Introduction
Since the reunification of the Federal Republic of Germany with the German Democratic Republic in 1990, Germany, situated in middle Europe, has become the most populous country in Europe with 83.5 million inhabitants. With a gross domestic product of 3.8 trillion U.S. dollars (2020), it is the largest national economy in the European Union and the fourth worldwide. As a result of the political reorganization after World War II, a federal organization has been adopted, delegating a large number of tasks to each of the 16 federal states, thereby enabling a more regionalized approach (e.g., education or the health system). Health insurance is mandatory for all citizens and statutory insurance is the backbone for roughly 90% of the population. However, either as additional or for distinct occupational groups (e.g., civil servants, self-employed workers, or higher income groups), alternative private insurances also exist. Expenditures of the statutory health care system are financed by means of fees paid equally by employees and employers and account for 12% of the gross domestic product per capita and 4.900 € per year. Thus, social
solidarity guarantees equal access to health care resources independently from income.

**Epidemiology and Smoking Features**

Since 2010, the Robert-Koch-Institut, a federal authority in charge of disease recognition, prevention, and control, collects and regularly publishes national cancer statistics using anonymized data from the individual federal cancer registries. Cancer is the second most frequent cause of death, accounting for 25% of all deaths. In men, lung cancer ranks second after cardiovascular disease, accounting for 6.5% of all-cause mortality. With an age-standardized incidence rate of 32.7 and 52.1 (per 100,000) in women and men, respectively, lung cancer ranks third in women and second in men (accounting for 9.4% and 13.3% of all newly diagnosed cancers, respectively). In 2018, 57,000 newly diagnosed lung cancers were encountered. The median age at cancer diagnosis is 69 (women) and 70 years (men), respectively, 52% of all patients present with stage IV. Because of long-term changes in smoking habits, incidence rates in women and men have converged since the 1990s. Currently, every fifth woman (20.8%) and every fourth man (27.0%) regularly smokes. However, following stricter regulations in advertising and broad information campaigns, smoking incidence in adolescents markedly decreased from 28% in 2001 to 7% in 2018. With regard to mortality, lung cancer is the most frequent cancer-related cause of death in men (22.8%), and the second most frequent in women (15.8%). Because of an unchanged low 5-year survival rate (22% in women, 17% in men), the median age at death is 71 years.

**Lung Cancer Screening**

After a significant reduction of lung cancer-specific mortality by performing systematic low-dose computed tomography (CT) scan has been confirmed in various randomized trials, a prospective risk benefit evaluation has been performed by the Federal Office for Radiation Protection and the Institute for Quality and Efficiency in Health Care. In the preparation for potential approval and reimbursement of lung cancer screening by German health care providers, both committees stated a significant value of low-dose CT screening in clearly defined risk populations, which overrules the potential health risk of radiation exposure. In addition, a number of quality-reassuring conditions have been defined, including clear clinical risk criteria, a standardized radiologic nodule classification, controlled diagnostics, and therapeutic pathways together with a national registry of screening data. An implementation of lung cancer screening in the German health care system is expected in the upcoming years. In preparation, the HANSE trial, a prospective holistic trial, is investigating the feasibility of controlled lung cancer screening, screening for relevant cardiac and pulmonary comorbidities together with assessment of potential predictive biomarkers in 5000 high-risk candidates in the Northern German region (NCT04913155). The screening is facilitated by a mobile CT truck, which is rotating among three approved lung cancer centers. In addition, Germany is participating with two sites in the European "4 in the Lung Run – Study", a prospective trial, which is investigating several innovative modifications of screening including personalized recruitment approaches, individualized screening intervals, improved radiological criteria, and others (H2020-SC1-BHC-2018-2020).

**Diagnosis**

Diagnosis and staging follow the national evidence- and consensus-based guidelines, first published in 2006, updated in 2010 and 2018, and, again, currently under revision. The German Respiratory Society (Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V.) and German Cancer Society (Deutsche Krebsgesellschaft e.V. [DKG]) act as central coordinators and are guided by the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.), a national network founded in 1962, combining 175 scientific member societies from all medical specialties. A representative committee (integrating all relevant medical associations and patient representatives) conducts a systematic review and synthesis of evidence and develops a structured consensus to generate high quality, up-to-date guidelines. However, because of the rapidly evolving field of diagnostic and therapeutic options in lung cancer, this time-proven but also time-consuming approach strains the bounds of practical feasibility. Thus, alternative guidelines—for example, the internet-based onkopedia.de platform—offers more rapidly updated recommendations. All newly diagnosed patients with lung cancer should be preferentially treated in one of the 79 certified lung cancer centers accredited by the DKG (Fig. 1).

**Pathology**

After the histology-based establishment of the diagnosis of lung cancer, predictive molecular profiling is
currently recommended for all patients with NSCLC of either clinical stage IV, unresectable stage III, or patients not suitable for chemoradiation or after disease relapse. Recommended molecular diagnostics include testing for activating alterations in ALK, BRAF, EGFR, HER2, KRAS, MET, NTRK, RET, and ROS1, although the test frequencies regarding the different molecular alterations vary significantly (Fig. 2). Most recently, optional EGFR testing of earlier stages of NSCLC has been added to the syllabus. Historically, molecular testing of tumors has been made available in more than 50 Departments of Pathology and Molecular Medicine in Germany over the past two decades without a centralized steering effort, quite in contrast to other European countries such as France and the United Kingdom. Nevertheless, to surmount the problematic reimbursement of testing of hospitalized patients and to establish better comparable standards of quality and panel completeness, a National Network for Genomic Medicine (nNGM) has been founded in 2018 driven by an initiative from the Lung Cancer Group of the University of Cologne (see Fig. 1 for all nNGM sites and Fig. 3 for the distribution of [actionable] genomic alterations in 25,730 consecutively genotyped patients with stage IIIB/IV NSCLC from the nNGM). All 23 currently participating centers have to fulfill a stringent catalog of criteria for participation, including the mandatory use of a standardized and regularly updated gene panel, centralized quality control of next-generation sequencing, and harmonized therapy recommendations. Costs are fully reimbursed even for hospitalized patients at primary diagnosis and in the relapse of the disease for rebiopsies, independent from histologic type. In Northwestern Germany, the NorthEast-West Lung network represents a regional network with a comparable approach and structure. In addition, the German Network for Personalized Medicine (Deutsches Netzwerk für personalisierte Medizin) is currently expanding the scope of molecular testing to other solid organ tumors.

Treatment

After an initiative from the DKG, dedicated lung cancer centers have been established since 2009. Institutions willing to be certified must prove a minimum number of quantitative (e.g., primary cases, resections) and qualitative indicators (e.g., 30-d postoperative mortality, percentage of patients with ALK, EGFR, programmed death-ligand 1 testing). With regard to general oncologic care in Germany, the German National Cancer Plan designates organ cancer centers (like lung cancer

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**Figure 1.** (A) Geographic position of Germany in Western Europe and (B) locations of certified lung cancer centers and sites of the National Network Genomic Medicine (n > 1 in one city not marked separately).
centers), oncology centers, and comprehensive cancer centers.15,16 Currently, 64 lung cancer centers at 79 institutions have been certified nationwide, accounting for 40% of all newly diagnosed patients (2020).17 For historical reasons, dedicated respiratory hospitals coming from tuberculosis units play an important role in thoracic oncology in Germany.

**Surgery**

Surgical treatment for lung cancer is predominantly provided by specialized departments of general thoracic surgery, often located at traditional lung hospitals. In 2018, a total of 12,067 anatomical lung resections were performed for the diagnosis of lung cancer (International Classification of Diseases 10: C34), 55% of them at 50 high-volume centers, performing at least 75 resections per year. The remaining 45% of resections were provided by another 260 institutions, most departments of general or visceral surgery. In high-volume centers, lung cancer operations are regularly performed by board-certified general thoracic surgeons; in low-volume centers, however, mostly by general or visceral surgeons. Cardiothoracic surgery does not play a significant role in the care of patients with lung cancer in Germany. The specialist examination for general thoracic surgery was introduced in Germany in 1991. As of December 31, 2020, 373 board-certified general thoracic surgeons are actively involved in patient care. The association between hospital volume and survival for oncological diseases has been discussed intensively in recent years. At the same time, the mandatory diagnosis-related groups (DRG) documentation of all hospital treatments enabled a comprehensive and nationwide evaluation of the hospital discharge data. Using this data, recent retrospective cohort studies have reported that high procedure volume is strongly associated with improved survival after lung cancer surgery. In hospitals with fewer than 25 procedures per year, in-hospital mortality was almost twice as high as in high-volume centers with at least 75 resections per year.18,19

After a comprehensive evaluation of the available evidence by the German Institute for Quality and Efficiency in Healthcare and the Federal Joint Committee (Gemeinsame Bundesausschuss), the Federal Joint Committee defines which specific healthcare services are paid for by statutory health insurance, which finally specified minimum quantities for lung cancer surgeries in Germany. From January 1, 2025, a minimum volume of 75 resections per year and hospital site will apply for lung cancer operations in Germany.20

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**Figure 2.** Evolution of testing rates for PD-L1 staining and (actionable) genomic alterations in stage IV NSCLC (nonsquamous histologic type displayed left, squamous histologic type displayed right) at diagnosis from 2016 until 2021 (preliminary). Data from the nationwide CRISP registry (NCT02622581). PD-L1, programmed death-ligand 1.
Radiation Oncology

Radiation Oncology is a well-available resource in the German health system. According to the German Society for Radiation Oncology, there are currently more than 700 institutions providing radiotherapy services in Germany, of whom 65 are part of certified lung cancer centers, in which the availability of radiotherapy is mandatory. In total, 200,000 radiotherapy treatment series for malignant diseases are applied annually in German centers. In 2020, a median of 123 patients with lung cancer (range 53–514) underwent radiotherapy in certified centers respectively. However, patterns of care are rather heterogeneous—for example, with regard to the rates of primary chemoradiation in stage III NSCLC (applied to a median of 45% but with a wide range of 14%–85%). In this context, the consensus process of the guideline helps to provide evidence-based guidance for interdisciplinary discussion. High-precision radiotherapy, for example, for stereotactic body radiation therapy and safe intensity-modulated radiation therapy/image-guided radiation therapy technology, is widely available. The working group for high-precision radiotherapy within the German Society for Radiation Oncology published a series of recommendations and database analyses, providing high standardization and increasing outcome quality. For patients with locally advanced lung cancer, a large number of radiotherapy centers are motivated to follow the standards of national and international protocols within clinical trials. In recent years, the EsPaTue trial on multimodal treatment and the PET-Plan trial on chemoradiation for locally advanced NSCLC were initiated in Germany. Both trials found an overall outcome quality comparable to other international series. Furthermore, close cooperation between radiation oncologists and medical oncologists/pneumologists is well established for concomitant or sequential systemic treatment, for example, with regard to the new standard of adjuvant immunotherapy.

Systemic Treatment

With the identification of genetic alterations (e.g., EGFR, ALK, ROS1, MET, RET, BRAF, and KRAS) NSCLC has become a paradigmatic molecular disease. Molecularly
driven metastatic NSCLC accounts for approximately 40% of all cases, and, with the exception of KRAS, targeted therapy has become the standard of care in the first-line setting (Fig. 4B). Furthermore, improved disease-free survival for EGFR-mutant NSCLC after surgery in a curative approach led to the approval of

Figure 4. (A) Current treatment recommendations according to the S3 consensus guideline and Onkopedia guideline for NSCLC, stage IV without targetable mutations (only reimbursable substances listed). Green boxes indicate first-line options, orange boxes second-line, and gray boxes third-line options. (B) Current treatment recommendations according to the S3 consensus guideline and Onkopedia guideline for NSCLC, stage IV with targetable mutations (only reimbursable substances listed). Green boxes indicate first-line and orange boxes second-line options. *Cemiplimab has, furthermore, been approved for nonresectable stage III, not suitable for chemoradiation. Cis, cisplatin; ECOG, Eastern Cooperative Oncology Group; IC, immune cell; IO, immuno-oncologic treatment; nab, nanoparticle albumin-bound; NSq, nonsquamous; PD-L1, Programmed death-ligand 1; PS, performance status; Sq, squamous; TC, tumor cell; VEGF, vascular endothelial growth factor.
osimertinib in the adjuvant setting. Treatment with immune checkpoint inhibitors (ICIs), either as monotherapy (programmed death-ligand 1 [PD-L1] ≥50%) or in combination with chemotherapy (irrespective of PD-L1 expression) is the current standard of care in stage IV without targetable genomic alterations (Fig. 4A). Furthermore, ICI strategies have been adopted in the curative setting after chemoradiation for PD-L1–positive NSCLC (defined as PD-L1 expression ≥1% on the tumor cells) and will most likely be approved in the adjuvant and neoadjuvant setting for resectable NSCLC in the near future, paving the way for reflex broad molecular testing in NSCLC irrespective from the stage. In SCLC, the addition of ICI to standard chemotherapy is highly effective in patients with extensive-stage IV disease. As the systemic treatment in most patients with advanced disease is palliative and symptom burden is often high, patients’ quality of life should be a priority in lung cancer.

Figure 4. (continued).

Figure 5. OS in stage IV NSCLC (and stage IIIB/C without local curative treatment) in patients without actionable genomic alterations from the nationwide CRISP registry (NCT02622581). CI, confidence interval; OS, overall survival.
management, along with improving response rates, progression-free, and overall survival.

The prospective, multicenter, longitudinal CRISP registry platform (A10-TRK0315) was initiated in 2015 (NCT02622581) to create a representative database to study patients with lung cancer in Germany. CRISP collects data on routine care of patients with NSCLC and SCLC (all stages), treated in certified cancer centers, university and community hospitals, and office-based practices. Key features are the multicenter design including currently over 180 sites, the long patient follow-up (until death), and the large size of the study cohort (currently >9800 patients, recruitment ongoing), resulting in a high number of quality-controlled, prospectively collected data sets (see Fig. 5 for overall survival of the CRISP NSCLC wild-type stage IV cohort). On the one hand, published data from CRISP reveal evidence-based guideline-concordant treatment in the real-world setting with first survival data comparable to clinical trials, on the other hand, the frequency of testing rates for molecular markers needs to be improved (Fig. 2).

Conclusions
Lung cancer causes significant morbidity, mortality, and socioeconomic costs in Germany. However, restrictions in advertising and information campaigns led to a marked decrease in smoking in adolescents over the past decades. Treatment of patients is highly standardized and follows consensus-based national guidelines. Dedicated lung cancer centers guarantee a continuously high quality of care with regard to staging and multimodal treatments. Albeit molecular profiling of NSCLC without a curative treatment option is well established, testing rates in everyday clinical practice still need to be improved, especially given the recent and continuous approvals of new drugs for oncogenic-addicted NSCLC. However, a more standardized national approach for implementing personalized lung cancer care within the National Network Genomic Medicine aims at both implementing personalized lung cancer care within the Federal Office of Statistics. Statistical yearbook 2019, section: health. https://www.destatis.de/DE/Themen/Querschnitt/Jahrbuch/jb-gesundheit.pdf?__blob=publicationFile. Accessed February 2, 2022.

References

CRediT Authorship Contribution Statement
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