

Lung Cancer in South Africa



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Background and Epidemiology

South Africa is the southernmost country in Africa. In 2018, the population of South Africa was estimated at more than 57 million. South Africa is a very diverse and multicultural country that consists of different racial groups (Fig. 1). These demographics account for the differences in genetic, ethnic, and epidemiological risk factors for lung cancer. South Africa consists of nine provinces, and the incidence of lung cancer and treatment options available differ between provinces (Fig. 2).

South Africa is classified as an upper middle-income economy. However, there is inequality, with contrasting areas of wealth and poverty and a mixture of rural and suburban areas. Socioeconomic status also contributes to the different risk profiles in various population groups.

The National Cancer Registry was initially established in 1986 to provide statistics on the incidence of cancer in South Africa. It is a pathology-based system and was last updated in 2014. The incidence of lung cancer in South Africa is probably underreported.

The South African health care system is divided into public (83%) and private (17%) sectors. In rural areas, mostly basic primary health care is provided. Patients with lung cancer are referred to a tertiary institution for management. The public health care system is understaffed and there is a lack of resources. In contrast, the private sector is modern and provides state-of-the-art treatment. A high proportion of doctors (including oncologists) work in the private sector.

Patients in the public sector often present with advanced disease. Possible reasons include lack of education, difficult access, and delayed referrals.

The private sector is structured according to a tier system based on the monthly contribution to the medical aid scheme or insurance by the patients and their employers. Patients on different tiers do not have the same access to treatments.

Screening, Smoking Prevalence, and Smoking Laws

There are no official screening programs for lung cancer in South Africa. Nonprofit organizations such as

the Cancer Association of South Africa assist with providing support for cancer research, education of the public regarding symptoms, early detection, screening, and risk reduction.

It is estimated that 26.5% of adult males in South Africa are smokers and 5.5% are female. The data on smoking prevalence are outdated and probably underestimated.¹ The prevalence of snuff use (the predominant form of tobacco use among black South African women) has been reported to range from 6% to 16%.^{1,2}

The WHO has published a guide for its Africa region pertaining to the enforcement and compliance of tobacco control legislation; the guide includes a specific chapter for South Africa. The first regulations were initially implemented in 1993, with amendments over time. The guide includes regulations regarding manufacturing, bans on marketing and sponsorship, as well as regulations on smoking in public places. Challenges in enforcing these laws lie with the unwillingness to investigate or prosecute noncompliant cases, which stems from South Africa having a high rate of violent crime, as a result of which, tobacco laws are regarded as low-priority.³

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Disclosure: Dr. Rapoport reports grants and personal fees from MSD, AstraZeneca, Roche South Africa, and BMS South Africa outside the submitted work. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864

<https://doi.org/10.1016/j.jtho.2019.06.032>

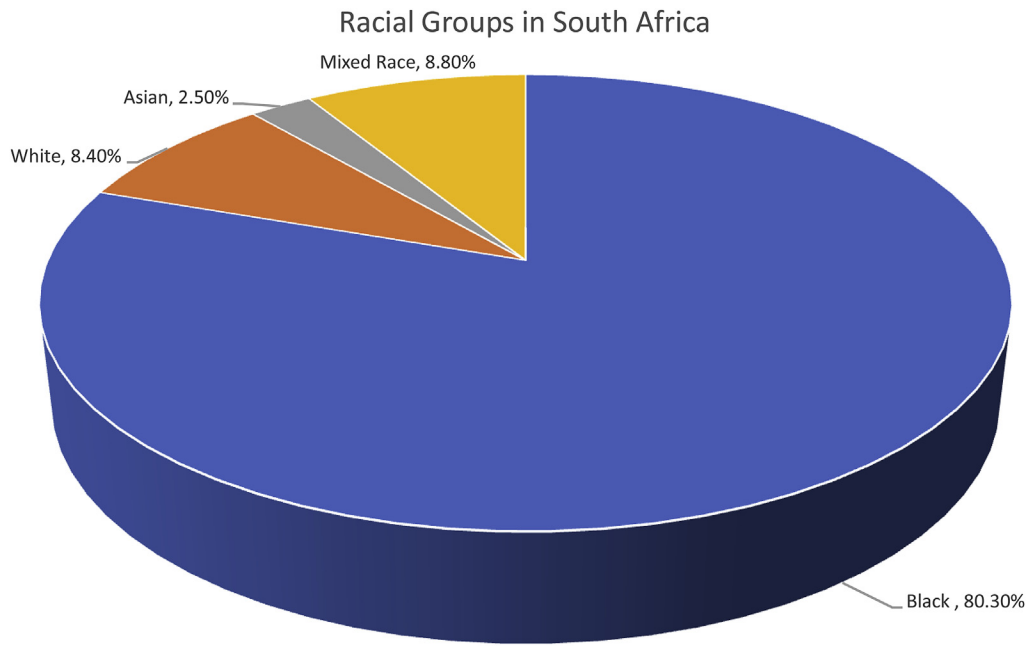


Figure 1. Racial groups in South Africa.

Management of Lung Cancer in South Africa

Diagnosis, Staging, and Pathology

Staging is usually done by means of computed tomography (CT) scan. Occasionally, because the public sector services most of the population, there can be delays in obtaining these scans. In private practice, CT is easily accessible. Positron emission tomography is available in both the public and private sectors and is usually used for staging in cases that are considered for

curative surgery, for early-stage cancer, or in cases in which staging is unclear on CT.

The cases of most patients are discussed in a multidisciplinary setting in which the cardiothoracic surgeon, radiologist, pathologist, and medical and radiation oncologists are present, as is a nuclear medicine physician when possible. In these meetings, biopsy strategy, decisions on molecular testing, and patient management are decided on collectively.

Once malignancy has been confirmed on pathological examination, the diagnosis of SCLC or NSCLC based on



Figure 2. Provinces in South Africa.

morphologic features is determined. The distinction is then made between squamous cell carcinoma and adenocarcinoma. A full panel of diagnostic biomarkers is available, including cytokeratin 7 (*CK7*), *CK20*, *CK5/6*, p63, p40, thyroid transcription factor 1, and Napsin A, which can be used in questionable cases in which the diagnosis is not clear.

These tests are routinely done in both settings. Even though there is a range of targetable mutations, testing in the public setting is futile, as treatment for patients with oncogenic drivers is not funded.

Biomarkers, including DNA mutations, can be tested by using immunohistochemistry and fluorescence in situ hybridization. Next-generation sequencing is available in the private sector to use in selected cases. The OncoPrint Focus Assay (Thermo Fisher Scientific) is the most commonly used platform. Multiplex real-time polymerase chain reaction is also available for *EGFR*, *RAF*, and *RAS*, and real-time reverse-transcriptase polymerase chain reaction is available for anaplastic lymphoma kinase (*ALK*) and *ROS1* fusions. Testing for *ALK* is usually done by immunohistochemistry, but this is not recommended and requires fluorescence in situ hybridization for confirmation.

Results from these specialized tests can take up to 2 weeks, which can have an impact on treatment decisions for patients and maintenance of their performance status. Liquid biopsy is also available in South Africa but is not used routinely, and some laboratories use liquid biopsies only for *EGFR* testing.

There are few data on the incidence of these mutations in South Africa, especially *ALK1* and *ROS1* mutations. The data on *EGFR* mutations in Africa as a whole seem to be consistent with the current literature on such mutations in Western countries.⁴ According to a 2014 retrospective study, *EGFR* mutations were present in 21.3% of South African patients.⁵ Exon 20 mutations were detected more frequently in Africa and the Middle East than in Europe.⁶

Programmed death ligand 1 (PD-L1) testing is available in select laboratories and is usually done on request from the treating oncologist and not as a routine practice. Appropriately trained pathologists perform the assessment, which includes the clones 22C3 (Dako) and SP263 (Ventana).

Surgery

South Africa has a history of quality thoracic surgical care that was pioneered by the late Andrew Logan and Benjamin le Roux in the 1970s. Since that era, thoracic surgery has expanded and now delivers service in all nine provinces. Most surgical procedures are performed

in centers in Gauteng, Western Cape, Free State, Kwazulu Natal, and the Eastern Cape. The remaining provinces are also serviced, but to a lesser extent. Access to resources in the public and private sectors depends on the available funding.

Surgical diagnostic and staging procedures routinely available in private and academic institutions include the following: flexible or rigid bronchoscopies; open surgical (thoracotomy or minithoracotomy) or video-assisted thoracic surgery, pleural, or lymph node biopsy; and mediastinoscopy. Only few centers have access to transbronchial needle aspirations guided by endobronchial ultrasound for diagnostic purposes.

Diagnostic material can be obtained by means of brush cytology, exfoliative cytology, or fine-needle aspiration biopsy. Material is often limited, but diagnostic yield can be improved by cell block preparation. Interventional radiology also assists with obtaining percutaneous cytological or tumor specimens in cases in which other techniques are not available or feasible.

The vast majority of surgical procedures (routine oncological lobectomies and pneumonectomies) are performed by using open surgical approaches. Only a few centers in the country have mastered these operations by video-assisted thoracic surgery. There is no robotic surgery available in our country to date.

The standard surgical management by staging would include the following: for stage I, standard anatomical resection (mostly lobectomy), in which case wedge resections would be reserved only for candidates without physiological reserve. Complete staging lymph node dissection and pleural fluid sampling would be performed; for stage II with N1 disease and treatment would be the same as for stage I disease. For stage II with N2 disease, if known preoperatively, cases in this category would not be accepted for surgery unless downstaged with use of systemic therapy and accurately restaged. Treatment for Stage III would be in the same manner as for nonsurgical disease.

Medical Oncology

All chemotherapeutic agents for SCLC and NSCLC are available in South Africa. Only cost-effective generic chemotherapies are available in public hospitals. In most provinces, pemetrexed is not funded for nonsquamous NSCLC. Specialized drugs such as targeted therapies, including bevacizumab, are not available in the public sector. In the private sector, for patients with *EGFR* mutations only erlotinib is registered. Osimertinib has recently been registered for use in the second line setting for patients who have a documented resistant *T790m* mutation. Crizotinib was

Table 1. Systemic Therapies Available according to Treatment Approach (Non- Resource-Stratified)

Neoadjuvant	Adjuvant	First-Line Metastatic	Second-Line Metastatic	Third-Line Metastatic
Platinum chemotherapy doublet (cisplatin or carboplatin with taxane/ gemcitabine/ navelbine/ etoposide/pemetrexed) Concurrent therapy and radiation	Platinum chemotherapy doublet	Targeted therapies (erlotinib and crizotinib) Platinum chemotherapy doublet Antiangiogenic therapy (bevacizumab)	Pembrolizumab (PD-L1 ≥1%) Targeted therapies (osimertinib [with proven T790m mutation]) Any single-agent chemotherapy	Any single-agent therapy

PD-L1, programmed death ligand 1.

recently registered and is the only drug available for ALK-positive patients. For *ROS1*-positive patients, the registration is pending.

No checkpoint inhibitors are currently registered for use in the first-line setting. Pembrolizumab is the only agent available, and it is registered for second-line use with patients with programmed death ligand 1 positivity of 1% or more (see Table 1).

There is a lengthy registration process for new therapies; it can take up to 5 years in some cases. New agents are sometimes available through compassionate use programs. Newer therapies can be accessed through private funding on special importation permits (Section 21). There are many approved clinical trial units in public and private centers. If patients are eligible for a clinical trial, every effort is made to enroll them.

There is limited access to expensive novel agents in the private sector, as most medical funders exclude these from their schemes. Funders who do reimburse these treatments make it available exclusively to patients only on their top tiers (approximately 20%). Most funders require a minimum copayment of 25% for targeted therapies or immunotherapy agents. This results in large amounts of money that most South Africans cannot afford. The differences in treatment available in the public and private sectors are summarized in resource-stratified algorithms (Figs 3–5).

There are fewer than 40 medical oncologists in South Africa. Most of them are situated in Gauteng Province. The training centers for medical oncology are in Pretoria and Johannesburg. In other provinces, clinical and radiation oncologists administer both chemotherapy and radiation therapy. Recently in Kwazulu-Natal, a crisis emerged as all the oncologists working in the academic/public department resigned. This resulted in backlogs and patients dying before receiving any treatment. This crisis has been covered extensively in the media of late.

Radiation Oncology

Radiotherapy plays an important role in the management of patients with lung carcinoma. As in other areas of oncology, technological developments in the discipline of radiation oncology contribute to improved outcomes in patients with this disease. Intensity-modulated radiotherapy, including volumetric modulated arc therapy and stereotactic radiotherapy, are examples of the advanced techniques utilized.

Radiotherapy services in South Africa vary widely as a result of numerous factors. One of the major determinants, once again, is the division of public and private sectors in the health care system.

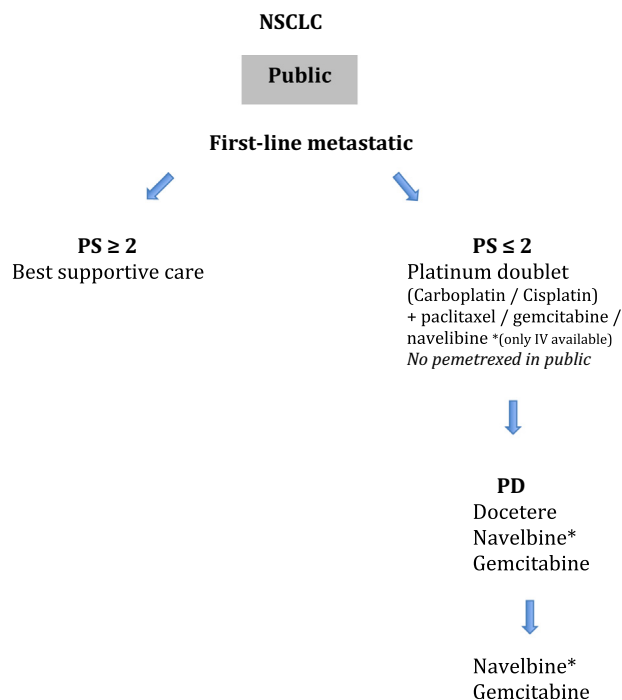


Figure 3. Resource-stratified algorithm for the treatment of metastatic NSCLC in South Africa: public sector. PS, performance status; PD, progressive disease. *Intravenous or oral formulation can be used.

1st line metastatic

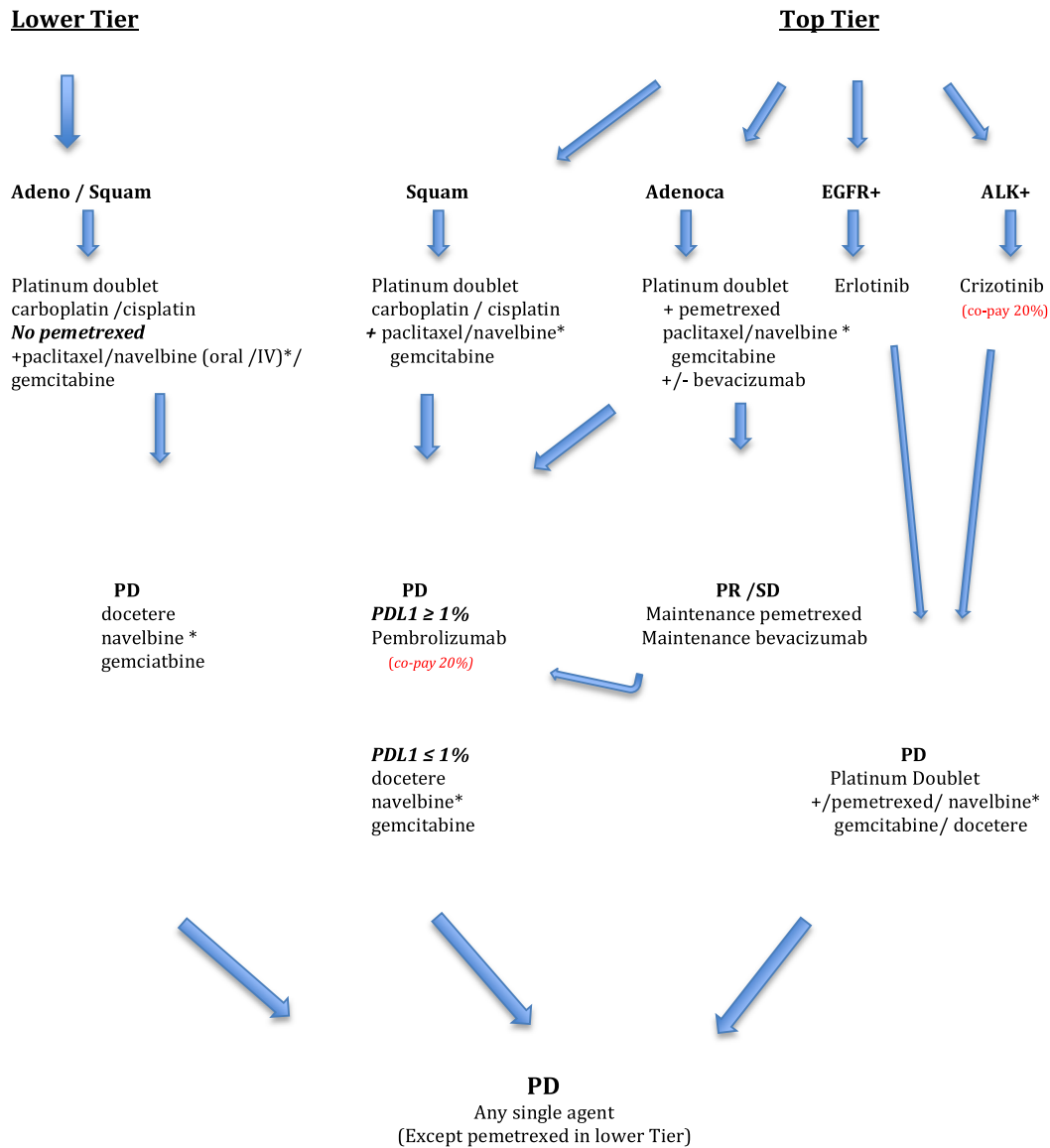


Figure 4. Resource-stratified algorithm for the treatment of metastatic NSCLC in South Africa: private sector. Adeno, adenocarcinoma; Squam, squamous carcinoma; ALK, anaplastic lymphoma kinase; IV, intravenous; PD, progressive disease; PDL-1, programmed death ligand 1; PR, partial response.

There are slightly more than 200 clinical or radiation oncologists in South Africa; however, there is a disparity in resources, as only approximately 20% of them are employed in the public health sector. Roughly 80% of clinical or radiation oncologists work in the private sector. Further disparities complicating the access to radiotherapy for most patients include the number and location of radiotherapy units. There are approximately 83 teletherapy units in the country. Of these, about 64

(77%) are located in only three of the country's nine provinces. Four other provinces share approximately 17 units (20%) between them, with the remaining two provinces having only one radiotherapy facility each; however, these are private units, and there are no state facilities in these two provinces (Fig. 6). Furthermore, radiotherapy units are mostly located in larger cities, thereby limiting the access to patients in rural areas.

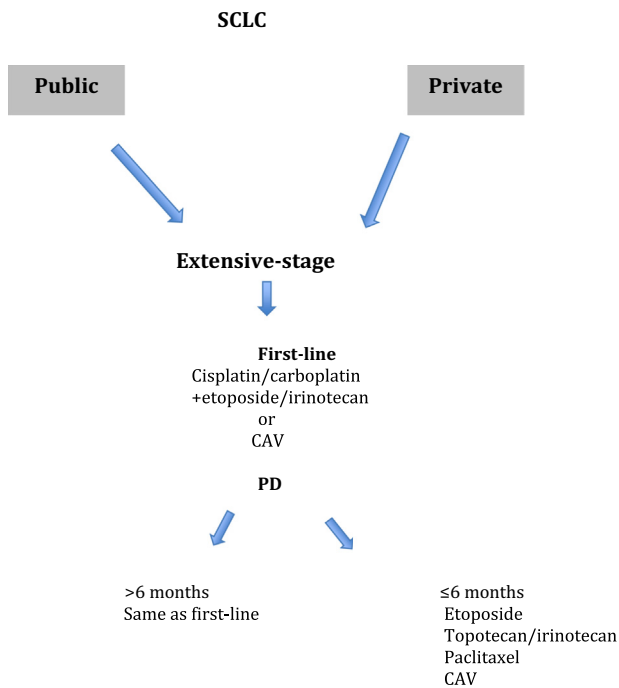


Figure 5. Resource-stratified algorithm for the treatment of metastatic SCLC in South Africa: public and private sector. CAV, cyclophosphamide plus doxorubicin plus vincristine; PD, progressive disease.

Regarding the health care split, about 52 of the 83 units (63%) service the private sector, compared with about 31 units (37%) that service the public sector. Less than half of the units have volumetric modulated arc therapy capabilities, and even fewer can provide stereotactic radiotherapy. The units that can provide state-of-the-art radiotherapy are mostly clustered in the larger cities, and availability is mostly limited to the insured population.

Conclusion

Advanced thoracic surgery, specialized systemic treatments, specific pathological examination, and improved radiotherapy techniques for lung carcinomas are available in South Africa, but primarily in the private sector. Patients with lung cancer in the public sector have limited access to treatment, and those who do are often managed with use of simpler techniques and very basic therapies.

There has been a move to institute a national health insurance to serve the entire population. Potentially, national health insurance could improve access to care and outcomes in the treatment of patients with lung cancer in South Africa.

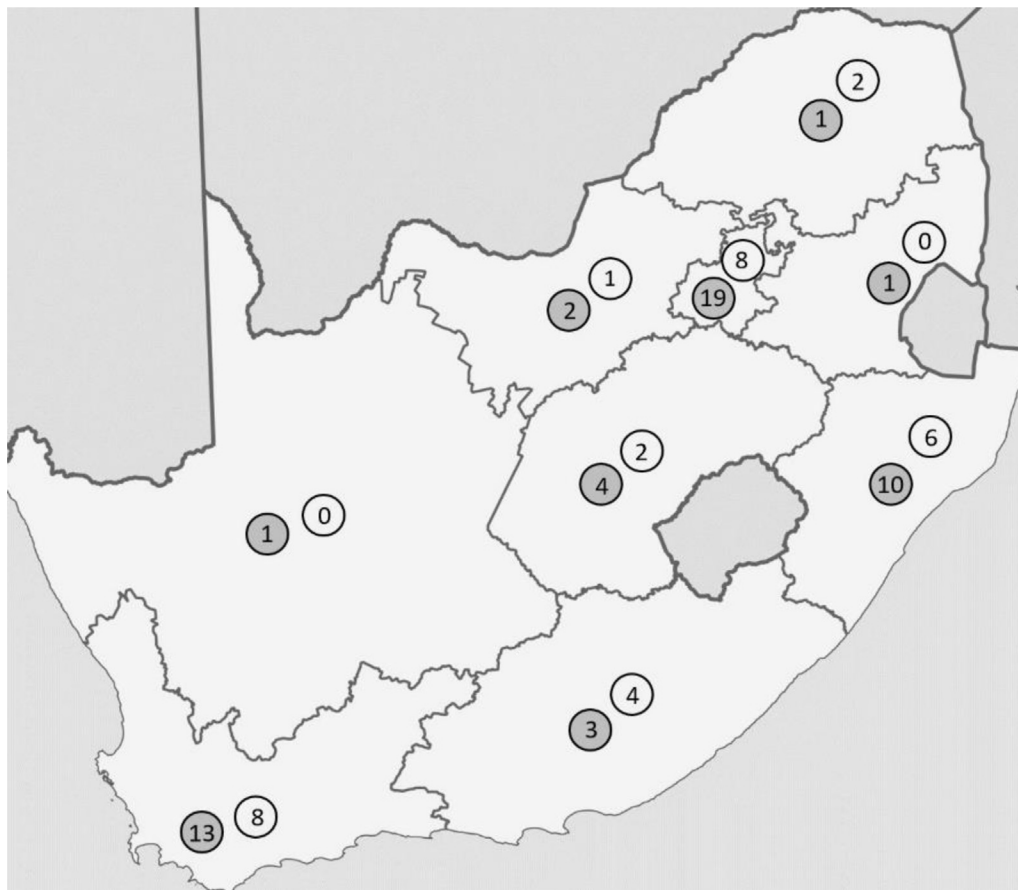


Figure 6. Teletherapy units by province. Number of teletherapy units by province. Shaded circles represent units in the private sector. Nonshaded circles represent units in the state sector.

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