosis of asbestos-induced mesotheliomas. It has been suggested that mesotheliomas containing biallelic *BAP1* inactivation may have a better prognosis (16.8 versus 8.3 mo) compared with those containing other types of inactivating mutations as they may be more susceptible to therapy. However, germline testing was not conducted, and therefore, it is possible that patients with L-BAM were included in these trials and may have confounded the results.[312]

The rare mesotheliomas containing activating fusion genes are a different disease compared with asbestos-induced mesothelioma. The occurrence of this new variant of mesothelioma was first reported by a medical research team from Thailand carrying an activating ALK fusion gene.[58] In 2018, the fusion partners of ALK in peritoneal mesothelioma were identified.[313] These findings were later confirmed by multiple studies.[314,315] These mesotheliomas, for the most part peritoneal mesotheliomas, occur in the peritoneum of young patients (including children) with no evidence of asbestos exposure, do not contain BAP1, CDKN2A, or other mutations that are often found in asbestos-induced mesotheliomas, and respond to therapy. Most of these patients experience prolonged survival.[58,313–315]

Mesothelioma Biomarkers: Progress in 20 Years

The past two decades have revealed a steady progression in the search for reliable biomarkers in malignant PM (MPM). The effort began in 2005 with osteopontin,[316] which initially appeared promising but ultimately lacked specificity in asbestos-exposed populations. In contrast, soluble mesothelin-related peptides (SMRP)[316–318] soon became established as the most robust early blood biomarker, validated through the MESOMARK assay. Around the same time, calretinin was developed as a blood-based enzyme-linked immunosorbent assay marker,[318] and tumor-based microRNA profiling revealed miR-29c* as a strong prognostic factor.[319] Together, these discoveries provided the first clinically applicable tools for diagnosis and prognosis.

Between 2011 and 2015, the focus shifted to genetics and tissue biomarkers. Landmark studies demonstrated that BAP1 loss was frequent in sporadic mesothelioma,[52,320] whereas germline *BAP1* mutations conferred familial risk of developing mesothelioma and other cancers.[51,300] Strikingly, carriers with germline mutations demonstrated a sevenfold survival advantage,[53] findings confirmed by multiple studies,[299,301–303] highlighting BAP1 as a powerful, reliable, diagnostic, and prognostic marker.[41] Fibulin-3 initially generated enthusiasm,[321] but later prospective studies failed to confirm its clinical utility.[322] These findings underscored the need for rigorous validation and spurred exploration of inflammatory mediators, such as HMGB1.[291,296]

From 2016 to 2020, research advanced toward clinical integration. Bueno et al.[57] published a comprehensive genomic atlas, mapping recurrent mutations, fusions, and splicing events, laying the foundation for molecular stratification. Circulating hyperacetylated HMGB1 was proposed as a highly specific

biomarker,[291,296] though replication remains ongoing. Prospective cohort studies revealed that combining calretinin with mesothelin could detect nearly half of mesotheliomas up to a year before diagnosis,[323] whereas multimarker panels achieved area under the curves approaching 0.94.[324] These advances established the superiority of combined biomarker strategies.

In 2021–2025, the emphasis shifted to real-world validation and prognostic modeling. The DIAPHRAGM study reaffirmed mesothelin as the clinical benchmark and excluded fibulin-3 from further consideration.[322] Large population studies demonstrated the high specificity of calretinin and mesothelin but noted renal dysfunction as a confounder.[325] Serum calretinin gained strong validation, especially when combined with SMRP. Meanwhile, molecular prognostic signatures matured: a six-gene tissue classifier and a blood panel incorporating calretinin with MALAT1 and GAS5[326] predicted recurrence and survival with high accuracy.

In conclusion, in 20 years, mesothelioma biomarker research has progressed from single-analyte discovery to multimarker panels and genomic classifiers. Current evidence supports combining blood biomarkers with tissue and transcriptomic assays to improve early detection, diagnostic accuracy, and individualized prognostic stratification.

Evolution of the Pathologic Diagnosis of Mesothelioma

The pathologic diagnosis of mesothelioma has become increasingly multimodal from morphology alone to expanded IHC panels followed by targeted molecular tests (especially BAP1 IHC and CDKN2A/p16 FISH or MTAP IHC, NF2/Merlin biomarkers). Emerging epigenetic and LB approaches have to be considered. These combined approaches improve sensitivity and specificity and help resolve difficult cases.

In the WHO third edition (2004), the focus was primarily on diagnosis.[327] There was an established recognition of mesothelioma localized/diffuse in three subtypes of epithelioid, biphasic, and sarcomatoid. Epithelioid the major subtype has an impact on prognosis and treatment (surgery versus nonsurgery in non-epithelioid subtypes). The sarcomatoid-desmoplastic variant was discussed as both a mimic for reactive processes (potential misdiagnosis) and in the context of its adverse prognosis. Improvements in immunochemistry in the past 20 years have reduced misdiagnosis from metastatic carcinomas of various sites.[328] The adenomatoid tumor and well-differentiated papillary mesothelioma (WDPM) were identified as distinct pathologic entities.[329] Molecular analyses revealed common deletions at 3p, 9p, and 22q associated with BAP-1, p16, and NF2, respectively.[330–332]

In the WHO fourth edition (2015), the criteria for redefining the separation between mesothelioma from reactive mesothelial proliferations was refined,[333,334] including reclassifying pleomorphic epithelioid mesothelioma (EM) as having a poor prognosis similar to that of sarcomatoid mesothelioma (SM).[335–337] The STAT6 antibody was identified as a reliable marker of solitary fibrous tumor[338] the WWTR1/CAMTA1 fusions with the specific CAMTA1 antibody to diagnose epithelioid hemangioendothelioma[339] and the CTNNB1 gene mutation expressing β-catenin to diagnose desmoid fibromatosis.[340,341] All are morphologically mimics of mesothelioma (Supplementary Fig. 5).

Since 2015, the scientific literature[333] has been dominated by molecular genetic developments.[57,342–345] These are discussed elsewhere. BAP1 mutations are more common in epithelioid histotype, peritoneal > pleural whereas CDKN2A/MTAP and NF2/Merlin alterations are more common in SM.[315,346,347]

At least 12% of mesotheliomas occur in carriers of pathogenic germline genetic mutations and are associated with distinct clinicopathologic features.[41,302,348] These are discussed elsewhere.

The WHO fifth edition (2021) included significant modifications[349,350]: (1) The name of "well-differentiated papillary mesothelioma" (WDPM) was changed to "well-differentiated papillary mesothelial tumor" (WDPMT) because of its indolent behavior and to steer clear of confusion with mesothelioma.[351,352] Most peritoneal WDPMT exhibit somatic missense mutations in the TRAF7 or missense mutations in the CDC42, so far not observed in the pleural location.[353] (2) Mesothelioma in situ (MIS) was recognized as a precursor lesion of invasive mesothelioma that can be diagnosed when tumor cells have lost BAP-1 and/or MTAP by IHC or have homozygous deletion (HD) of CDKN2A by FISH.[354–356] A new TNM staging AJCC/UICC is in progress.[354,357] (3) The prefix "malignant" in localized and diffuse mesothelioma was removed.[350] Transitional mesothelioma was reclassified with SM.[358–360] Furthermore, a two-tier, low-grade to high-grade mesothelioma tumor grading schema was adopted based on nuclear atypia, mitotic activity, and necrosis for EM.[349]

Since 2021, there is a recognized subset of mesothelial neoplasms which are associated with gene fusions encoding aberrant chimeric transcription factors. These are disproportionately represented among peritoneal tumors, with EM in younger subjects, arising independently of asbestos exposure, some have distinct pathologic features. These rare mesothelial neoplasms are discussed elsewhere.

Solid papillary mesothelial tumor is a new described neoplasm in the female peritoneum with distinct molecular signature (lacking recurrent BAP1, CDKN2A/B, NF2, TP53, LATS2, and SETD22) with a benign clinical course.[361]

MTAP is a tumor suppressor gene located at the telomere side adjacent to CDKN2A on chromosome 9p21 which is co-deleted in up to 90% of cases with CDKN2A HD.[362] CDKN2A HD is a reliable marker of malignancy in mesothelial lesions. Immunohistochemical loss of cytoplasmic MTAP expression reveals 74% to 82% sensitivity and approximately 100% specificity for detecting CDKN2A HD, and it is often used as a surrogate for CDKN2A deletion when FISH technology is not available.[363–365]

Advances in Systemic Therapy for Mesothelioma

In 2003, pemetrexed/(cis)platin (P/C) chemotherapy was established as the standard first-line treatment for patients with PM, based on phase III randomized controlled trial (P3RCT), with median OS (mOS) of 12.1 months.[50] Adding anti-vascular endothelial growth factor (VEGF) antibodies, bevacizumab, to P/C resulted in longer mOS versus P/C alone in MAPS P3RCT (18.8 versus 16.1 mo; HR, 0.77).[42] In ATOMIC P3RCT, arginine deprivation by addition of pegylated arginine deiminase to P/C led to increased mOS versus P/C (9.3 versus 7.7 mo; HR, 0.71) in non-epithelioid PM.[366] But these two last strategies have not been approved.

Leveraging the host immunity to fight mesothelioma is now a standard therapy. Dual immune checkpoint inhibition targeting CTLA4 and PD1 with ipilimumab and nivolumab respectively (IpiNivo) in the CheckMate-753 P3RCT was superior to chemotherapy alone (no bevacizumab) (mOS 18.1 versus 14.1 mo; HR, 0.73).[61] Combined PD-1 inhibition with chemotherapy was superior to chemotherapy alone in the IND227 P3RCT; mOS 20.4 versus 17.0 months; HR, 0.83.[367] Sarcomatoid mesotheliomas appear to be the variant that benefits from immunotherapy, but the potential benefit in epithelioid mesothelioma is controversial as real-life studies failed to reproduce the encouraging results reported in clinical trials.[368,369] This issue has been debated in two recent articles in *JTO*, and we refer the readers to them.[43,44]

Precision medicine involving synthetic lethal approaches is evolving. For example, targeting *MTAP* deletion via MTA-cooperative inhibition of PRMT5 has revealed a promising phase 1 signal in mesothelioma.[370]

Adoptive cell therapy is an area of active investigation in mesothelioma. Chimeric antigen receptor (CAR) T cells targeting the tumor antigen mesothelin have revealed antitumor activity in some patients, but there is clearly a need to develop better CAR T cells.[371–373] Ongoing clinical trials focused on improving their efficacy using novel CAR engineering techniques.[374] Dendritic cell therapy consisting of autologous dendritic cells loaded with an allogenic tumor cell lysate has also been evaluated in mesothelioma. Although a randomized clinical trial of this therapy as maintenance after chemotherapy was negative,[375] ongoing studies are exploring its use with immune checkpoint treatment (NCT03546426).

Thymomic Epithelial Tumors

Background

The thymus plays a crucial role in immune cell development.[376,377] Tumors arising from the epithelial compartment of the thymus are broadly classified into thymomas, thymic carcinomas, and thymic neuroendocrine tumors.[378] Within the past decade, several major studies have helped unravel the cellular, molecular, and immunologic features of TETs.[379–382] (Fig. 2*A*) Meanwhile, advanced laboratory techniques, such as single-cell spatial transcriptomics, have provided important insights into interactions between the epithelial and hematological compartments of the thymus and advanced our knowledge of thymoma-associated autoimmune diseases (ADs), such as myasthenia gravis.[383,384]

Translation of emerging knowledge related to the biology of TETs into clinical interventions continues to be a work in progress. Despite an improved understanding of genomic alterations in TETs, there continues to be a paucity of druggable targets resulting in a limited role for molecular-targeted therapies at present.[385] Immunotherapy has emerged as one of the most promising approaches for treating several cancers, but its adoption for the management of TETs is constrained by an increased risk of immune-mediated toxicity.[386] Nevertheless, the use of ICIs for the management of thymic carcinomas has been facilitated by a recognition of potential biomarkers of response and toxicity of immunotherapy in TETs.[387,388] Insights into the biology of thymoma-associated ADs, such as autoimmune pneumonitis, have also resulted in the development of clinically relevant interventions for these conditions.[389,390] Figure 2*B* outlines the progress in drug development for TETs, including notable advances within the past 10 years.

A renewed focus on cutting edge technologies such as in vitro organoid culture of TET-derived cells might further enable the basic science of TETs to be translated into clinically meaningful applications for the management of these rare tumors.

Evolution of the Pathologic Diagnosis of Thymic Carcinoma

In 2006, the 2004 WHO replaced the type C thymoma with thymic carcinoma specifying the subtype (squamous, mucoepidermoid).[391] In 2008, Verghese[392] reported the poor reproducibility of TET histotype, and the ITMIG[393,394] and the ESP organized a consensus workshop establishing the basis for the 2015 WHO classification.[391] The role of IHC (e.g., co-expression of CD5 and CD117 in thymic squamous cell carcinoma to differentiate from B3 thymoma and lung squamous cell carcinoma) was underscored. To distinguish thymic carcinoma from thymoma, an immunopanel of MTAP with BAP1, CD117, and TdT yields a sensitivity of approximately 88% for thymic carcinoma.[395] In 2018, the TCGA study based on 117 cases of thymoma and thymic carcinoma found very few targetable mutations. In addition, this molecular analysis identified four molecular subtypes (A, -like, AB-like, B-like, and thymic carcinomas) supporting the current WHO classification.[379] It is hoped that novel markers will improve pathologic classification. In 2021 (WHO fifth edition[349]), a new provisional entity considered as a subtype of squamous cell carcinoma of the thymus was identified "micronodular thymic carcinoma with lymphoid hyperplasia" mimicking micronodular thymoma with lymphoid stroma. In 2024, ITMIG with the French RYTHMIC group underlined that pT staging on slides was an issue particularly for thymoma and made some recommendations to improve the reproducibility[396] A new TNM classification was validated by UICC in 2025[397] and will be used starting January 2026. Mediastinal pleura invasion, poorly reproducible, is no longer defining stage, and the size of the tumor is now incorporated in the new TNM.

Conclusions

There have been major advances and improvements in thoracic oncology in the past 20 years. First, and most importantly, the campaign against tobacco worked! The number of smokers has decreased and so has the percentage of LCs caused by smoking. Similarly, the measures introduced in the 80s in the Western world to eliminate or at least drastically reduce exposure to commercial asbestos fibers worked: the percentage of mesotheliomas caused by asbestos has significantly decreased in the recent past.[35] Research demonstrated that the old definition of LC was too simplistic: this malignancy is driven by different genetic alterations which respond to different targeted therapies which in turn benefit only specific subgroups of LC patients. Twenty years ago, mesothelioma was considered an invariably incurable disease with a dismal median survival of 6 to 18 months. Researchers have now identified a new variant of mesothelioma caused by *BAP1* germline mutations, which respond to therapy, and it is associated with prolonged survival and, at times, with a cure.[41,62] Notable advances in drug development for TETs have also occurred during this period, and a better understanding of TET-associated autoimmune diseases has resulted in an improvement in clinical outcomes. New therapeutic options for mesothelioma and thymic malignancies have resulted in some improvement in survival. New technologies, spatial transcriptomics, multiplex immunofluorescences, RNA-seq, single-cell RNA-seq, whole-genome sequencing long-read and short-reads, etc., have the potential to revolutionize and improve the therapies for thoracic malignancies in the near future. The cost of these methodologies, however, is prohibitive for academic researchers that rely on grants, whose size has not increased during the past 20 years. The NIH modular R01—the standard NIH grant—was $250,000 in 2000, and it is $250,000 in 2025: except that the pay-line (i.e., percentage of grant applications that are funded) has gone from 27% (2000) to 4% in 2025 to 2026. In other words, we have developed the technology and knowledge to make revolutionary improvements in cancer research; however, we do not have the resources to use this new technology. It is hoped that the public and private sectors will join forces to generate the funds necessary to perform cutting-edge medical research to find novel and more effective options to prevent and cure thoracic malignancies and all types of cancer.

CRediT Authorship Contribution Statement

Michele Carbone: Conceptualization, Writing - original draft, Writing - review & editing.

Christopher Amos: Conceptualization, Writing - original draft, Writing - review & editing.

Richard Attanoos: Conceptualization, Writing - original draft, Writing - review & editing.

Mattia Boeri: Conceptualization, Writing - original draft, Writing - review & editing.

Raphael Bueno: Conceptualization, Writing - original draft, Writing - review & editing.

Paul A. Bunn: Conceptualization, Writing - original draft, Writing - review & editing.

Lucian R. Chirieac: Conceptualization, Writing - original draft, Writing - review & editing.

Benjamin Cooper: Conceptualization, Writing - original draft, Writing - review & editing.

Dean Fennell: Conceptualization, Writing - original draft, Writing - review & editing.

Francoise Galateau-Salle: Conceptualization, Writing - original draft, Writing - review & editing.

Lydia Giannakou: Conceptualization, Writing - original draft, Writing - review & editing.

Chandra V. Goparaju: Conceptualization, Writing - original draft, Writing - review & editing.

Raffit Hassan: Conceptualization, Writing - original draft, Writing - review & editing.

Paul Hofman: Conceptualization, Writing - original draft, Writing - review & editing.

Mark G. Kris: Conceptualization, Writing - original draft, Writing - review & editing.

Weimin Mao: Conceptualization, Writing - original draft, Writing - review & editing.

Michael Minaai: Conceptualization, Writing - original draft, Writing - review & editing.

Tsetsuya Mitsudomi: Conceptualization, Writing - original draft, Writing - review & editing.

Thierry Molina: Conceptualization, Writing - original draft, Writing - review & editing.

Luis M. Montuenga: Conceptualization, Writing - original draft, Writing - review & editing.

Kazuki Nabeshima: Conceptualization, Writing - original draft, Writing - review & editing.

Antonio Passaro: Conceptualization, Writing - original draft, Writing - review & editing.

Solange Peters: Conceptualization, Writing - original draft, Writing - review & editing.

Arun Rajan: Conceptualization, Writing - original draft, Writing - review & editing.

David B. Richardson: Conceptualization, Writing - original draft, Writing - review & editing.

Hilary Robbins: Conceptualization, Writing - original draft, Writing - review & editing.

Christian Rolfo: Conceptualization, Writing - original draft, Writing - review & editing.

Charles M. Rudin: Conceptualization, Writing - original draft, Writing - review & editing.

Jonathan M. Samet: Conceptualization, Writing - original draft, Writing - review & editing.

Arnaud Scherpereel: Conceptualization, Writing - original draft, Writing - review & editing.

David S. Schrump: Conceptualization, Writing - original draft, Writing - review & editing.

Gabriella Sozzi: Conceptualization, Writing - original draft, Writing - review & editing.

Emanuela Taioli: Conceptualization, Writing - original draft, Writing - review & editing.

Silvia Visonà: Conceptualization, Writing - original draft, Writing - review & editing.

Haining Yang: Conceptualization, Writing - original draft, Writing - review & editing.

Yoshie Yoshikawa: Conceptualization, Writing - original draft, Writing - review & editing.

An Zhao: Conceptualization, Writing - original draft, Writing - review & editing.

Harvey I. Pass: Conceptualization, Writing - original draft, Writing - review & editing.

Disclosure

This work is funded through the National Institutes of Health (NIH)/National Cancer Institute (NCI) and U.S. Department of Defense (DoD) grants to Dr Carbone and Yang and by donations to the University of Hawaii Foundation. Drs Carbone and Yang report receiving funding from the NCI 1R01CA290173-01 (Drs Yang, Carbone, and Robert Taylor Ripley), 1R01CA237235-01A1 (Drs Carbone and Yang), and 1R01CA198138 (Dr Carbone), the National Institute of Environmental Health Sciences (NIEHS) 1R01ES030948-01 (Drs Carbone and Yang), the U.S. DoD W81XWH-16-1-0440 (Drs Yang, Carbone, and Pass), and the UH Foundation through donations that they received from Barry and Virginia Weinman; the Riviera United-4-a Cure (Drs Carbone and Yang), the Melohn Family Endowment, the Honeywell International Inc., Richard L. and Susan Fried; Richard and Ray Turbin, the Germaine Hope Brennan Foundation, and the Maurice and Joanna Sullivan Family Foundation (Dr Carbone). Drs Carbone and Yang have a patent issued for "Using Anti-HMGB1 Monoclonal Antibody or other HMGB1 Antibodies as a Novel Mesothelioma Therapeutic Strategy" and a patent issued for "HMGB1 As a Biomarker for Asbestos Exposure and Mesothelioma Early Detection." Dr Carbone is a board-certified pathologist and provides consultation for pleural pathology, including medical-legal. Drs Pass and Yang report receiving funding from the Early Detection Research Network NCI 5U01CA214195-04 and from NCI 1U2CCA271890-01A1. Dr Pass reports receiving funding from Genentech, Belluck, and Fox LLP. The funding sources did not have any role in the work presented here. Pharma had no role in any aspect of this research and the related manuscript. Drs Kriss and Bunn report receiving funding from NCI grants P30 CA008748 (MSK Cancer Center Support Grant) and P01 CA 129243. Dr Kriss reports receiving consulting from AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Merus, Pfizer, and Sanofi; editorial support from AstraZeneca and Genentech; and serving on the DSMB of Merck. Dr Bunn reports providing consulting/DMC in AstraZeneca, Genentech, Aveo, Bristol Myers Squibb, Merck, Daiichi Sankyo, Natera, and Ascentage; serving on the board of directors of Verastem. Dr Rudin reports receiving funding from NIH awards NCI R35 CA263816 and NCI U24 CA213274. Dr Montuenga reports receiving funding by the Spanish Ministry of Health Fondo de Investigación Sanitaria Fondo Europeo de Desarrollo Regional (PI25/00123) and the European Union

Programme HORIZON-MISS-2023-CANCER-01: SPACE-TIME. Dr Montuenga has a patent on LC early biomarkers and reports receiving grants from Siemens and AstraZeneca with no relation to this manuscript. The remaining authors declare no conflict of interest.

Acknowledgments

This work was supported in part by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute, Center for Cancer Research. The contributions of the NIH authors were made as part of their official duties as NIH federal employees, are in compliance with agency policy requirements, and are considered Works of the U.S. Government. However, the findings and conclusions presented in this paper are those of the authors and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services. Where authors are identified as personnel of the International Agency for Research on Cancer/WHO, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/WHO.

Contributions

Introduction (by Michele Carbone and Harvey I. Pass)

Epidemiology (by Emanuela Taioli and Silvia Visona)

The Environment and Lung Cancer (by Jonathan M. Samet and David B. Richardson)

Genetic Predisposition of Lung Cancer (LC) (by Christopher Amos)

Lung Cancer Screening (Harvey I. Pass)

Genomics and Targeted Therapies for Lung Cancers (by Mark G Kris and Paul A Bunn)

Radiation Oncology (Harvey I. Pass and Benjamin Cooper MD)

Immunotherapy science and lung cancer (by Antonio Passaro and Solange Peters)

Cell-Free DNA and Other Circulating Biomarkers in Lung Cancer (by Christian Rolfo, Tsetsuya Mitsudomi, and Luis M. Montuenga)

Circulating Biomarkers for Lung Cancer Early Detection, Diagnosis and Prognosis (by Hilary Robbins, Mattia Boeri, Gabriella Sozzi, & Luis M. Montuenga)

Small Cell Lung cancer (by Charles M. Rudin)

Advances in Diagnosis and Surgery for Lung Cancer (Harvey I. Pass)

Asbestos Carcinogenesis (by Lydia Giannakou & Haining Yang)

Mesothelioma (by Michele Carbone, Michael Minaai, Yoshie Yoshikawa, David S. Schrump, Haining Yang, Harvey I. Pass)

Mesothelioma Genomics (Harvey I. Pass, Rafael Bueno, Lucian R. Chirieac, Michele Carbone)

Mesothelioma Biomarkers: Progress over 20 Years (by Harvey I. Pass and Chandra V. Goparaju)

Advances in Systemic Therapy for Mesothelioma (by Arnaud Sherpereel, Dean A. Fennell, Raffit Hassan)

Evolution of Diagnosis of Lung Cancer, Mesothelioma and Thymic carcinoma– Past 20 years (by Francoise Galateau Sallé, Richard Attanoos, Paul Hofman, Thierry Molina, Kazuki Nabeshima)

Thymic Tumors (by An Zhao, Arun Rajan, Weimin Mao)

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2025.11.002.

References

1. World Health Organization. WHO global report on trends in prevalence of tobacco use 2000-2030. https://www.who.int/publications/i/item/9789240088283. Accessed October 8, 2025.
2. U.S. Centers for Disease Control and Prevention. Current cigarette smoking among adults in the United States. https://www.cdc.gov/tobacco/php/data-statistics/adult-data-cigarettes/index.html. Accessed October 8, 2025.
3. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 08/04/2011:365.
4. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med*. 2020;382:503-513.
5. Riely GJ, Wood DE, Ettinger DS, et al. Non-small cell lung cancer, version 4.2024, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2024;22:249-274.
6. Westphalen CB, Boscolo Bielo L, Aftimos P, et al. ESMO Precision Oncology Working Group recommendations on the structure and quality indicators for molecular tumour boards in clinical practice. *Ann Oncol*. 2025;36:614-625.
7. The Lancet. Lung cancer treatment: 20 years of progress. *Lancet*. 2024;403:2663.
8. Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376:629-640.
9. Tsuboi M, Herbst RS, John T, et al. Overall survival with osimertinib in resected EGFR-mutated NSCLC. *N Engl J Med*. 2023;389:137-147.
10. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823-1833.

11. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627–1639.
12. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in Stage III NSCLC. *N Engl J Med*. 2018;379:2342–2350.
13. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386:1973–1985.
14. Altorki N, Wang X, Kozono D, et al. Lobar or sublobar resection for peripheral stage IA non-small-cell lung cancer. *N Engl J Med*. 2023;388:489–498.
15. Murgu S, Chen AC, Gilbert CR, et al. A prospective, multicenter evaluation of safety and diagnostic outcomes with robotic-assisted bronchoscopy: results of the transbronchial biopsy assisted by robot guidance in the evaluation of tumors of the lung (TARGET) trial. *Chest*. 2025;168:539–555.
16. Reddington H, Ballinger Z, Guart J, et al. National adoption of robotic-assisted thoracoscopic surgery for oncologic lung resections. *J Robot Surg*. 2025;19:557.
17. Timmerman RD, Hu C, Michalski JM, et al. Long-term results of stereotactic body radiation therapy in medically inoperable Stage I non-small cell lung cancer. *JAMA Oncol*. 2018;4:1287–1288.
18. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395–409.
19. US Preventive Services Task Force, Krist AH, Davidson KW, et al. Screening for lung cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;325:962–970.
20. McKenna RJ Jr, Houck W, Fuller CB. Video-assisted thoracic surgery lobectomy: experience with 1,100 cases. *Ann Thorac Surg*. 2006;81:421–426.
21. Saji H, Okada M, Tsuboi M, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. *Lancet*. 2022;399:1607–1617.
22. Cerfolio RJ, Cichos KH, Wei B, Minnich DJ. Robotic lobectomy can be taught while maintaining quality patient outcomes. *J Thorac Cardiovasc Surg*. 2016;152:991–997.
23. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA*. 2010;303:1070–1076.
24. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol*. 2015;16:630–637.
25. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in Stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919–1929.
26. Kleber T, Hooda Z, Dong W, et al. Ten-year outcomes of the revised STARS trial comparing radiation and surgery for early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2025;123:S119.
27. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368:2385–2394.
28. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123–135.
29. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113–125.
30. Wu YL, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. *N Engl J Med*. 2020;383:1711–1723.
31. Spicer JD, Garassino MC, Wakelee H, et al. Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2024;404:1240–1252.
32. Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without chemotherapy in EGFR-mutated advanced NSCLC. *N Engl J Med*. 2023;389:1935–1948.
33. Videtic GMM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: executive summary of an ASTRO evidence-based guideline. *Pract Radiat Oncol*. 2017;7:295–301.
34. Zer A, Ahn MJ, Barlesi F, et al. Early and locally advanced non-small-cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2025;36:1245–1262.
35. Carbone M, Yang H, Pass HI, Taioli E. Did the ban on asbestos reduce the incidence of mesothelioma? *J Thorac Oncol*. 2023;18:694–697.
36. Huang J, Chan SC, Pang WS, et al. Global incidence, risk factors, and temporal trends of mesothelioma: a population-based study. *J Thorac Oncol*. 2023;18:792–802.
37. Walker-Bone K, Benke G, MacFarlane E, et al. Incidence and mortality from malignant mesothelioma 1982-2020 and relationship with asbestos exposure: the Australian mesothelioma Registry. *Occup Environ Med*. 2023;80:186–191.
38. Carbone M, Adusumilli PS, Alexander HR Jr, et al. Mesothelioma: scientific clues for prevention, diagnosis, and therapy. *CA Cancer J Clin*. 2019;69:402–429.
39. Lee M, Alexander HR, Burke A. Diffuse mesothelioma of the peritoneum: a pathological study of 64 tumours treated with cytoreductive therapy. *Pathology*. 2013;45:464–473.
40. Malpica A, Euscher ED, Marques-Piubelli ML, et al. Malignant mesothelioma of the peritoneum in women: a clinicopathologic study of 164 cases. *Am J Surg Pathol*. 2021;45:45–58.
41. Carbone M, Minaai M, Kittaneh M, et al. Clinical and pathologic phenotyping of mesotheliomas developing in carriers of germline BAP1 mutations. *J Thorac Oncol*. 2025;20:1683–1698.
42. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the mesothelioma Avastin cisplatin pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2016;387:1405–1414.

43. Smesseim I, Baas P. Immunotherapy is a good standard option for patients with malignant pleural mesothelioma, despite the real-world results from Australia. *J Thorac Oncol*. 2024;19:547–550.
44. Gray SG, Meirson T, Mutti L. Based on the real-world results from Australia, immunotherapy is not a good option for patients with mesothelioma. *J Thorac Oncol*. 2024;19:541–546.
45. Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. *J Thorac Cardiovasc Surg*. 2008;135:620–626.e621-23.
46. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol*. 2011;12:763–772.
47. Lim E, Waller D, Lau K, et al. Extended pleurectomy decortication and chemotherapy versus chemotherapy alone for pleural mesothelioma (MARS 2): a phase 3 randomised controlled trial. *Lancet Respir Med*. 2024;12:457–466.
48. Lim E, Opitz I, Woodard G, et al. A perspective on the MARS2 trial. *J Thorac Oncol*. 2025;20:262–272.
49. Roushdy-Hammady I, Siegel J, Emri S, Testa JR, Carbone M. Genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. *Lancet*. 2001;357:444–445.
50. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol*. 2003;21:2636–2644.
51. Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. *Nat Genet*. 2011;43:1022–1025.
52. Nasu M, Emi M, Pastorino S, et al. High Incidence of Somatic BAP1 alterations in sporadic malignant mesothelioma. *J Thorac Oncol*. 2015;10:565–576.
53. Baumann F, Flores E, Napolitano A, et al. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. *Carcinogenesis*. 2015;36:76–81.
54. Guo G, Chmielecki J, Goparaju C, et al. Whole-exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A, and CUL1 in malignant pleural mesothelioma. *Cancer Res*. 2015;75:264–269.
55. Lo Iacono M, Monica V, Righi L, et al. Targeted next-generation sequencing of cancer genes in advanced stage malignant pleural mesothelioma: a retrospective study. *J Thorac Oncol*. 2015;10:492–499.
56. Yoshikawa Y, Emi M, Hashimoto-Tamaoki T, et al. High-density array-CGH with targeted NGS unmask multiple noncontiguous minute deletions on chromosome 3p21 in mesothelioma. *Proc Natl Acad Sci U S A*. 2016;113:13432–13437.
57. Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet*. 2016;48:407–416.
58. Loharamtaweethong K, Puripat N, Aoonjai N, Sutepvarnon A, Bandidwattanawong C. Anaplastic lymphoma kinase (ALK) translocation in paediatric malignant peritoneal mesothelioma: a case report of novel ALK-related tumour spectrum. *Histopathology*. 2016;68:603–607.
59. Bononi A, Giorgi C, Patergnani S, et al. BAP1 regulates IP3R3-mediated Ca2+ flux to mitochondria suppressing cell transformation. *Nature*. 2017;546:549–553.
60. Novelli F, Bononi A, Wang Q, et al. BAP1 forms a trimer with HMGB1 and HDAC1 that modulates gene × environment interaction with asbestos. *Proc Natl Acad Sci U S A*. 2021;118:e2111946118.
61. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *Lancet*. 2021;397:375–386.
62. Novelli F, Yoshikawa Y, Vitto VAM, et al. Germline BARD1 variants predispose to mesothelioma by impairing DNA repair and calcium signaling. *Proc Natl Acad Sci U S A*. 2024;121:e2405231121.
63. Wu X, Hernandez F V, Wang H, et al. Prospective analysis of mesotheliomas in subjects with BAP1 cancer syndrome: clinical characteristics and epigenetic correlates of disease. *J Thorac Oncol*. 2025;20:1699–1715.
64. Hsu CH, Chan JK, Yin CH, Lee CC, Chern CU, Liao CI. Trends in the incidence of thymoma, thymic carcinoma, and thymic neuroendocrine tumor in the United States. *PLoS One*. 2019;14:e0227197.
65. Yamada D, Matsusako M, Kurihara Y. Review of clinical and diagnostic imaging of the thymus: from age-related changes to thymic tumors and everything in between. *Jpn J Radiol*. 2024;42:217–234.
66. Shin DW, Cho JH, Ha J, Jung KW. Trends in incidence and survival of patients with thymic epithelial tumor in a high-incidence Asian country: analysis of the Korean central cancer registry 1999 to 2017. *J Thorac Oncol*. 2022;17:827–837.
67. Sato J, Satouchi M, Itoh S, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (remora): a multicentre, phase 2 trial. *Lancet Oncol*. 2020;21:843–850.
68. Flores R, Patel P, Alpert N, Pyenson B, Taioli E. Association of stage shift and population mortality among patients with non-small cell lung cancer. *JAMA Netw Open*. 2021;4:e2137508.
69. Howlader N, Forjaz G, Mooradian MJ, et al. The effect of advances in lung-cancer treatment on population mortality. *N Engl J Med*. 2020;383:640–649.
70. Delgermaa V, Takahashi K, Park EK, Le GV, Hara T, Sorahan T. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. *Bull World Health Organ*. 2011;89, 724A–724C.
71. Han J, Park S, Yon DK, et al. Global, regional, and national burden of mesothelioma 1990–2019: a systematic analysis of the global burden of disease Study 2019. *Ann Am Thorac Soc*. 2023;20:976–983.
72. Roden AC, Ahmad U, Cardillo G, et al. Thymic carcinomas-A concise multidisciplinary update on recent developments from the thymic carcinoma

working group of the international thymic malignancy interest group. *J Thorac Oncol*. 2022;17:637–650.
73. Alexandrov LB, Ju YS, Haase K, et al. Mutational signatures associated with tobacco smoking in human cancer. *Science*. 2016;354:618–622.
74. Loomis D, Grosse Y, Lauby-Secretan B, et al. The carcinogenicity of outdoor air pollution. *Lancet Oncol*. 2013;14:1262–1263.
75. Díaz-Gay M, Zhang T, Hoang PH, et al. The mutagenic forces shaping the genomes of lung cancer in never smokers. *Nature*. 2025;644:133–144.
76. Richardson DB, Rage E, Demers PA, et al. Lung cancer and radon: pooled analysis of uranium Miners Hired in 1960 or later. *Environ Health Perspect*. 2022;130:57010.
77. Institute for Health Metrics and Evaluation. GBD results. https://vizhub.healthdata.org/gbd-results/. Accessed December 4, 2025.
78. Ang L, Chan CPY, Yau WP, Seow WJ. Association between family history of lung cancer and lung cancer risk: a systematic review and meta-analysis. *Lung Cancer*. 2020;148:129–137.
79. Sellers TA, Bailey-Wilson JE, Elston RC, et al. Evidence for Mendelian inheritance in the pathogenesis of lung cancer. *J Natl Cancer Inst*. 1990;82:1272–1279.
80. Bailey-Wilson JE, Sellers TA, Elston RC, Evens CC, Rothschild H. Evidence for a major gene effect in early-onset lung cancer. *J La State Med Soc*. 1993;145:157–162.
81. Sellers TA, Chen PL, Potter JD, Bailey-Wilson JE, Rothschild H, Elston RC. Segregation analysis of smoking-associated malignancies: evidence for Mendelian inheritance. *Am J Med Genet*. 1994;52:308–314.
82. Yang P, Schwartz AG, McAllister AE, Swanson GM, Aston CE. Lung cancer risk in families of nonsmoking probands: heterogeneity by age at diagnosis. *Genet Epidemiol*. 1999;17:253–273.
83. Bailey-Wilson JE, Amos CI, Pinney SM, et al. A major lung cancer susceptibility locus maps to chromosome 6q23-25. *Am J Hum Genet*. 2004;75:460–474.
84. Amos CI, Pinney SM, Li Y, et al. A susceptibility locus on chromosome 6q greatly increases lung cancer risk among light and never smokers. *Cancer Res*. 2010;70:2359–2367.
85. Hwang SJ, Cheng LS, Lozano G, Amos CI, Gu X, Strong LC. Lung cancer risk in germline p53 mutation carriers: association between an inherited cancer predisposition, cigarette smoking, and cancer risk. *Hum Genet*. 2003;113:238–243.
86. Kleinerman RA, Tarone RE, Abramson DH, Seddon JM, Li FP, Tucker MA. Hereditary retinoblastoma and risk of lung cancer. *J Natl Cancer Inst*. 2000;92:2037–2039.
87. Bell DW, Gore I, Okimoto RA, et al. Inherited susceptibility to lung cancer may be associated with the T790M drug resistance mutation in EGFR. *Nat Genet*. 2005;37:1315–1316.
88. Gazdar A, Robinson L, Oliver D, et al. Hereditary lung cancer syndrome targets never smokers with germline EGFR gene T790M mutations. *J Thorac Oncol*. 2014;9:456–463.
89. Yamamoto H, Yatabe Y, Toyooka S. Inherited lung cancer syndromes targeting never smokers. *Transl Lung Cancer Res*. 2018;7:498–504.
90. Tode N, Kikuchi T, Sakakibara T, et al. Exome sequencing deciphers a germline MET mutation in familial epidermal growth factor receptor-mutant lung cancer. *Cancer Sci*. 2017;108:1263–1270.
91. Tomoshige K, Matsumoto K, Tsuchiya T, et al. Germline mutations causing familial lung cancer. *J Hum Genet*. 2015;60:597–603.
92. Brudon A, Legendre M, Mageau A, et al. High risk of lung cancer in surfactant-related gene variant carriers. *Eur Respir J*. 2024;63:2301809.
93. Luyapan J, Bossé Y, Li Z, et al. Candidate pathway analysis of surfactant proteins identifies CTSH and SFTA2 that influences lung cancer risk. *Hum Mol Genet*. 2023;32:2842–2855.
94. Wang Y, Kuan PJ, Xing C, et al. Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer. *Am J Hum Genet*. 2009;84:52–59.
95. Xiong D, Wang Y, Kupert E, et al. A recurrent mutation in PARK2 is associated with familial lung cancer. *Am J Hum Genet*. 2015;96:301–308.
96. Xiong D, Wang Y, You M. PARK2 gene and familial lung cancer: what is the link? *Future Oncol*. 2015;11:1707–1710.
97. Ji X, Mukherjee S, Landi MT, et al. Protein-altering germline mutations implicate novel genes related to lung cancer development. *Nat Commun*. 2020;11:2220.
98. Cannon-Albright LA, Teerlink CC, Stevens J, et al. A rare FGF5 candidate variant (rs112475347) for predisposition to nonsquamous, nonsmall-cell lung cancer. *Int J Cancer*. 2023;153:364–372.
99. Xu J, Xu W, Choi J, et al. Large-scale whole exome sequencing studies identify two genes,CTSL and APOE, associated with lung cancer. *PLoS Genet*. 2023;19:e1010902.
100. Chen LS, Baker TB, Miller JP, et al. Genetic variant in CHRNA5 and response to varenicline and combination nicotine replacement in a randomized placebo-controlled trial. *Clin Pharmacol Ther*. 2020;108:1315–1325.
101. Chen LS, Baker TB, Ramsey A, Amos CI, Bierut LJ. Genomic medicine to reduce tobacco and related disorders: translation to precision prevention and treatment. *Addict Neurosci*. 2023;7:100083.
102. Chen LS, Hung RJ, Baker T, et al. CHRNA5 risk variant predicts delayed Smoking Cessation and earlier lung cancer diagnosis-a meta-analysis. *J Natl Cancer Inst*. 2015;107:djv100.
103. Chen T., Pham G, Fox L, et al. Genomic insights for personalized care: motivating at-risk individuals toward evidence-based health practices. https://www.medrxiv.org/content/10.1101/2024.03.19.24304556v5.full. Accessed December 4, 2025.
104. Chenoweth MJ, Lerman C, Knight J, Tyndale RF. Influence of CYP2A6 genetic variation, nicotine dependence severity, and treatment on smoking cessation success. *Nicotine Tob Res*. 2023;25:1207–1211.
105. Bossé Y, Li Z, Xia J, et al. Transcriptome-wide association study reveals candidate causal genes for lung cancer. *Int J Cancer*. 2020;146:1862–1878.

106. Landi MT, Chatterjee N, Yu K, et al. A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. *Am J Hum Genet*. 2009;85:679–691.
107. Qin N, Li Y, Wang C, et al. Comprehensive functional annotation of susceptibility variants identifies genetic heterogeneity between lung adenocarcinoma and squamous cell carcinoma. *Front Med*. 2021;15:275–291.
108. Kachuri L, Amos CI, McKay JD, et al. Fine mapping of chromosome 5p15.33 based on a targeted deep sequencing and high density genotyping identifies novel lung cancer susceptibility loci. *Carcinogenesis*. 2016;37:96–105.
109. Kachuri L, Helby J, Bojesen SE, et al. Investigation of leukocyte telomere length and genetic variants in chromosome 5p15.33 as prognostic markers in lung cancer. *Cancer Epidemiol Biomarkers Prev*. 2019;28:1228–1237.
110. McKay JD, Hung RJ, Han Y, et al. Large-scale association analysis identifies new lung cancer susceptibility loci and heterogeneity in genetic susceptibility across histological subtypes. *Nat Genet*. 2017;49:1126–1132.
111. Ferreiro-Iglesias A, Lesseur C, McKay J, et al. Fine mapping of MHC region in lung cancer highlights independent susceptibility loci by ethnicity. *Nat Commun*. 2018;9:3927.
112. Hematian Larki M, Ashouri E, Barani S, Ghayumi SMA, Ghaderi A, Rajalingam R. KIR-HLA gene diversities and susceptibility to lung cancer. *Sci Rep*. 2022;12:17237.
113. Krishna C, Tervi A, Saffern M, et al. An immunogenetic basis for lung cancer risk. *Science*. 2024;383:eadi3808.
114. Amos CI, Gorlov IP, Dong Q, et al. Nicotinic acetylcholine receptor region on Chromosome 15q25 and lung cancer risk among African Americans: a case-control study. *J Natl Cancer Inst*. 2010;102:1199–1205.
115. Amos CI, Wu X, Broderick P, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. *Nat Genet*. 2008;40:616–622.
116. Byun J, Han Y, Ostrom QT, et al. The shared genetic architectures between lung cancer and multiple polygenic phenotypes in genome-wide association studies. *Cancer Epidemiol Biomarkers Prev*. 2021;30:1156–1164.
117. Chen T, Pham G, Fox L, et al. Genomic insights for personalised care in lung cancer and smoking cessation: motivating at-risk individuals toward evidence-based health practices. *EBiomedicine*. 2024;110:105441.
118. Hung RJ, Spitz MR, Houlston RS, et al. Lung cancer risk in never-smokers of European descent is associated with genetic variation in the $5_p15.33$ TERT-CLPTM1Ll region. *J Thorac Oncol*. 2019;14:1360–1369.
119. Amos CI, Dennis J, Wang Z, et al. The OncoArray consortium: a network for understanding the genetic architecture of common cancers. *Cancer Epidemiol Biomarkers Prev*. 2017;26:126–135.
120. Vineis P, Hoek G, Krzyzanowski M, et al. Lung cancers attributable to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study. *Environ Health*. 2007;6:7.
121. Lerner NB, Platania BL, LaBella S. Newborn sickle cell screening in a region of Western New York State. *J Pediatr*. 2009;154:121–125.
122. HEATH CW. Differences between smokers and nonsmokers. *AMA Arch Intern Med*. 1958;101:377–388.
123. Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2007. http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_12.pdf. Accessed December 5, 2012.
124. Chong JX, Buckingham KJ, Jhangiani SN, et al. The genetic basis of Mendelian phenotypes: discoveries, challenges, and opportunities. *Am J Hum Genet*. 2015;97:199–215.
125. Black WC. Computed tomography screening for lung cancer in the national lung screening trial: a cost-effectiveness analysis. *J Thorac Imaging*. 2015;30:79–87.
126. Villani A, Shore A, Wasserman JD, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. *Lancet Oncol*. 2016;17:1295–1305.
127. Hung RJ, Warkentin MT, Brhane Y, et al. Assessing lung cancer absolute risk trajectory based on a polygenic risk model. *Cancer Res*. 2021;81:1607–1615.
128. US Preventive Services Task Force. Final recommendation statement. Lung cancer: screening. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/lung-cancer-screening. Accessed December 4, 2025.
129. Centers for Medicare & Medicaid Services. National coverage determination (NCD): lung cancer screening with low dose computed tomography (LDCT). https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=364&ncdver=1. Accessed December 4, 2025.
130. Agrawal R, Ahuja J, Strange CD, et al. Lung-RADS v2022 update. *Radiol Clin North Am*. 2025;63:507–516.
131. Centers for Medicare & Medicaid Services. National coverage determination (NCD) 210.14 reconsideration – screening for lung cancer with low dose computed tomography (LDCT). https://www.cms.gov/files/document/mm12691-national-coverage-determination-ncd-21014-reconsideration-screening-lung-cancer-low-dose.pdf. Accessed December 4, 2025.
132. Wolf AMD, Oeffinger KC, Shih TY, et al. Screening for lung cancer: 2023 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2024;74:50–81.
133. Bandi P, Star J, Ashad-Bishop K, Kratzer T, Smith R, Jemal A. Lung cancer screening in the US, 2022. *JAMA Intern Med*. 2024;184:882–891.
134. Stehelin D, Varmus HE, Bishop JM, Vogt PK. DNA related to the transforming gene(s) of avian sarcoma viruses is present in normal avian DNA. *Nature*. 1976;260:170–173.
135. Weinstein IB, Joe A. Oncogene addiction. *Cancer Res*. 2008;68:3077–3080.

136. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304:1497–1500.
137. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350:2129–2139.
138. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci USA*. 2004;101:13306–13311.
139. Swanton C, Govindan R. Clinical implications of genomic discoveries in lung cancer. *N Engl J Med*. 2016;374:1864–1873.
140. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311:1998–2006.
141. Jordan EJ, Kim HR, Arcila ME, et al. Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies. *Cancer Discov*. 2017;7:596–609.
142. Pao W, Kris MG, Iafrate AJ, et al. Integration of molecular profiling into the lung cancer clinic. *Clin Cancer Res*. 2009;15:5317–5322.
143. Sholl LM, Aisner DL, Varella-Garcia M, et al. Multi-institutional oncogenic driver mutation analysis in lung adenocarcinoma: the lung cancer mutation consortium experience. *J Thorac Oncol*. 2015;10:768–777.
144. Aisner DL, Sholl LM, Berry LD, et al. The impact of smoking and TP53 mutations in lung adenocarcinoma patients with targetable mutations-the lung cancer mutation consortium (LCMC2). *Clin Cancer Res*. 2018;24:1038–1047.
145. Villaruz LC, Socinski MA, Abberbock S, et al. Clinicopathologic features and outcomes of patients with lung adenocarcinomas harboring BRAF mutations in the Lung Cancer Mutation Consortium. *Cancer*. 2015;121:448–456.
146. Pillai RN, Behera M, Berry LD, et al. HER2 mutations in lung adenocarcinomas: a report from the Lung Cancer Mutation Consortium. *Cancer*. 2017;123:4099–4105.
147. Steuer CE, Behera M, Berry L, et al. Role of race in oncogenic driver prevalence and outcomes in lung adenocarcinoma: results from the Lung Cancer Mutation Consortium. *Cancer*. 2016;122:766–772.
148. El Osta B, Behera M, Kim S, et al. Characteristics and outcomes of patients with metastatic KRAS-mutant lung adenocarcinomas: the lung cancer mutation consortium experience. *J Thorac Oncol*. 2019;14:876–889.
149. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med*. 2010;363:1693–1703.
150. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with KRAS p.G12C Mutation. *N Engl J Med*. 2021;384:2371–2381.
151. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated $BRAF^{V600E}$-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol*. 2017;18:1307–1316.
152. Wolf J, Seto T, Han JY, et al. Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. *N Engl J Med*. 2020;383:944–957.
153. Li BT, Smit EF, Goto Y, et al. Trastuzumab Deruxtecan in HER2-mutant non-small-cell lung cancer. *N Engl J Med*. 2022;386:241–251.
154. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947–957.
155. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11:121–128.
156. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12:735–742.
157. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13:239–246.
158. Yun CH, Mengwasser KE, Toms AV, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci U S A*. 2008;105:2070–2075.
159. Keating GM. Afatinib: a review of its use in the treatment of advanced non-small cell lung cancer. *Drugs*. 2014;74:207–221.
160. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31:3327–3334.
161. Ramalingam SS, Yang JC, Lee CK, et al. Osimertinib as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer. *J Clin Oncol*. 2018;36:841–849.
162. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20:1655–1669.
163. Hosomi Y, Morita S, Sugawara S, et al. Gefitinib alone versus gefitinib plus chemotherapy for non-small-cell lung cancer with mutated epidermal growth factor receptor: NEJ009 study. *J Clin Oncol*. 2020;38:115–123.
164. Lu S, Kato T, Dong X, et al. Osimertinib after chemoradiotherapy in Stage III EGFR-mutated NSCLC. *N Engl J Med*. 2024;391:585–597.
165. Cho BC, Lu S, Felip E, et al. Amivantamab plus lazertinib in previously untreated EGFR-mutated advanced NSCLC. *N Engl J Med*. 2024;391:1486–1498.
166. Zhou C, Tang KJ, Cho BC, et al. Amivantamab plus chemotherapy in NSCLC with EGFR Exon 20 insertions. *N Engl J Med*. 2023;389:2039–2051.
167. Zhong WZ, Wang Q, Mao WM, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for

stage II-IIIA (N1-N2) EGFR-mutant NSCLC: final overall survival analysis of CTONG1104 Phase III trial. *J Clin Oncol*. 2021;39:713–722.
168. Yue D, Xu S, Wang Q, et al. Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): a randomised, open-label, phase 2 trial. *Lancet Respir Med*. 2018;6:863–873.
169. Yue D, Xu S, Wang Q, et al. Updated overall survival and exploratory analysis from randomized, Phase II EVAN study of erlotinib versus vinorelbine plus cisplatin adjuvant therapy in stage IIIA epidermal growth factor receptor+ non-small-cell lung cancer. *J Clin Oncol*. 2022;40:3912–3917.
170. Zhong WZ, Yan HH, Chen KN, et al. Erlotinib versus gemcitabine plus cisplatin as neoadjuvant treatment of stage IIIA-N2 EGFR-mutant non-small-cell lung cancer: final overall survival analysis of the EMERGING-CTONG 1103 randomised phase II trial. *Signal Transduct Target Ther*. 2023;8:76.
171. He J, Tsuboi M, Weder W, et al. Neoadjuvant osimertinib for resectable EGFR-mutated non-small cell lung cancer. *J Clin Oncol*. 2025;43:2875–2887.
172. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med*. 2005;2:e73.
173. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2005;352:786–792.
174. Wu YL, Dziadziuszko R, Ahn JS, et al. Alectinib in resected ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2024;390:1265–1276.
175. Nassar AH, Kim SY, Aredo JV, et al. Consolidation Osimertinib versus Durvalumab versus observation after concurrent chemoradiation in unresectable EGFR-mutant NSCLC: a multicenter retrospective cohort study. *J Thorac Oncol*. 2024;19:928–940.
176. Timmerman RD, Hu C, Michalski J, et al. Long-term results of RTOG 0236: a phase II trial of stereotactic body radiation therapy (SBRT) in the treatment of patients with medically inoperable Stage I non-small cell lung cancer. *Int J Radiat Oncol*. 2014;90:S30.
177. Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. *Lancet Oncol*. 2019;20:494–503.
178. Chun SG, Hu C, Komaki RU, et al. Long-term prospective outcomes of intensity modulated radiotherapy for locally advanced lung cancer: a secondary analysis of a randomized clinical trial. *JAMA Oncol*. 2024;10:1111–1115.
179. Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. *J Clin Oncol*. 2017;35:56–62.
180. Nestle U, Schimek-Jasch T, Kremp S, et al. Imaging-based target volume reduction in chemoradiotherapy for locally advanced non-small-cell lung cancer (PET-Plan): a multicentre, open-label, randomised, controlled trial. *Lancet Oncol*. 2020;21:581–592.
181. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in Stage III non-small-cell lung cancer. *J Clin Oncol*. 2022;40:1301–1311.
182. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379:2220–2229.
183. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (Caspian): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394:1929–1939.
184. Cheng Y, Spigel DR, Cho BC, et al. Durvalumab after chemoradiotherapy in limited-stage small-cell lung cancer. *N Engl J Med*. 2024;391:1313–1327.
185. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol*. 2020;21:645–654.
186. Paz-Ares L, Borghaei H, Liu SV, et al. Efficacy and safety of first-line maintenance therapy with lurbinectedin plus atezolizumab in extensive-stage small-cell lung cancer (IMforte): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. 2025;405:2129–2143.
187. Ahn MJ, Cho BC, Felip E, et al. Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med*. 2023;389:2063–2075.
188. Mountzios G, Sun L, Cho BC, et al. Tarlatamab in small-cell lung cancer after platinum-based chemotherapy. *N Engl J Med*. 2025;393:349–361.
189. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366:2443–2454.
190. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12:252–264.
191. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. *J Clin Oncol*. 2012;30:2046–2054.
192. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540–1550.
193. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med*. 2020;383:1328–1339.
194. Sezer A, Kilickap S, Gümüş M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet*. 2021;397:592–604.
195. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092.

196. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040–2051.
197. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381:2020–2031.
198. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:198–211.
199. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. 2021;398:1344–1357.
200. O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol*. 2022;23:1274–1286.
201. Heymach JV, Harpole D, Mitsudomi T, et al. Perioperative durvalumab for resectable non-small-cell lung cancer. *N Engl J Med*. 2023;389:1672–1684.
202. Bestvina CM, Garassino MC, Neal JW, Wakelee HA, Diehn M, Vokes EE. Early-stage lung cancer: using circulating tumor DNA to get personal. *J Clin Oncol*. 2023;41:4093–4096.
203. Semenkovich NP, Szymanski JJ, Earland N, Chauhan PS, Pellini B, Chaudhuri AA. Genomic approaches to cancer and minimal residual disease detection using circulating tumor DNA. *J Immunother Cancer*. 2023;11:e006284.
204. Passaro A, Jänne PA, Peters S. Antibody-drug conjugates in lung cancer: recent advances and implementing strategies. *J Clin Oncol*. 2023;41:3747–3761.
205. Passaro A, Brahmer J, Antonia S, Mok T, Peters S. Managing resistance to immune checkpoint inhibitors in lung cancer: treatment and novel strategies. *J Clin Oncol*. 2022;40:598–610.
206. Rolfo C, Mack P, Scagliotti GV, et al. Liquid biopsy for advanced NSCLC: a consensus statement from the International Association for the Study of Lung Cancer. *J Thorac Oncol*. 2021;16:1647–1662.
207. Normanno N, Morabito A, Rachiglio AM, et al. Circulating tumour DNA in early stage and locally advanced NSCLC: ready for clinical implementation? *Nat Rev Clin Oncol*. 2025;22:215–231.
208. Kimura H, Kasahara K, Kawaishi M, et al. Detection of epidermal growth factor receptor mutations in serum as a predictor of the response to gefitinib in patients with non-small-cell lung cancer. *Clin Cancer Res*. 2006;12:3915–3921.
209. Mok T, Wu YL, Lee JS, et al. Detection and dynamic changes of EGFR mutations from circulating tumor DNA as a predictor of survival outcomes in NSCLC patients treated with first-line intercalated erlotinib and chemotherapy. *Clin Cancer Res*. 2015;21:3196–3203.
210. Oxnard GR, Paweletz CP, Kuang Y, et al. Noninvasive detection of response and resistance in EGFR-mutant lung cancer using quantitative next-generation genotyping of cell-free plasma DNA. *Clin Cancer Res*. 2014;20:1698–1705.
211. Lanman RB, Mortimer SA, Zill OA, et al. Analytical and clinical validation of a digital sequencing panel for quantitative, highly accurate evaluation of cell-free circulating tumor DNA. *PLoS One*. 2015;10:e0140712.
212. Aggarwal C, Rolfo CD, Oxnard GR, Gray JE, Sholl LM, Gandara DR. Strategies for the successful implementation of plasma-based NSCLC genotyping in clinical practice. *Nat Rev Clin Oncol*. 2021;18:56–62.
213. Leighl NB, Page RD, Raymond VM, et al. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. *Clin Cancer Res*. 2019;25:4691–4700.
214. Russo A, Lee JK, Pasquina LW, et al. Liquid biopsy of lung cancer before pathological diagnosis is associated with shorter time to treatment. *JCO Precis Oncol*. 2024;8:e2300535.
215. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature*. 2017;545:446–451.
216. Chaudhuri AA, Chabon JJ, Lovejoy AF, et al. Early detection of molecular residual disease in localized lung cancer by circulating tumor DNA profiling. *Cancer Discov*. 2017;7:1394–1403.
217. Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34:339–357.
218. Rolfo C, Russo A. Navigating into a stormy sea: liquid biopsy enters peri-operative management in early-stage non-small cell lung cancer. *Ann Oncol*. 2024;35:147–149.
219. Dipasquale A, Pisapia P, Reduzzi C. Liquid biopsy through non-blood fluids: the show must go on. *J Liq Biopsy*. 2024;6:100272.
220. Seijo LM, Peled N, Ajona D, et al. Biomarkers in lung cancer screening: achievements, promises, and challenges. *J Thorac Oncol*. 2019;14:343–357.
221. Feng X, Goodley P, Alcala K, et al. Evaluation of risk prediction models to select lung cancer screening participants in Europe: a prospective cohort consortium analysis. *Lancet Digit Health*. 2024;6:e614–e624.
222. McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med*. 2013;369:910–919.
223. Paci M, Maramotti S, Bellesia E, et al. Circulating plasma DNA as diagnostic biomarker in non-small cell lung cancer. *Lung Cancer*. 2009;64:92–97.
224. Sozzi G, Roz L, Conte D, et al. Plasma DNA quantification in lung cancer computed tomography screening: five-year results of a prospective study. *Am J Respir Crit Care Med*. 2009;179:69–74.
225. Baldwin DR, Callister ME, Crosbie PA, et al. Biomarkers in lung cancer screening: the importance of study design. *Eur Respir J*. 2021;57:2004367.
226. Fortunato O, Huber V, Segale M, et al. Development of a molecular blood-based immune signature classifier as

biomarker for risks assessment in lung cancer screening. *Cancer Epidemiol Biomarkers Prev*. 2022;31:2020–2029.
227. Massion PP, Healey GF, Peek LJ, et al. Autoantibody signature enhances the positive predictive power of computed tomography and nodule-based risk models for detection of lung cancer. *J Thorac Oncol*. 2017;12:578–584.
228. Boeri M, Verri C, Conte D, et al. MicroRNA signatures in tissues and plasma predict development and prognosis of computed tomography detected lung cancer. *Proc Natl Acad Sci U S A*. 2011;108:3713–3718.
229. Khodayari Moez E, Warkentin MT, Brhane Y, et al. Circulating proteome for pulmonary nodule malignancy. *J Natl Cancer Inst*. 2023;115:1060–1070.
230. Lung Cancer Cohort Consortium (LC3. The blood proteome of imminent lung cancer diagnosis. *Nat Commun*. 2023;14:3042.
231. Sullivan FM, Mair FS, Anderson W, et al. Earlier diagnosis of lung cancer in a randomised trial of an autoantibody blood test followed by imaging. *Eur Respir J*. 2021;57:2000670.
232. Pastorino U, Boeri M, Sestini S, et al. Baseline computed tomography screening and blood microRNA predict lung cancer risk and define adequate intervals in the BioMILD trial. *Ann Oncol*. 2022;33:395–405.
233. Boeri M, Sabia F, Ledda RE, et al. Blood microRNA testing in participants with suspicious low-dose CT findings: follow-up of the BioMILD lung cancer screening trial. *Lancet Reg Health Eur*. 2024;46:101070.
234. Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL) Consortium for Early Detection of Lung Cancer, Guida F, Sun N, et al. Assessment of lung cancer risk on the basis of a biomarker panel of circulating proteins. *JAMA Oncol*. 2018;4:e182078.
235. Robbins HA, Alcala K, Moez EK, et al. Design and methodological considerations for biomarker discovery and validation in the Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL) Program. *Ann Epidemiol*. 2023;77:1–12.
236. Nicholson BD, Oke J, Virdee PS, et al. Multi-cancer early detection test in symptomatic patients referred for cancer investigation in England and Wales (SYMPLIFY): a large-scale, observational cohort study. *Lancet Oncol*. 2023;24:733–743.
237. Mathios D, Johansen JS, Cristiano S, et al. Detection and characterization of lung cancer using cell-free DNA fragmentomes. *Nat Commun*. 2021;12:5060.
238. Klein EA, Richards D, Cohn A, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann Oncol*. 2021;32:1167–1177.
239. Mazzone PJ, Bach PB, Carey J, et al. Clinical validation of a cell-free DNA fragmentome assay for augmentation of lung cancer early detection. *Cancer Discov*. 2024;14:2224–2242.
240. Boeri M, Zanghì A, Pastorino U. New horizons in lung cancer screening: eligibility criteria, risk models, and emerging challenges. *J Thorac Oncol*. 2025;20:422–424.
241. Moreira AL, Ocampo PSS, Xia Y, et al. A grading system for invasive pulmonary adenocarcinoma: a proposal from the International Association for the Study of Lung Cancer pathology committee. *J Thorac Oncol*. 2020;15:1599–1610.
242. Tang Y, He Z, Zhu Q, Qiao G. The 2011 IASLC/ATS/ERS pulmonary adenocarcinoma classification: a landmark in personalized medicine for lung cancer management. *J Thorac Dis*. 2014;6:S589–S596.
243. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. Introduction to the 2015 World Health Organization classification of tumors of the lung, pleura, thymus, and heart. *J Thorac Oncol*. 2015;10:1240–1242.
244. Travis WD. The 2015 WHO classification of lung tumors. *Pathologe*. 2014;35:188.
245. Nicholson AG, Tsao MS, Beasley MB, et al. The 2021 WHO classification of lung tumors: impact of advances since 2015. *J Thorac Oncol*. 2022;17:362–387.
246. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*. 2018;378:2093–2104.
247. Ernst SM, Aldea M, von der Thüsen JH, et al. Utilizing ctDNA to discover mechanisms of resistance to targeted therapies in patients with metastatic NSCLC: towards more informative trials. *Nat Rev Clin Oncol*. 2025;22:371–378.
248. Gouda MA, Janku F, Wahida A, et al. Liquid biopsy response evaluation criteria in solid tumors (LB-RECIST). *Ann Oncol*. 2024;35:267–275.
249. Pantel K, Alix-Panabières C. Minimal residual disease as a target for liquid biopsy in patients with solid tumours. *Nat Rev Clin Oncol*. 2025;22:65–77.
250. Jamshidi A, Liu MC, Klein EA, et al. Evaluation of cell-free DNA approaches for multi-cancer early detection. *Cancer Cell*. 2022;40:1537–1549.e12.
251. Cheng C, Nguyen TT, Tang M, et al. Immune infiltration in tumor and adjacent non-neoplastic regions Codetermines patient clinical outcomes in early-stage lung cancer. *J Thorac Oncol*. 2023;18:1184–1198.
252. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. *Chest*. 2009;136:260–271.
253. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol*. 2007;2:706–714.
254. Rusch VW, Asamura H, Watanabe H, et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009;4:568–577.
255. Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11:39–51.
256. Detterbeck FC, Woodard GA, Bader AS, et al. The proposed ninth edition TNM classification of lung cancer. *Chest*. 2024;166:882–895.

257. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143:e211S–e250S.
258. De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *Eur J Cardiothorac Surg*. 2014;45:787–798.
259. Gilbert CR, Dust C, Argento AC, et al. Acquisition and handling of endobronchial ultrasound transbronchial needle samples: an American College of Chest Physicians clinical practice guideline. *Chest*. 2025;167:899–909.
260. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. *J Thorac Cardiovasc Surg*. 2011;141:662–670.
261. Lee J, Hong YS, Cho J, et al. Reclassifying the International Association for the Study of Lung Cancer residual tumor classification according to the extent of nodal dissection for NSCLC: one size does not fit all. *J Thorac Oncol*. 2022;17:890–899.
262. Hernandez-Vaquero D, Vigil-Escalera C, Pérez-Méndez I, et al. Survival after thoracoscopic surgery or open lobectomy: systematic review and meta-analysis. *Ann Thorac Surg*. 2021;111:302–313.
263. Gonzalez-Rivas D, Paradela M, Fernandez R, et al. Uniportal video-assisted thoracoscopic lobectomy: two years of experience. *Ann Thorac Surg*. 2013;95:426–432.
264. Ng CSH, Gonzalez-Rivas D, D'Amico TA, Rocco G. Uniportal VATS-a new era in lung cancer surgery. *J Thorac Dis*. 2015;7:1489–1491.
265. Mirza W, Javid A, Khan ME, et al. Robotic-assisted vs video-assisted thoracoscopic lobectomy for non-small cell lung cancer: a GRADE-assessed systematic review and meta-analysis of randomized controlled trials on surgical quality, perioperative, and oncologic outcomes. *J Robot Surg*. 2025;19:651.
266. Mao J, Tang Z, Mi Y, et al. Robotic and video-assisted lobectomy/segmentectomy for non-small cell lung cancer have similar perioperative outcomes: a systematic review and meta-analysis. *Transl Cancer Res*. 2021;10:3883–3893.
267. Law JJ, Harris R, Long H, et al. PLO3.13 survival outcome of VATS compared to open lobectomy for lung cancer: an individual patient data meta-analysis of randomised trials. *J Clin Oncol*. 2025;20:S6–S7.
268. Altorki N, Wang X, Damman B, et al. Lobectomy, segmentectomy, or wedge resection for peripheral clinical T1aN0 non-small cell lung cancer: A post hoc analysis of CALGB 140503 (Alliance). *J Thorac Cardiovasc Surg*. 2024;167:338–347.e1.
269. Hsieh CP, Liu YH, Wu YC, Hsieh MJ, Chao YK. Indocyanine green fluorescence-navigated robotic segmentectomy. *Surg Endosc*. 2017;31:3347–3348.
270. Chen X, Xu H, Qi Q, et al. AI-based chest CT semantic segmentation algorithm enables semi-automated lung cancer surgery planning by recognizing anatomical variants of pulmonary vessels. *Front Oncol*. 2022;12:1021084.
271. Forde PM, Spicer JD, Provencio M, et al. Overall survival with neoadjuvant nivolumab plus chemotherapy in lung cancer. *N Engl J Med*. 2025;393:741–752.
272. Provencio M, Nadal E, González-Larriba JL, et al. Perioperative nivolumab and chemotherapy in Stage III non-small-cell lung cancer. *N Engl J Med*. 2023;389:504–513.
273. Felip E, Altorki N, Zhou C, et al. Five-year survival outcomes with atezolizumab after chemotherapy in resected stage IB-IIIA non-small cell lung cancer (IMpower010): an open-label, randomized, Phase III trial. *J Clin Oncol*. 2025;43:2343–2349.
274. Baumann F, Ambrosi JP, Carbone M. Asbestos is not just asbestos: an unrecognised health hazard. *Lancet Oncol*. 2013;14:576–578.
275. Chen B, Zhan Z, Yu S, et al. Burden of laryngeal cancer attributable to occupational asbestos exposure in China: a comprehensive analysis from 1990 to 2021. *PLoS One*. 2025;20:e0330878.
276. Chen Z, Cai Y, Ou T, et al. Global burden of mesothelioma attributable to occupational asbestos exposure in 204 countries and territories: 1990–2019. *J Cancer Res Clin Oncol*. 2024;150:282.
277. Li WZ, Liang H, Wang W, et al. Global mortality burden of lung cancer and mesothelioma attributable to occupational asbestos exposure and the impact of national asbestos ban policies: a population-based study, 1990–2021. *BMJ Public Health*. 2025;3:e001717.
278. Markowitz S. Asbestos-related lung cancer and malignant mesothelioma of the pleura: selected current issues. *Semin Respir Crit Care Med*. 2015;36:334–346.
279. Seyyedsalehi MS, Boffetta P. Occupational asbestos exposure and risk of esophageal cancer: a systematic review and meta-analysis. *Int J Cancer*. 2024;154:1920–1929.
280. Baumann F, Buck BJ, Metcalf RV, McLaurin BT, Merkler DJ, Carbone M. The presence of asbestos in the natural environment is likely related to mesothelioma in young individuals and women from Southern Nevada. *J Thorac Oncol*. 2015;10:731–737.
281. Carbone M, Baris YI, Bertino P, et al. Erionite exposure in North Dakota and Turkish villages with mesothelioma. *Proc Natl Acad Sci U S A*. 2011;108:13618–13623.
282. Carbone M, Emri S, Dogan AU, et al. A mesothelioma epidemic in Cappadocia: scientific developments and unexpected social outcomes. *Nat Rev Cancer*. 2007;7:147–154.
283. Emri SA. The Cappadocia mesothelioma epidemic: its influence in Turkey and abroad. *Ann Transl Med*. 2017;5:239.
284. Carbone M, Yang H. Molecular pathways: targeting mechanisms of asbestos and erionite carcinogenesis in mesothelioma. *Clin Cancer Res*. 2012;18:598–604.
285. Huang SXL, Partridge MA, Ghandhi SA, Davidson MM, Amundson SA, Hei TK. Mitochondria-derived reactive intermediate species mediate asbestos-induced genotoxicity and oxidative stress-responsive signaling pathways. *Environ Health Perspect*. 2012;120:840–847.

286. Ito F, Yanatori I, Maeda Y, et al. Asbestos conceives Fe(II)-dependent mutagenic stromal milieu through ceaseless macrophage ferroptosis and beta-catenin induction in mesothelium. *Redox Biol*. 2020;36:101616.
287. Yang H, Rivera Z, Jube S, et al. Programmed necrosis induced by asbestos in human mesothelial cells causes high-mobility group box 1 protein release and resultant inflammation. *Proc Natl Acad Sci U S A*. 2010;107:12611–12616.
288. Dostert C, Pétrilli V, Van Bruggen R, Steele C, Mossman BT, Tschopp J. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science*. 2008;320:674–677.
289. Carbone M, Minaai M, Takinishi Y, Pagano I, Yang H. Preventive and therapeutic opportunities: targeting BAP1 and/or HMGB1 pathways to diminish the burden of mesothelioma. *J Transl Med*. 2023;21:749.
290. Xue J, Patergnani S, Giorgi C, et al. Asbestos induces mesothelial cell transformation via HMGB1-driven autophagy. *Proc Natl Acad Sci U S A*. 2020;117:25543–25552.
291. Xue J, Suarez JS, Minaai M, et al. HMGB1 as a therapeutic target in disease. *J Cell Physiol*. 2021;236:3406–3419.
292. Yang H, Bocchetta M, Kroczynska B, et al. TNF-α inhibits asbestos-induced cytotoxicity via a NF-κB-dependent pathway, a possible mechanism for asbestos-induced oncogenesis. *Proc Natl Acad Sci U S A*. 2006;103:10397–10402.
293. Zhang J, Shao S, Han D, et al. High mobility group box 1 promotes the epithelial-to-mesenchymal transition in prostate cancer PC3 cells via the RAGE/NF-κB signaling pathway. *Int J Oncol*. 2018;53:659–671.
294. Qi F, Okimoto G, Jube S, et al. Continuous exposure to chrysotile asbestos can cause transformation of human mesothelial cells via HMGB1 and TNF-alpha signaling. *Am J Pathol*. 2013;183:1654–1666.
295. Suarez JS, Novelli F, Goto K, et al. HMGB1 released by mesothelial cells drives the development of asbestos-induced mesothelioma. *Proc Natl Acad Sci U S A*. 2023;120:e2307999120.
296. Carbone M, Yang H. Mesothelioma: recent highlights. *Ann Transl Med*. 2017;5:238.
297. Yang H, Pellegrini L, Napolitano A, et al. Aspirin delays mesothelioma growth by inhibiting HMGB1-mediated tumor progression. *Cell Death Dis*. 2015;6:e1786.
298. Shukla A, Hillegass JM, MacPherson MB, et al. Blocking of ERK1 and ERK2 sensitizes human mesothelioma cells to doxorubicin. *Mol Cancer*. 2010;9:314.
299. Wu X, Hernandez FV, Wang H, et al. Prospective analysis of mesotheliomas in subjects with BAP1 cancer syndrome: clinical characteristics and epigenetic correlates of disease. *J Thorac Oncol*. 2025;20:1699–1715.
300. Carbone M, Harbour JW, Brugarolas J, et al. Biological mechanisms and clinical significance of BAP1 mutations in human cancer. *Cancer Discov*. 2020;10:1103–1120.
301. Pastorino S, Yoshikawa Y, Pass HI, et al. A subset of mesotheliomas with improved survival occurring in carriers of BAP1 and other germline mutations. *J Clin Oncol*. 2018;36:JCO2018790352.
302. Panou V, Gadiraju M, Wolin A, et al. Frequency of germline mutations in cancer susceptibility genes in malignant mesothelioma. *J Clin Oncol*. 2018;36:2863–2871.
303. Hassan R, Morrow B, Thomas A, et al. Inherited predisposition to malignant mesothelioma and overall survival following platinum chemotherapy. *Proc Natl Acad Sci U S A*. 2019;116:9008–9013.
304. Passiglia F, Righi L, Bironzo P, et al. Niraparib plus Dostarlimab in pleural mesothelioma or non-small cell lung cancer harboring HRR mutations: interim results of the UNITO-001 Phase II prospective trial. *Clin Cancer Res*. 2024;30:959–964.
305. Bononi A, Goto K, Ak G, et al. Heterozygous germline BLM mutations increase susceptibility to asbestos and mesothelioma. *Proc Natl Acad Sci U S A*. 2020;117:33466–33473.
306. Prassas B, Shi Z, Tran H, et al. Estimating cancer penetrance in carriers of BRCA2 pathogenic variants using cancer-specific polygenic scores. *Cancer Med*. 2025;14:e70990.
307. Bononi A, Yang H, Giorgi C, et al. Germline BAP1 mutations induce a Warburg effect. *Cell Death Differ*. 2017;24:1694–1704.
308. Bononi A, Wang Q, Zolondick AA, et al. BAP1 is a novel regulator of HIF-1alpha. *Proc Natl Acad Sci U S A*. 2023;120:e2217840120.
309. Affar EB, Carbone M. BAP1 regulates different mechanisms of cell death. *Cell Death Dis*. 2018;9:1151.
310. Xu Y, Medina CG, Surman DR, et al. Co-targeting BCL-xL with MCL-1 induces lethal mitochondrial dysfunction in diffuse mesothelioma. *Mol Cancer Ther*. 2025:OF1–OF13.
311. Carbone M, Gaudino G, Yang H. Recent insights emerging from malignant mesothelioma genome sequencing. *J Thorac Oncol*. 2015;10:409–411.
312. Louw A, Panou V, Szejniuk WM, et al. BAP1 loss by immunohistochemistry predicts improved survival to first-line platinum and pemetrexed chemotherapy for patients with pleural mesothelioma: a validation study. *J Thorac Oncol*. 2022;17:921–930.
313. Hung YP, Dong F, Watkins JC, et al. Identification of ALK rearrangements in malignant peritoneal mesothelioma. *JAMA Oncol*. 2018;4:235–238.
314. Benzerdjeb N, Dartigues P, Kepenekian V, et al. Update on gene fusions and the emerging clinicopathological landscape of peritoneal and pleural mesotheliomas and other neoplasms. *ESMO Open*. 2024;9:103644.
315. Hung YP, Chirieac LR. Molecular and immunohistochemical testing in mesothelioma and other mesothelial lesions. *Arch Pathol Lab Med*. 2024;148:e77–e89.
316. Pass HI, Lott D, Lonardo F, et al. Asbestos exposure, pleural mesothelioma, and serum osteopontin levels. *N Engl J Med*. 2005;353:1564–1573.
317. Scherpereel A, Grigoriu B, Conti M, et al. Soluble mesothelin-related peptides in the diagnosis of malignant pleural mesothelioma. *Am J Respir Crit Care Med*. 2006;173:1155–1160.

318. Beyer HL, Geschwindt RD, Glover CL, et al. MESOMARK: a potential test for malignant pleural mesothelioma. *Clin Chem*. 2007;53:666–672.
319. Pass HI, Goparaju C, Ivanov S, et al. hsa-miR-29c* is linked to the prognosis of malignant pleural mesothelioma. *Cancer Res*. 2010;70:1916–1924.
320. Bott M, Brevet M, Taylor BS, et al. The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma. *Nat Genet*. 2011;43:668–672.
321. Pass HI, Levin SM, Harbut MR, et al. Fibulin-3 as a blood and effusion biomarker for pleural mesothelioma. *N Engl J Med*. 2012;367:1417–1427.
322. Tsim S, Alexander L, Kelly C, et al. Serum proteomics and plasma Fibulin-3 in differentiation of mesothelioma from asbestos-exposed controls and patients with other pleural diseases. *J Thorac Oncol*. 2021;16:1705–1717.
323. Johnen G, Burek K, Raiko I, et al. Prediagnostic detection of mesothelioma by circulating calretinin and mesothelin - a case-control comparison nested into a prospective cohort of asbestos-exposed workers. *Sci Rep*. 2018;8:14321.
324. Jiménez-Ramírez C, Casjens S, Juárez-Pérez CA, et al. Mesothelin, calretinin, and megakaryocyte potentiating factor as biomarkers of malignant pleural mesothelioma. *Lung*. 2019;197:641–649.
325. Casjens S, Johnen G, Raiko I, et al. Re-evaluation of potential predictors of calretinin and mesothelin in a population-based cohort study using assays for the routine application in clinical medicine. *BMJ Open*. 2021;11:e039079.
326. Klotz LV, Casjens S, Johnen G, et al. Combination of calretinin, MALAT1, and GAS5 as a potential prognostic biomarker to predict disease progression in surgically treated mesothelioma patients. *Lung Cancer*. 2024;192:107802.
327. Churg A, Roggli V, Galateau-Salle F. Tumours of the pleura: mesothelial tumours. In: Travis WD, BE HCC, Muller-Hermelink HK, eds. *World Health Organization Classification of Tumours, Pathology and Genetics: Tumours of the Lung, Pleura, Thymus and Heart*. Lyon, France: IARC; 2004:128–136.
328. Le Stang N, Burke L, Blaizot G, et al. Differential diagnosis of epithelioid malignant mesothelioma with lung and breast pleural metastasis: a systematic review compared with a standardized panel of antibodies-A new proposal that may influence pathologic practice. *Arch Pathol Lab Med*. 2020;144:446–456.
329. Galateau-Sallé F, Vignaud JM, Burke L, et al. Well-differentiated papillary mesothelioma of the pleura: a series of 24 cases. *Am J Surg Pathol*. 2004;28:534–540.
330. Yoshikawa Y, Sato A, Tsujimura T, et al. Frequent inactivation of the BAP1 gene in epithelioid-type malignant mesothelioma. *Cancer Sci*. 2012;103:868–874.
331. Dacic S, Kothmaier H, Land S, et al. Prognostic significance of p16/cdkn2a loss in pleural malignant mesotheliomas. *Virchows Arch*. 2008;453:627–635.
332. Sato T, Sekido Y. NF2/merlin inactivation and potential therapeutic targets in mesothelioma. *Int J Mol Sci*. 2018;19:988.
333. Galateau-Salle F, Churg A, Roggli V, Travis WD; World Health Organization Committee for Tumors of the Pleura. The 2015 World Health Organization classification of tumors of the pleura: advances since the 2004 classification. *J Thorac Oncol*. 2016;11:142–154.
334. Churg A, Galateau-Salle F. The separation of benign and malignant mesothelial proliferations. *Arch Pathol Lab Med*. 2012;136:1217–1226.
335. Galateau-Salle F, Le Stang N, Astoul P, et al. Malignant mesothelioma of the pleura with pleomorphic features: a series of 44 cases. *Lab Investig*. 75 VARICK ST: NATURE PUBLISHING GROUP, 9TH FLR, NEW YORK, NY 10013-1917 USA. 2010;90, 402A–402A.
336. Kadota K, Suzuki K, Sima CS, Rusch VW, Adusumilli PS, Travis WD. Pleomorphic epithelioid diffuse malignant pleural mesothelioma: a clinicopathological review and conceptual proposal to reclassify as biphasic or sarcomatoid mesothelioma. *J Thorac Oncol*. 2011;6:896–904.
337. Roy S, Galateau-Sallé F, Le Stang N, et al. Molecular characterization of pleomorphic mesothelioma: a multi-institutional study. *Mod Pathol*. 2022;35:82–86.
338. Huang SC, Li CF, Kao YC, et al. The clinicopathological significance of NAB2-STAT6 gene fusions in 52 cases of intrathoracic solitary fibrous tumors. *Cancer Med*. 2016;5:159–168.
339. Anderson T, Zhang L, Hameed M, Rusch V, Travis WD, Antonescu CR. Thoracic epithelioid malignant vascular tumors: a clinicopathologic study of 52 cases with emphasis on pathologic grading and molecular studies of WWTR1-CAMTA1 fusions. *Am J Surg Pathol*. 2015;39:132–139.
340. Wilson RW, Gallateau-Salle F, Moran CA. Desmoid tumors of the pleura: a clinicopathologic mimic of localized fibrous tumor. *Mod Pathol*. 1999;12:9–14.
341. An J, Woo HY, Lee Y, Kim HS, Jeong J, Kim SK. Clinicopathological features of 70 desmoid-type fibromatoses confirmed by beta-catenin immunohistochemical staining and CTNNB1 mutation analysis. *PLoS One*. 2021;16:e0250619.
342. Hmeljak J, Sanchez-Vega F, Hoadley KA, et al. Integrative molecular characterization of malignant pleural mesothelioma. *Cancer Discov*. 2018;8:1548–1565.
343. Alcala N, Mangiante L, Le-Stang N, et al. Redefining malignant pleural mesothelioma types as a continuum uncovers immune-vascular interactions. *EBiomedicine*. 2019;48:191–202.
344. Mangiante L, Alcala N, Sexton-Oates A, et al. Multiomic analysis of malignant pleural mesothelioma identifies molecular axes and specialized tumor profiles driving intertumor heterogeneity. *Nat Genet*. 2023;55:607–618.
345. Dagogo-Jack I, Madison RW, Lennerz JK, et al. Molecular characterization of mesothelioma: impact of histologic type and site of origin on molecular landscape. *JCO Precis Oncol*. 2022;6:e2100422.
346. Hiltbrunner S, Fleischmann Z, Sokol ES, Zoche M, Felley-Bosco E, Curioni-Fontecedro A. Genomic landscape of pleural and peritoneal mesothelioma tumours. *Br J Cancer*. 2022;127:1997–2005.

347. Husain AN, Chapel DB, Attanoos R, et al. Guidelines for pathologic diagnosis of mesothelioma: 2023 update of the consensus statement from the international mesothelioma interest group. *Arch Pathol Lab Med*. 2024;148:1251–1271.
348. Carbone M, Pass HI, Ak G, et al. Medical and surgical care of patients with mesothelioma and their relatives carrying germline BAP1 mutations. *J Thorac Oncol*. 2022;17:873–889.
349. Board W. CoTE. *Thoracic Tumours*. Lyon, France: IARC; 2021.
350. Sauter JL, Dacic S, Galateau-Salle F, et al. The 2021 WHO classification of tumors of the pleura: advances since the 2015 classification. *J Thorac Oncol*. 2022;17:608–622.
351. Churg A, Galateau-Salle F. Well differentiated papillary mesothelial tumor: a new name and new problems. *Mod Pathol*. 2022;35:1327–1333.
352. Galateau-Salle F, Hamilton T, MacNeill A, et al. Mesothelioma in situ mimicking well-differentiated papillary mesothelial tumor. *Am J Surg Pathol*. 2023;47:611–617.
353. Stevers M, Rabban JT, Garg K, et al. Well-differentiated papillary mesothelioma of the peritoneum is genetically defined by mutually exclusive mutations in TRAF7 and CDC42. *Mod Pathol*. 2019;32:88–99.
354. Churg A, Galateau-Salle F, Roden AC, et al. Malignant mesothelioma in situ: morphologic features and clinical outcome. *Mod Pathol*. 2020;33:297–302.
355. Churg A, Nabeshima K, Ali G, Bruno R, Fernandez-Cuesta L, Galateau-Salle F. Highlights of the 14th international mesothelioma interest group meeting: pathologic separation of benign from malignant mesothelial proliferations and histologic/molecular analysis of malignant mesothelioma subtypes. *Lung Cancer*. 2018;124:95–101.
356. Dacic S, Roy S, Lyons MA, Von Der Thusen JH, Galateau-Salle F, Churg A. Whole exome sequencing reveals BAP1 somatic abnormalities in mesothelioma in situ. *Lung Cancer*. 2020;149:1–4.
357. Dacic S. Pleural mesothelioma classification-update and challenges. *Mod Pathol*. 2022;35:51–56.
358. Shia J, Qin J, Erlandson RA, et al. Malignant mesothelioma with a pronounced myxoid stroma: a clinical and pathological evaluation of 19 cases. *Virchows Arch*. 2005;447:828–834.
359. Galateau Salle F, Le Stang N, Tirode F, et al. Comprehensive molecular and pathologic evaluation of transitional mesothelioma assisted by deep learning approach: a multi-institutional study of the international mesothelioma panel from the MESOPATH reference center. *J Thorac Oncol*. 2020;15:1037–1053.
360. Dacic S, Le Stang N, Husain A, et al. Interobserver variation in the assessment of the sarcomatoid and transitional components in biphasic mesotheliomas. *Mod Pathol*. 2020;33:255–262.
361. Churg A, Le Stang N, Dacic S, et al. Solid papillary mesothelial tumor. *Mod Pathol*. 2022;35:69–76.
362. Chapel DB, Schulte JJ, Berg K, et al. MTAP immunohistochemistry is an accurate and reproducible surrogate for CDKN2A fluorescence in situ hybridization in diagnosis of malignant pleural mesothelioma. *Mod Pathol*. 2020;33:245–254.
363. Hida T, Hamasaki M, Matsumoto S, et al. Immunohistochemical detection of MTAP and BAP1 protein loss for mesothelioma diagnosis: comparison with 9p21 FISH and BAP1 immunohistochemistry. *Lung Cancer*. 2017;104:98–105.
364. Chapel DB, Hornick JL, Barlow J, Bueno R, Sholl LM. Clinical and molecular validation of BAP1, MTAP, P53, and Merlin immunohistochemistry in diagnosis of pleural mesothelioma. *Mod Pathol*. 2022;35:1383–1397.
365. Berg KB, Dacic S, Miller C, Cheung S, Churg A. Utility of methylthioadenosine phosphorylase compared with BAP1 immunohistochemistry, and CDKN2A and NF2 fluorescence in situ hybridization in separating reactive mesothelial proliferations from epithelioid malignant mesotheliomas. *Arch Pathol Lab Med*. 2018;142:1549–1553.
366. Szlosarek PW, Creelan BC, Sarkodie T, et al. Pegargiminase plus first-line chemotherapy in patients with nonepithelioid pleural mesothelioma: the ATOMIC-Meso randomized clinical trial. *JAMA Oncol*. 2024;10:475–483.
367. Chu Q, Perrone F, Greillier L, et al. Pembrolizumab plus chemotherapy versus chemotherapy in untreated advanced pleural mesothelioma in Canada, Italy, and France: a phase 3, open-label, randomised controlled trial. *Lancet*. 2023;402:2295–2306.
368. Kerrigan K, Jo Y, Chipman J, et al. A real-world analysis of the use of systemic therapy in malignant pleural mesothelioma and the differential impacts on overall survival by practice pattern. *JTO Clin Res Rep*. 2022;3:100280.
369. McNamee N, Harvey C, Gray L, et al. Brief report: real-world toxicity and survival of combination immunotherapy in pleural mesothelioma-RIOMeso. *J Thorac Oncol*. 2024;19:636–642.
370. Engstrom LD, Aranda R, Waters L, et al. MRTX1719 is an MTA-cooperative PRMT5 inhibitor that exhibits synthetic lethality in preclinical models and patients with MTAP-deleted cancer. *Cancer Discov*. 2023;13:2412–2431.
371. Haas AR, Tanyi JL, O'Hara MH, et al. Phase I study of lentiviral-transduced chimeric antigen receptor-modified T cells recognizing mesothelin in advanced solid cancers. *Mol Ther*. 2019;27:1919–1929.
372. Adusumilli PS, Zauderer MG, Rivière I, et al. A Phase I trial of regional mesothelin-targeted CAR T-cell therapy in patients with malignant pleural disease, in combination with the anti-PD-1 agent pembrolizumab. *Cancer Discov*. 2021;11:2748–2763.
373. Hassan R, Butler M, O'Cearbhaill RE, et al. Mesothelin-targeting T cell receptor fusion construct cell therapy in refractory solid tumors: phase 1/2 trial interim results. *Nat Med*. 2023;29:2099–2109.
374. Patel KK, Tariveranmoshabad M, Kadu S, Shobaki N, June C. From concept to cure: the evolution of CAR-T cell therapy. *Mol Ther*. 2025;33:2123–2140.
375. Aerts JG, Belderbos R, Baas P, et al. Dendritic cells loaded with allogeneic tumour cell lysate plus best

supportive care versus best supportive care alone in patients with pleural mesothelioma as maintenance therapy after chemotherapy (DENIM): a multicentre, open-label, randomised, phase 2/3 study. *Lancet Oncol*. 2024;25:865–878.
376. Ruiz Pérez M, Vandenabeele P, Tougaard P. The thymus road to a T cell: migration, selection, and atrophy. *Front Immunol*. 2024;15:1443910.
377. Marx A, Yamada Y, Simon-Keller K, et al. Thymus and autoimmunity. *Semin Immunopathol*. 2021;43:45–64.
378. Marx A, Chan JKC, Chalabreysse L, et al. The 2021 WHO classification of tumors of the thymus and mediastinum: what is new in thymic epithelial, germ cell, and mesenchymal tumors? *J Thorac Oncol*. 2022;17:200–213.
379. Radovich M, Pickering CR, Felau I, et al. The integrated genomic landscape of thymic epithelial tumors. *Cancer Cell*. 2018;33:244–258.e10.
380. Yamada Y, Simon-Keller K, Belharazem-Vitacolonnna D, et al. A tuft cell-like signature is highly prevalent in thymic squamous cell carcinoma and delineates new molecular subsets among the major lung cancer histotypes. *J Thorac Oncol*. 2021;16:1003–1016.
381. Liu X, Wang C, Huang Y, et al. Abnormal cellular populations shape thymic epithelial tumor heterogeneity and anti-tumor by blocking metabolic interactions in organoids. *Adv Sci (Weinh)*. 2024;11:e2406653.
382. Xin Z, Lin M, Hao Z, et al. The immune landscape of human thymic epithelial tumors. *Nat Commun*. 2022;13:5463.
383. Yasumizu Y, Kinoshita M, Zhang MJ, et al. Spatial transcriptomics elucidates medulla niche supporting germinal center response in myasthenia gravis-associated thymoma. *Cell Rep*. 2024;43:114677.
384. Yayon N, Kedlian VR, Boehme L, et al. A spatial human thymus cell atlas mapped to a continuous tissue axis. *Nature*. 2024;635:708–718.
385. Girard N. Therapeutic management of metastatic thymoma and thymic carcinoma. *Curr Oncol Rep*. 2025;27:906–914.
386. Rajan A, Sivapiromrat AK, McAdams MJ. Immunotherapy for thymomas and thymic carcinomas: current status and future directions. *Cancers (Basel)*. 2024;16:1369.
387. Maniar R, Loehrer PJ Sr. Understanding the landscape of immunotherapy in thymic epithelial tumors. *Cancer*. 2023;129:1162–1172.
388. Mammen AL, Rajan A, Pak K, et al. Pre-existing anti-acetylcholine receptor autoantibodies and B cell lymphopaenia are associated with the development of myositis in patients with thymoma treated with avelumab, an immune checkpoint inhibitor targeting programmed death-ligand 1. *Ann Rheum Dis*. 2019;78:150–152.
389. Ferré EMN, Break TJ, Burbelo PD, et al. Lymphocyte-driven regional immunopathology in pneumonitis caused by impaired central immune tolerance. *Sci Transl Med*. 2019;11:eaav5597.
390. Ferré EMN, Nichols-Vinueza DX, Rosen LB, et al. Lymphocyte-directed immunomodulation remits thymoma-associated autoimmune pneumonitis. *J Clin Immunol*. 2024;44:156.
391. Travis W, Brambilla E, Müller-Hermelink H. *WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon, France: IARC Press; 2015.
392. Verghese ET, den Bakker MA, Campbell A, et al. Interobserver variation in the classification of thymic tumours–a multicentre study using the WHO classification system. *Histopathology*. 2008;53:218–223.
393. Detterbeck FC. The creation of the international thymic malignancies interest group as a model for rare diseases. *Am Soc Clin Oncol Educ Book*. 2012:471–474.
394. Marx A, Ströbel P, Badve SS, et al. ITMIG consensus statement on the use of the WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting. *J Thorac Oncol*. 2014;9:596–611.
395. Angirekula M, Chang SY, Jenkins SM, et al. CD117, BAP1, MTAP, and TdT is a useful immunohistochemical panel to distinguish thymoma from thymic carcinoma. *Cancers (Basel)*. 2022;14:2299.
396. Molina TJ, Roden AC, Szolkowska M, et al. International reproducibility study of thymic epithelial tumors staging: pT stage is an issue. Proposals for improvement. A RYTHMIC/ITMIG study. *Lung Cancer*. 2024;189:107479.
397. Ruffini E, Huang J, Cilento V, et al. The International Association for the Study of Lung Cancer thymic epithelial tumors staging project: proposal for a stage classification for the forthcoming (ninth) edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2023;18:1655–1671.