

Advances in Cytology and
Small Biopsies

TUESDAY JUNE 13, 2023

Pulmonary Cytology: Workup of NSCLC on FNA and Small Biopsy



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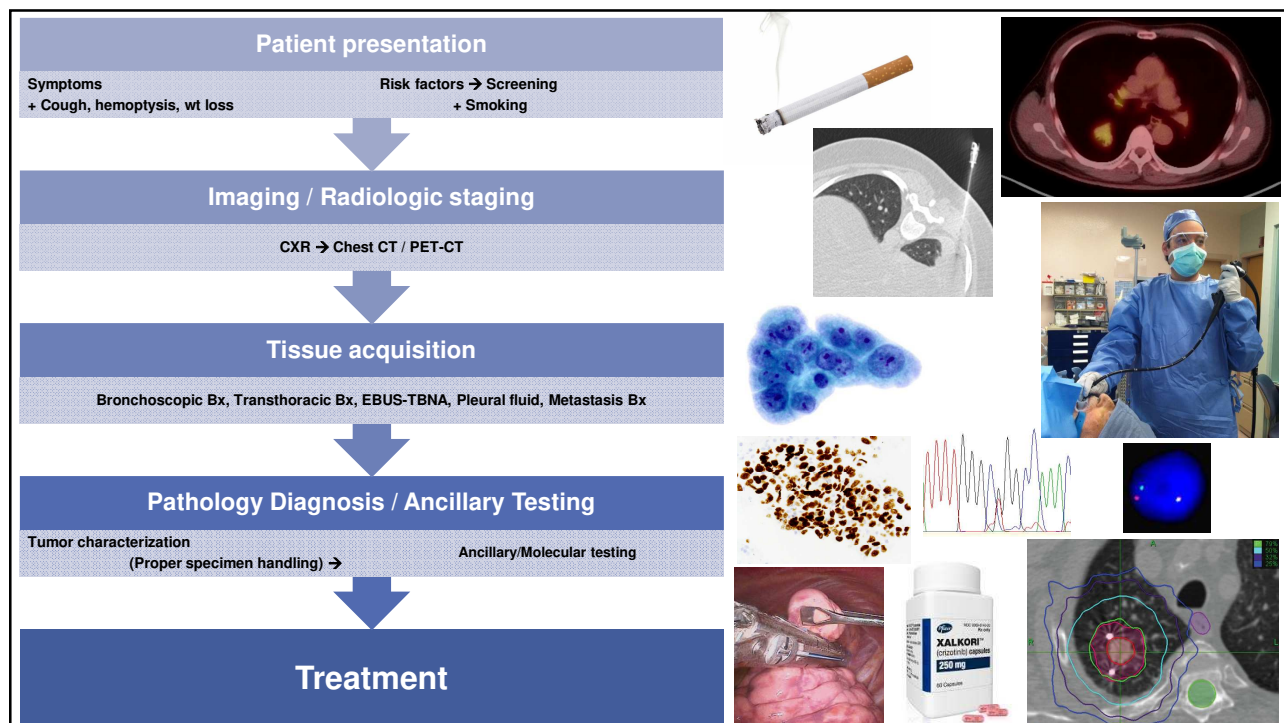
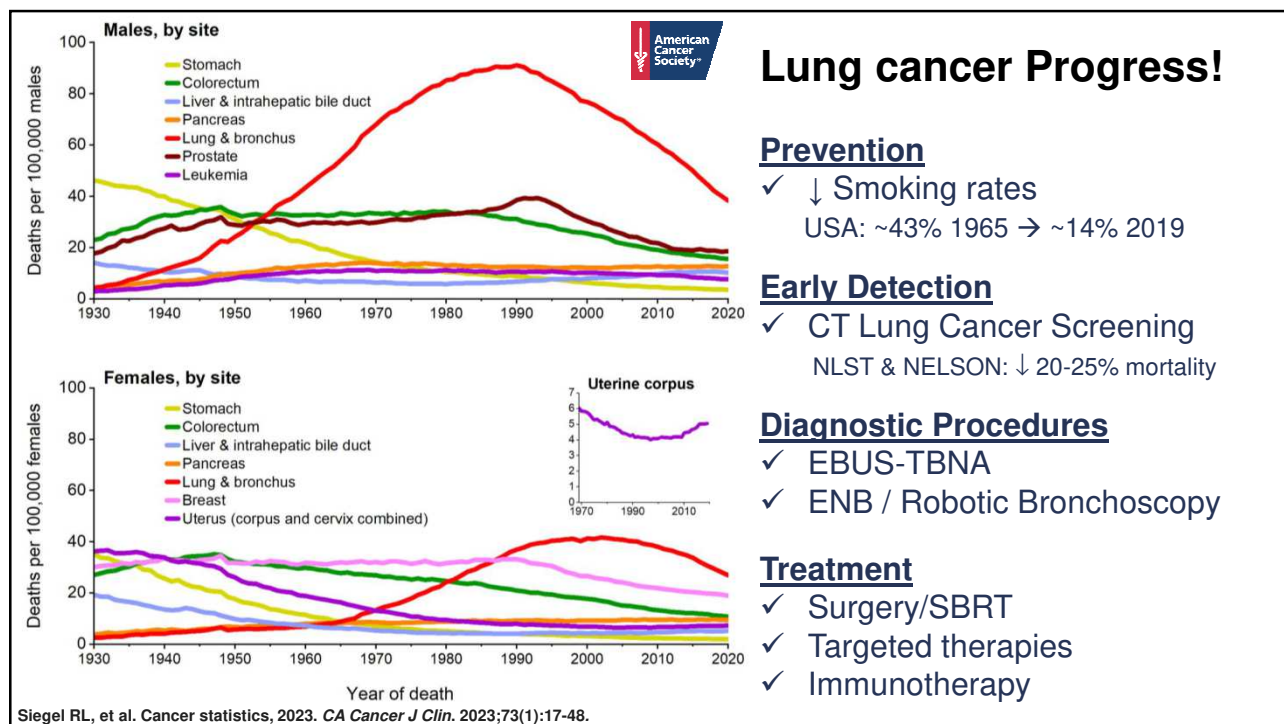


Disclosure of Relevant Financial Relationships

Paul VanderLaan reports the following relevant financial relationship(s) during the content development process for this activity, unrelated to the content of this talk:

Consulting fees:

- Gala Therapeutics
- Galvanize Therapeutics
- Intuitive Surgical
- Ruby Robotics



Pulmonary cytology and small biopsies

>2/3 of lung cancer patients present with advanced stage disease

✓ Dx: cytology / small biopsy specimen

Minimally invasive sampling techniques have become the preferred diagnostic modality

✓ Increase in cytology/small biopsy samples

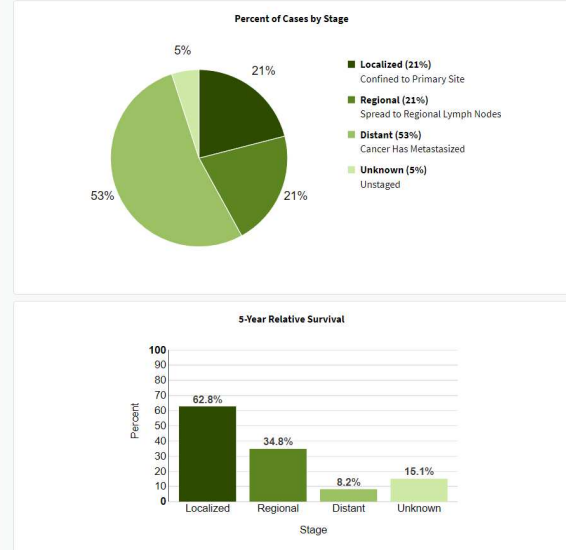
Cytology/small biopsy specimens are used for diagnosis *and* ancillary molecular testing

✓ Multiple objectives for the pathologist

With resistance mechanisms following TKI therapy, new paradigm of *repeated* biopsies to guide therapy

✓ Several biopsies from a patient over time

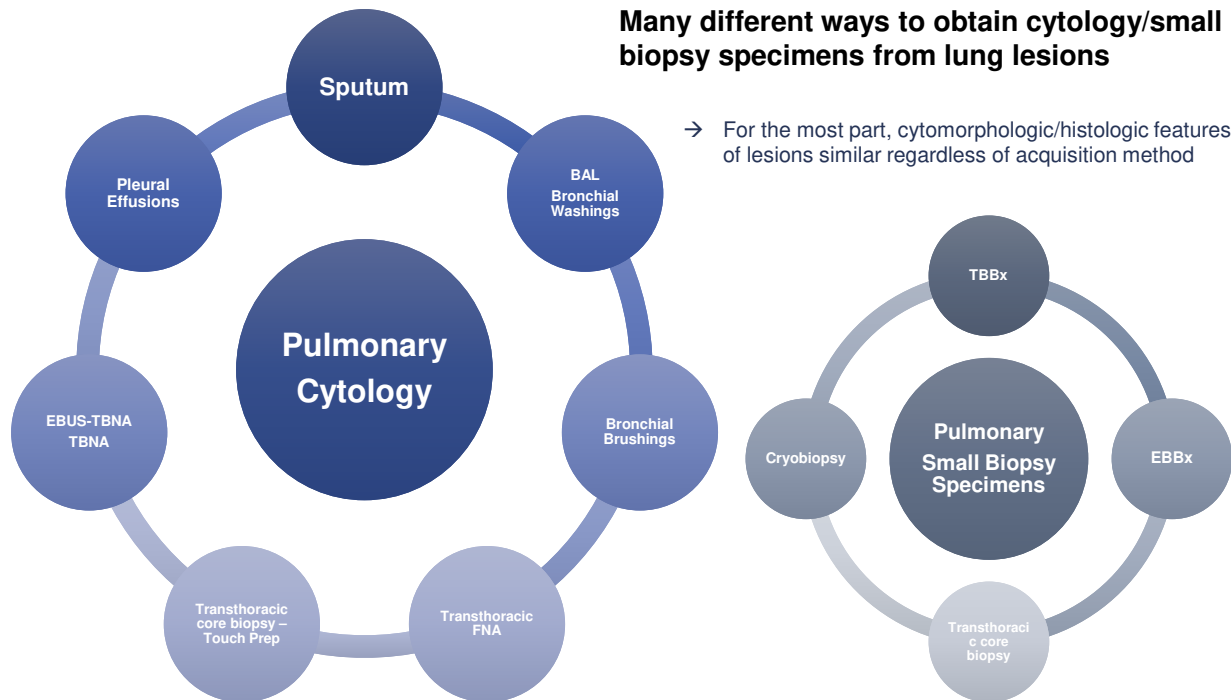
Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Lung and Bronchus Cancer

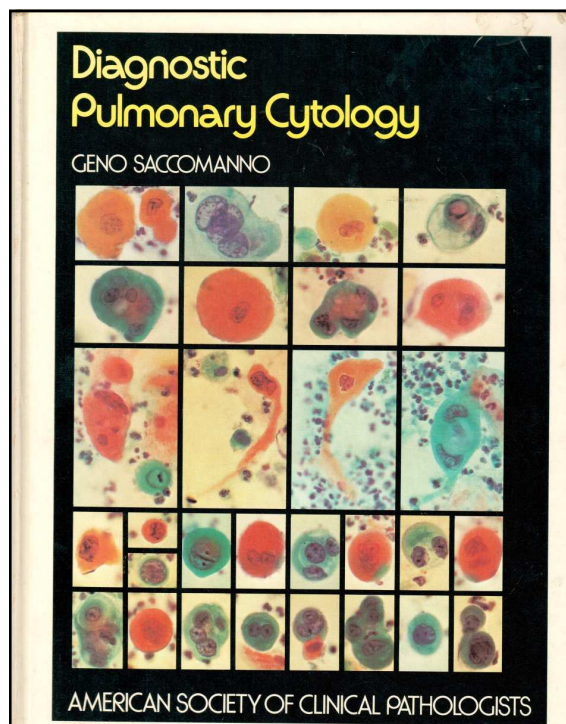


SEER 22 (Excluding IL/MA) 2013-2019, All Races, Both Sexes by SEER Combined Summary Stage

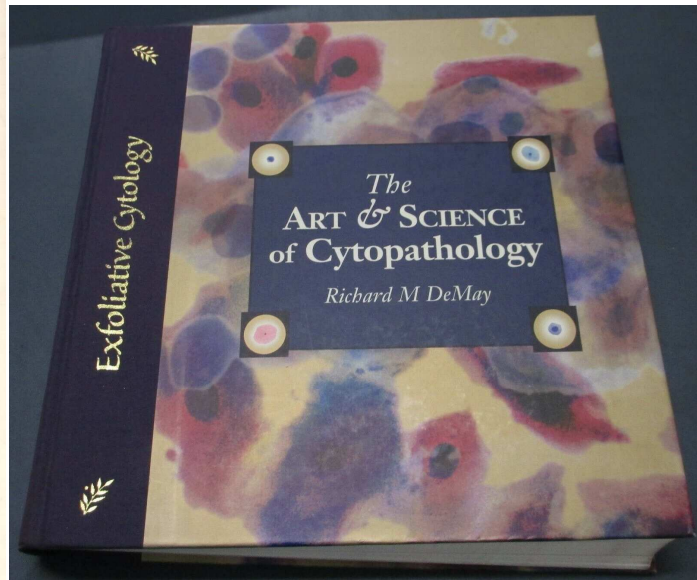
Many different ways to obtain cytology/small biopsy specimens from lung lesions

→ For the most part, cytomorphologic/histologic features of lesions similar regardless of acquisition method

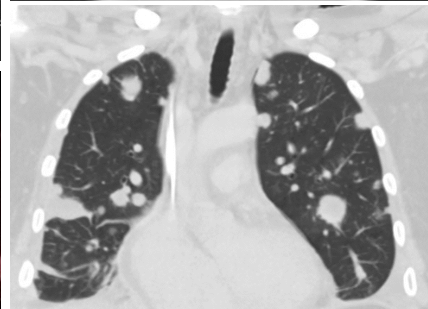
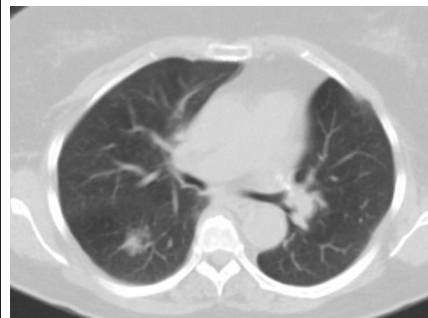
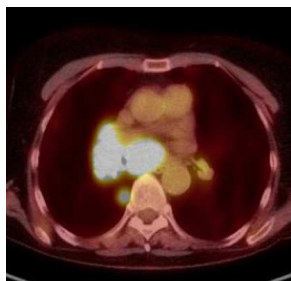
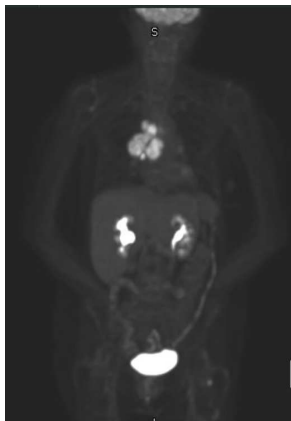




The cells still look the same...



Question:
Patient with lung mass,
is it cancer or not?

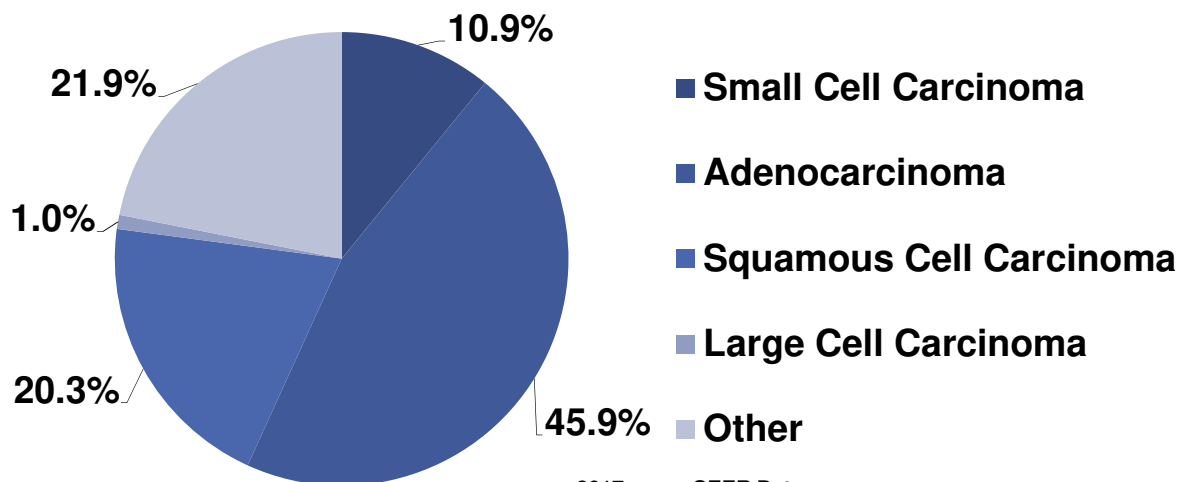




NATIONAL CANCER INSTITUTE

Surveillance, Epidemiology, and End Results Program

Cancer of the Lung and Bronchus



2017 year - SEER Data

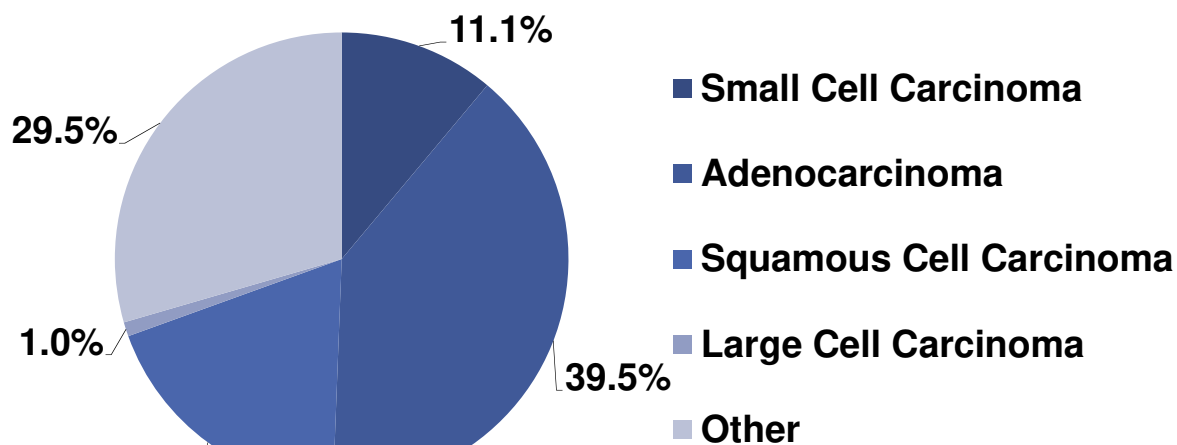
(Subtype, Both Sexes, All Races, All Ages, All Stages, Observed Rates)



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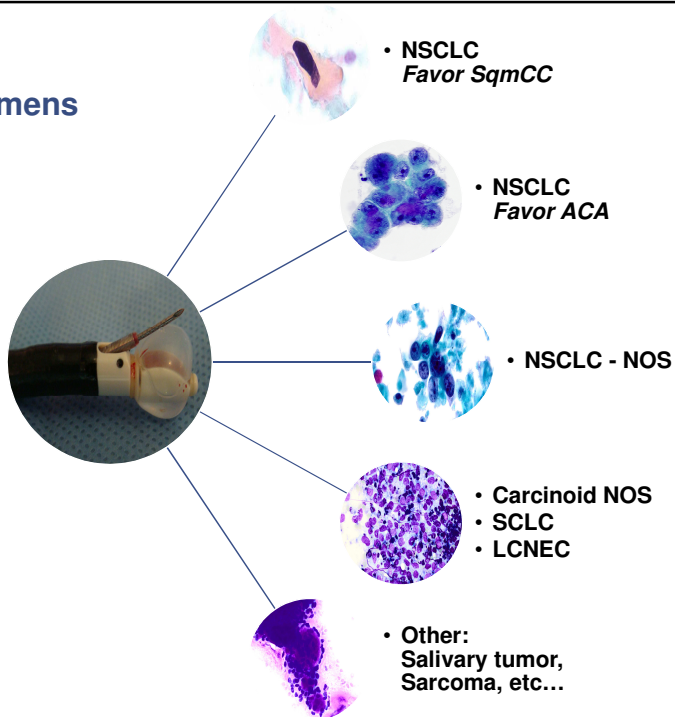
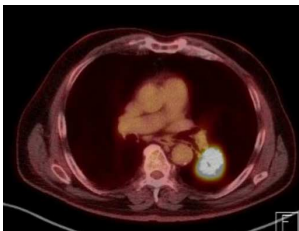
Cancer of the Lung and Bronchus



*2020 year - SEER Data (COVID: -11.88% incidence rate vs 2019)
(Subtype, Both Sexes, All Races, All Ages, All Stages, Observed Rates)

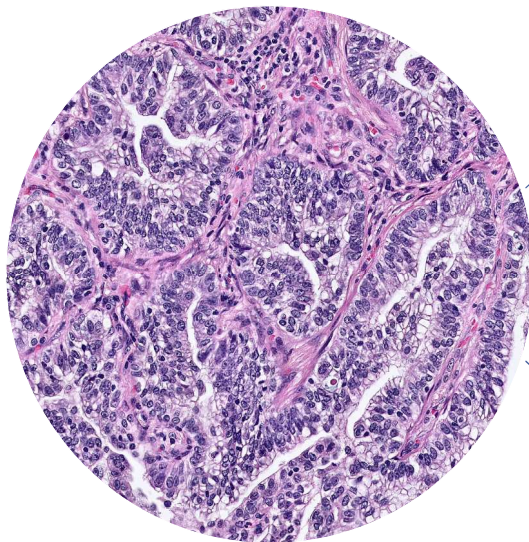
Our job

Cytology/small biopsy specimens



Advanced stage NSCLC

Three broad options for 1L therapy...



Targeted
Therapy

- EGFR
- ALK
- ROS1
- BRAF V600E
- MET ex 14 skipping
- RET
- NTRK

ICI
monotherapy

- If no driver mutation *and*
- PD-L1 IHC TPS $\geq 50\%$

Chemo
+
ICI

- If no driver mutation *and*
- PD-L1 IHC TPS $< 50\%$

Diagnostic work-up

Remember: *Morphology first* → *IHC for further characterization*

Journal of the American Society of Cytopathology (2020) 9, 332–345



Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jascyto.org/



Lung cancer cytology and small biopsy specimens: diagnosis, predictive biomarker testing, acquisition, triage, and management

Simon Sung, MD^{a,*,1}, Jonas J. Heymann, MD^{b,1},
John P. Crapanzano, MD^a, Andre L. Moreira, MD, PhD^c,
Catherine Shu, MD^d, William A. Bulman, MD^e, Anjali Saqi, MD, MBA^a

REVIEW

OPEN

Common Differential Diagnostic Issues in Lung Cytopathology: 3 Case Reports and a Review

Rachel Fanaroff, MD,^a Teklu B. Legesse, MD,^f and Kim R. Geisinger, MD^g

AJSP: Reviews & Reports 2021;26: 155–161

Diagnosis of Lung Carcinoma on Small Biopsy

Jian Jing, MD, PhD^a, Kristine E. Konopka, MD^{b,*,1}

Surg Pathol Clin. 2020;13(1):1-15.

KEYWORDS

• Lung nodule • Core needle biopsy • Fine needle aspiration • Small biopsies
• Specimen management

Key points

- Early detection of lung cancer significantly reduces mortality, and small biopsies play a key part in allowing for early medical and/or surgical intervention.
- Pathologists are encouraged to build awareness for appropriate tissue triage of small biopsies to preserve material for possible ancillary molecular testing.
- Differentiating benign from malignant epithelial changes on small biopsies may require correlation with the clinical and radiographic context to avoid an erroneous overall of malignancy.

Small diagnostic samples

Travis WD
Al-Dayel FH
Bubendorf L
Chung JH
Rekhtman N
Scagliotti GV

Rationale for classification in small biopsy and cytology specimens

Pathological diagnosis is key to the management of lung cancer, in addition to careful consideration of risk factors and signs and symptoms, assessment of the extent of the disease (locally and outside the thoracic boundaries), and – in the case of resectable disease – evaluation of the cardiopulmonary and metabolic status of the patient. For the 70% of lung cancer patients who

present with advanced-stage, unresectable disease, diagnosis must be based primarily on small biopsy and cytology specimens [3074].

Precise histological classification (and in many cases molecular and/or biomarker testing) of lung cancer is essential because of the clinical need for tailoring systemic therapies according to histological type as well as molecular/biomarker profiles [3068,3071,2760,1161]. However, achieving this goal can be

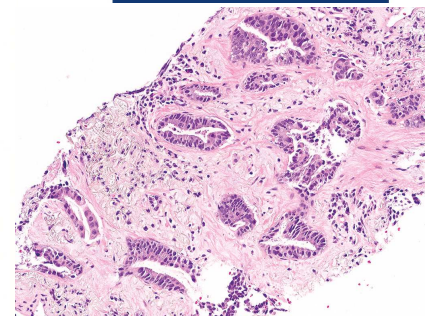
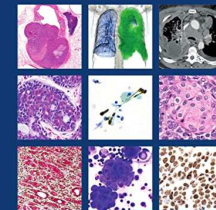
Box 1.01 Guidelines for good practice of small biopsies and cytological preparations [3073,3074]

1. For small biopsies and cytology, non-small cell carcinoma should be further classified into a more specific type, such as adenocarcinoma or squamous cell carcinoma, whenever possible.
2. The term "non-small cell lung carcinoma NOS" should be used as little as possible, and only when a more specific diagnosis is not possible.
3. When a diagnosis is made in a small biopsy or cytology specimen in conjunction with special studies, it should be clarified whether the diagnosis was established on the basis of light microscopy alone or whether special stains were required.
4. The term "non-squamous cell carcinoma" should not be used by pathologists in diagnostic reports. This categorization is used by clinicians to define groups of patients whose tumours comprise several histological types and who can be treated in a similar manner; in small biopsies and cytology, pathologists should classify non-small cell lung carcinoma as adenocarcinoma, squamous cell carcinoma, non-small cell lung carcinoma NOS, or other terms (see Table 1.04, p. 30).
5. The above classification of adenocarcinoma vs other histologies and the terminology in Table 1.04 (p. 30) and Table 1.05 (p. 31) should be used in routine diagnosis, future research, and clinical trials, to ensure a uniform classification of disease cohorts in relation to tumour subtypes, stratified according to diagnoses made by light microscopy alone vs diagnoses requiring special stains.
6. When paired cytology and biopsy specimens exist, they should be reviewed together to achieve the most specific and concordant diagnosis.
7. The terms "adenocarcinoma in situ" and "minimally invasive adenocarcinoma" should not be used for diagnosis of small biopsies or cytology specimens. If a non-invasive pattern is present in a small biopsy, it should be referred to as a lepidic growth pattern. Similarly, if a cytology specimen has the attributes of adenocarcinoma in situ, the tumour should be diagnosed as an adenocarcinoma, possibly with a comment that this may represent, at least in part, adenocarcinoma in situ.
8. The term "large cell carcinoma" should not be used for diagnosis in small biopsy or cytology specimens and should be restricted to resection specimens where the tumour is thoroughly sampled to exclude a differentiated component.
9. In biopsies of tumours that show sarcomatoid features (marked nuclear pleomorphism, malignant giant cells, or spindle cell morphology), these should be initially classified as above in relation to adenocarcinoma: non-small cell carcinoma, favour adenocarcinoma; squamous cell carcinoma; or non-small cell carcinoma, favour squamous cell carcinoma, because this is apt to influence management, with an additional statement that giant and/or spindle cell features (depending on what feature) are present. If such features are not present, the term "non-small cell carcinoma NOS" should be used, again with a comment on the sarcomatoid features.
10. Staining for neuroendocrine immunohistochemical markers should be performed only in cases where there is suspected neuroendocrine morphology.

WHO Classification of Tumours • 5th Edition

Thoracic Tumours

Edited by the WHO Classification of Tumours Editorial Board



The World Health Organization Reporting System for Lung Cytopathology

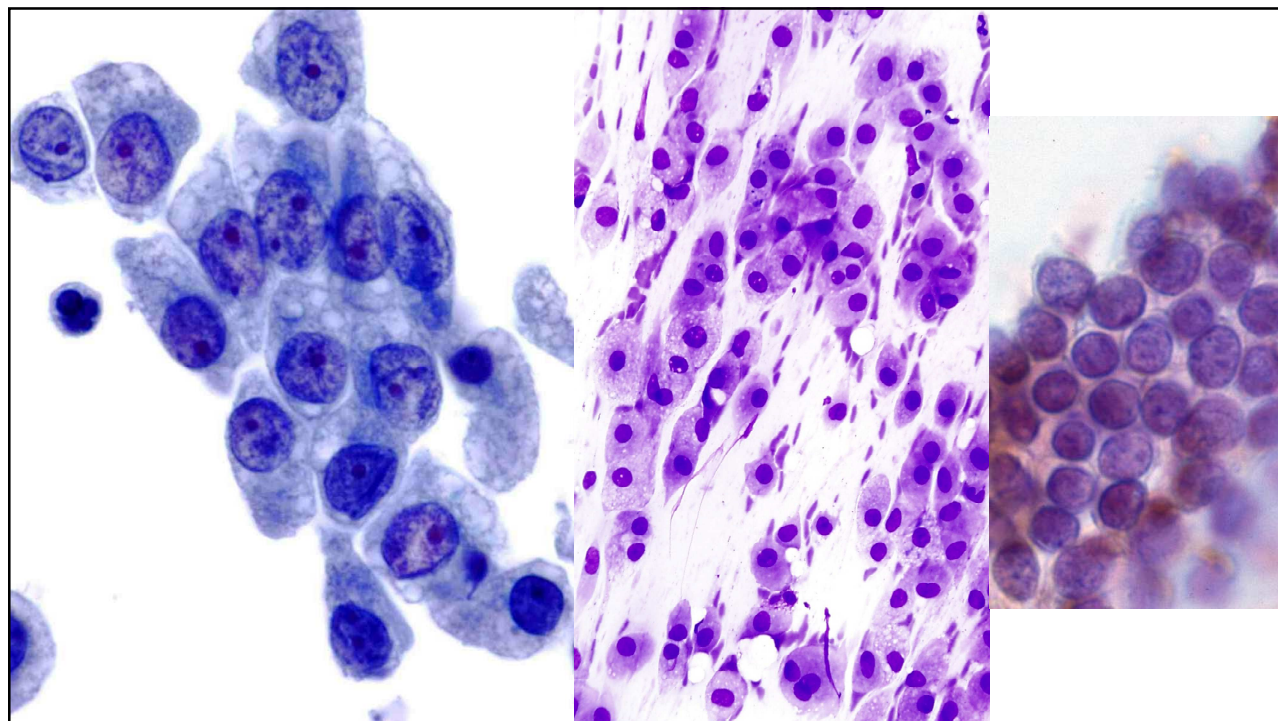
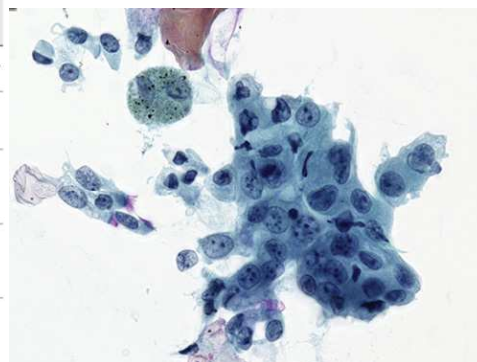
Fernando C. Schmitt^{a,b,c} Lukas Bubendorf^d Sule Canberk^{c,e,f} Ashish Chandra^g
Ian A. Cree^h Marianne Engelsⁱ Kenzo Hiroshima^j Deepali Jain^k Ivana Kholová^l
Lester Layfield^m Ravi Mehrotraⁿ Claire W. Michael^o Robert Osamura^p
Martha B. Pitman^q Sinchita Roy-Chowdhuri^r Yukitoshi Satoh^s Paul VanderLaan^t
Maureen F. Zakowski^u Andrew S. Field^v

Diagnostic category	Estimated risk of malignancy, %	Clinical management options
Insufficient/Inadequate/Non-diagnostic	43–53	Correlate with CLIN-IMG-MICRO, ideally discuss at a MDT meeting, and perform repeat FNAB with or without CNB
Benign/negative for malignancy	19–64	Correlate with CLIN-IMG-MICRO, and if these confirm benign diagnosis, then routine follow up at 3–6 months. If no correlation, then perform repeat FNAB with or without CNB
Atypical	46–55	Correlate with CLIN-IMG-MICRO, and ideally discuss at a MDT meeting. If all show a benign diagnosis, then routine follow up at 3–6 months. If no correlation, then perform repeat FNAB with ROSE with or without CNB
Suspicious for malignancy	75–88	Correlate with CLIN-IMG-MICRO, and ideally discuss at a MDT meeting. If all support a diagnosis of malignancy, consider definitive treatment. If no correlation that lesion is Malignant, perform repeat FNAB with ROSE with or without CNB
Malignant	87–100	Correlate with CLIN-IMG-MICRO, and ideally discuss at a MDT meeting. If all support a diagnosis of malignancy, provide definitive treatment. If no correlation that lesion is Malignant, consider repeat FNAB with ROSE with or without CNB

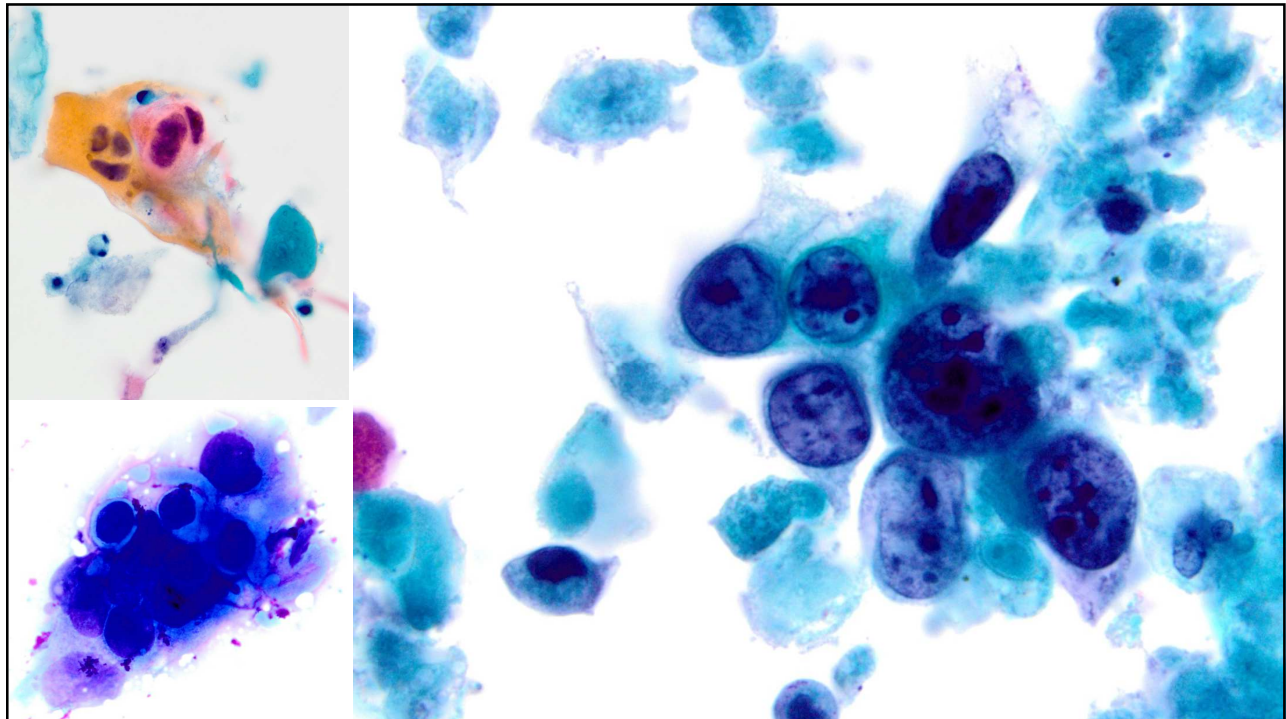
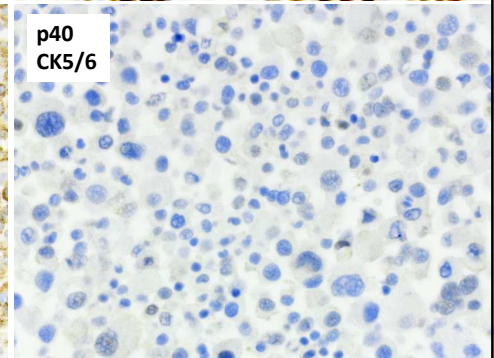
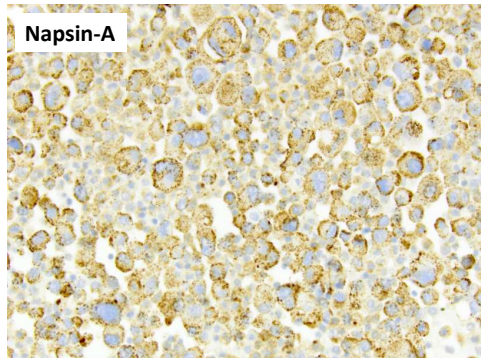
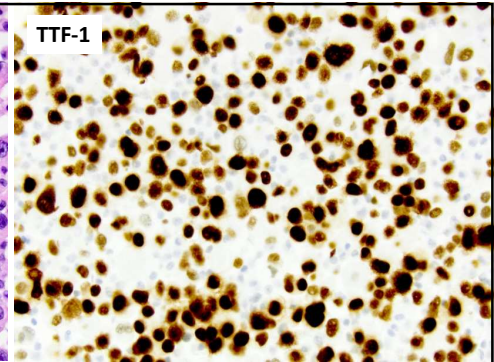
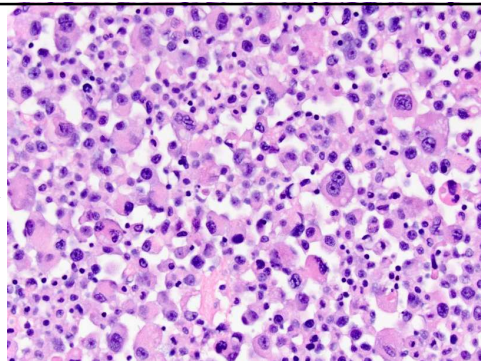


A brief review of the WHO reporting system for lung cytopathology

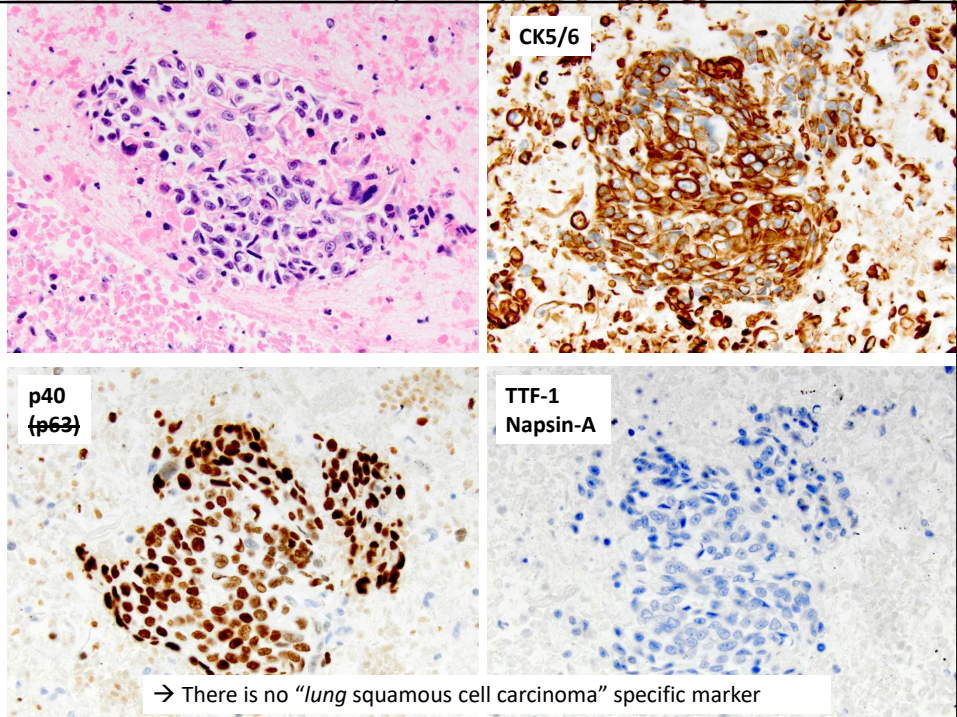
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Paul VanderLaan, MD, MIA^s, Maureen Zakowski, MD^t,
Fernando C. Schmitt, MD, PhD, FIAC^{u,v,w,x}



Lung Adenocarcinoma



Lung Squamous Cell Carcinoma

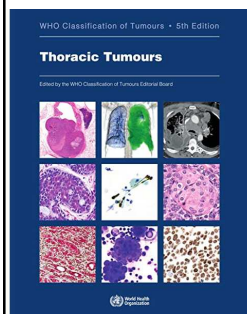


Pulmonary Neuroendocrine tumors

Grading →

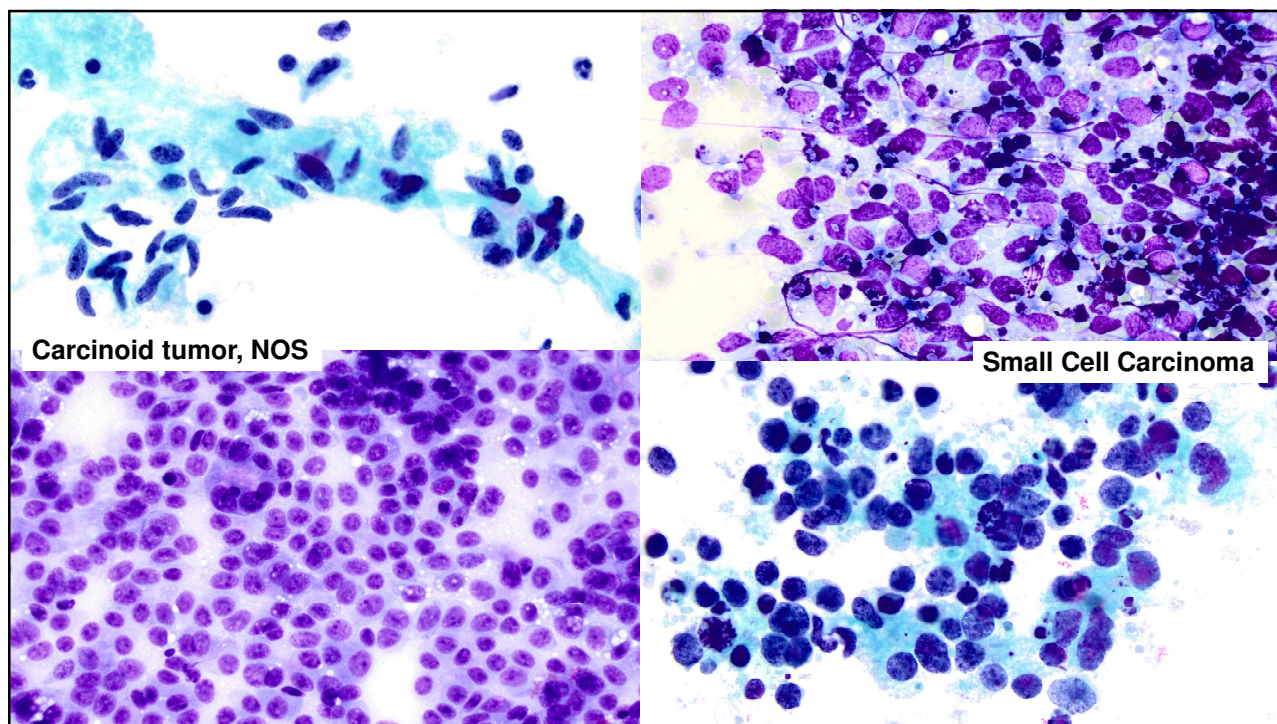


Cytology →
Small Biopsy



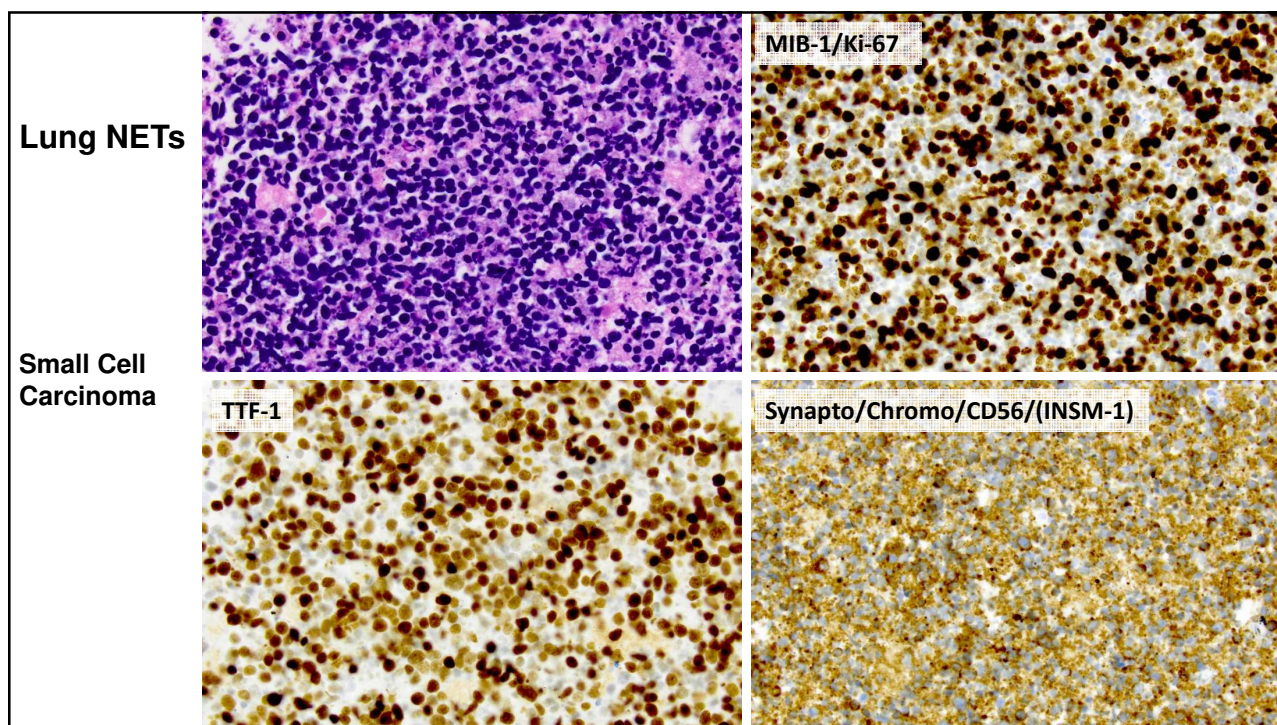
	Typical carcinoid	Atypical carcinoid	LCNEC	SCLC
Average age	Sixth decade	Sixth decade	Seventh decade	Seventh decade
Sex predominance	Female	Female	Male	Male
Diagnostic criteria				
Mitoses per 2 mm ²	< 2	2–10	> 10 (median: 70)	> 10 (median: 80)
Necrosis	No	Focal, if any	Yes	Yes
Neuroendocrine morphology	Yes	Yes	Yes	Yes
Ki-67 proliferation index	Up to 5%	Up to 30%	30–100%	30–100%
TTF1 expression	Mostly positive in peripheral, mostly negative in central tumours	Mostly positive in peripheral, mostly negative in central tumours	Positive (70%)	Positive (85%)
p40 expression	Negative	Negative	Negative	Negative
Combined with NSCC component	No	No	Up to 25% of resected LCNEC	Up to 25% of resected SCLC

WHO Classification of Tumours of the Lung, Pleura, Thymus, and Heart. 5th ed. 2021.



Carcinoid tumor, NOS

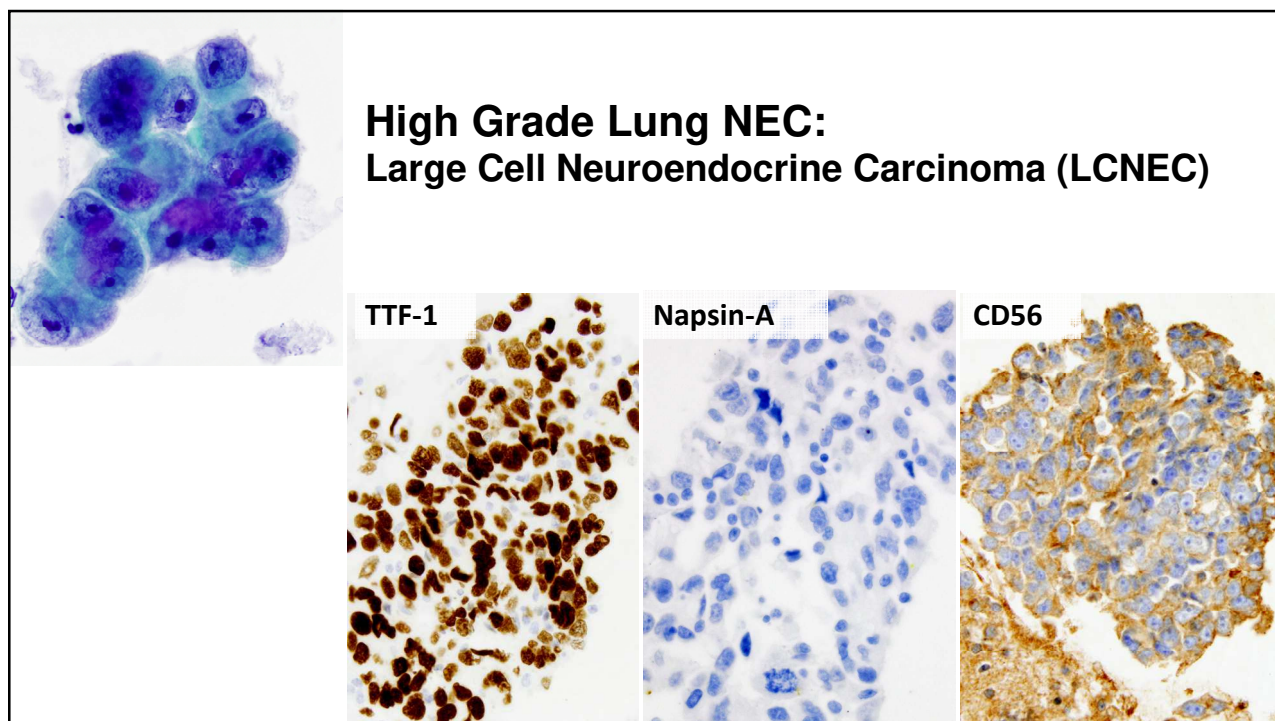
Small Cell Carcinoma



MIB-1/Ki-67

TTF-1

Synapto/Chromo/CD56/(INSM-1)



<p>SPECIAL ARTICLE</p> <p>IASLC</p> <p>Check for updates</p>	<p>Table 1. Key Questions and Recommendations for Diagnostic Immunohistochemistry in Lung Cancer</p>
<p>Best Practices Recommendations for Diagnostic Immunohistochemistry in Lung Cancer</p>	<p>Key Questions</p>
<p>Yasushi Yatabe, MD, PhD,^{a,*} Sanja Dacic, MD,^b Alain C. Borczuk, MD,^c Arne Warth, MD, PhD,^d Prudence A. Russell, FRCPA,^e Sylvie Lantuejoul, MD, PhD,^f Mary Beth Beasley, MD,^g Erik Thunnissen, MD, PhD,^h Giuseppe Pelosi, MD,ⁱ Natasha Rektman, MD, PhD,^j Lukas Bubendorf, MD,^k Mari Mino-Kenudson, MD,^l Akihiko Yoshida, MD, PhD,^m Kim R. Geisinger, MD,ⁿ Masayuki Noguchi, MD, PhD,^o Lucian R. Chirieac, MD,^p Johan Bolting, MD,^q Jin-Haeng Chung, MD, PhD,^r Teh-Ying Chou, MD, PhD,^s Gang Chen, MD,^t Claudia Poleri, MD,^u Fernando Lopez-Rios, MD, PhD,^v Mauro Papotti, MD,^w Lynette M. Sholl, MD,^x Anja C. Roden, MD,^y William D. Travis, MD,^z Fred R. Hirsch, MD, PhD,^{aa} Keith M. Kerr, MD, PhD,^{ab} Ming-Sound Tsao, MD, FRCP,^{ac} Andrew G. Nicholson, DM,^{ad} Ignacio Wistuba, MD,^{ae} Andre L. Moreira, MD^{af}</p>	<p>Short Answers</p>
<p>A</p>	<p>1. When IHC is needed for the subtyping of NSCC, TTF1 and p40 are the criterion standard, and these two markers are usually sufficient in clinical practice if there are no morphologic features of NE differentiation. p40 is preferable to p63 to identify squamous cell carcinoma</p>
<p>B</p>	<p>2. What extent of TTF1- and p40-positive reactions should we consider to be positive?</p>
<p>C</p>	<p>3. Are there any staining differences in lung adenocarcinoma between among TTF1 clones (SPT24, SP141, and 8G7G3/1)?</p>
<p>D</p>	<p>4. Should an NSCC that is diffusely positive for CK7 but negative for TTF1 and p40 be regarded as probably adenocarcinoma?</p>
<p>E</p>	<p>5. When should NE markers be applied to an NSCC?</p>
<p>F</p>	<p>6. What is the best antibody panel to differentiate NE tumors from other types of NSCC, and which one is the most reliable?</p>
<p>G</p>	<p>7. When should a proliferation marker be used in diagnosis?</p>
<p>H</p>	<p>8. Is IHC useful to render a specific diagnosis of uncommon lung cancer subtypes (sarcomatoid carcinoma, salivary gland-type tumors, and NUT carcinoma)?</p>
<p>I</p>	<p>9. What portion of the cytologic sample is best for immunostaining: the cell block, the air-dried smears, or the ethanol-fixed smears? Can destained smears be used adequately?</p>
<p>J</p>	<p>10. Which IHC panel is recommended to differentiate lung mucinous adenocarcinoma from metastatic mimics?</p>
<p>K</p>	<p>11. Are there any IHC or other markers to differentiate between primary lung cancers and metastases; between squamous cell carcinomas of lung primary and metastases from thymic, head and neck, endocervical, and the other cancers; and between adenocarcinomas of primary and metastases from gynecologic, mammary, uroepithelial, nonpulmonary NE, prostate, and liver cancers?</p>
<p>L</p>	<p>CD56, an alias for neural cell adhesion molecule 1 (NCAM 1); CK7, cytokeratin 7; IHC, immunohistochemistry; NE, neuroendocrine; NSCC, non-small cell carcinoma; NUT, nuclear protein in testis; TTF1, thyroid transcription factor 1.</p>

PVL – diagnostic approach to small biopsies

✓ Review (PET)CT:

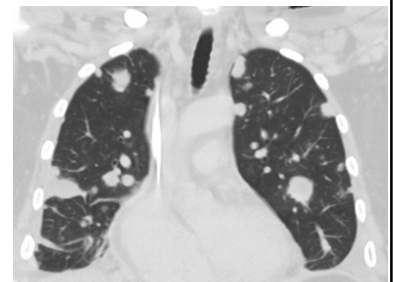
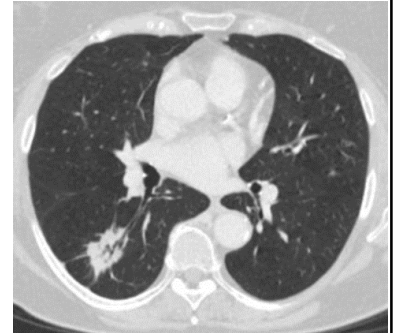
- Lung vs pleural vs thymic vs met

✓ Assess histo/cytomorphology

- Keratinizing squamous cell carcinoma: no stains needed
- Adenocarcinoma: TTF-1 and Napsin-A
- Squamous: p40, TTF-1
- PD NSCLC-NOS: TTF-1, Napsin-A, p40
- Neuroendocrine: TTF-1, Synaptophysin, Mib-1/Ki-67

✓ Inconclusive / poorly differentiated tumor

- Cytokeratins (CK5/6, CK7/20, cocktail)
- Mucicarmin stain
- Metastasis (CDX-2, PAX-8, GATA3, ER, NKX3.1, etc...)
- Consider salivary gland tumor, etc...



Priorities for cytology/small bx specimens in 2023

Primary diagnosis
suspected lung cancer

Establish malignancy dx

Tumor classification
(limited IHC panel)

Preserve tumor for
ancillary/molecular testing

Re-biopsy
disease progression

Confirm original histopathology
(? Small cell transformation)

Maintain material for
repeat ancillary/molecular
testing

Dichotomy for the pathologist...

Importance of **accurate tumor characterization**

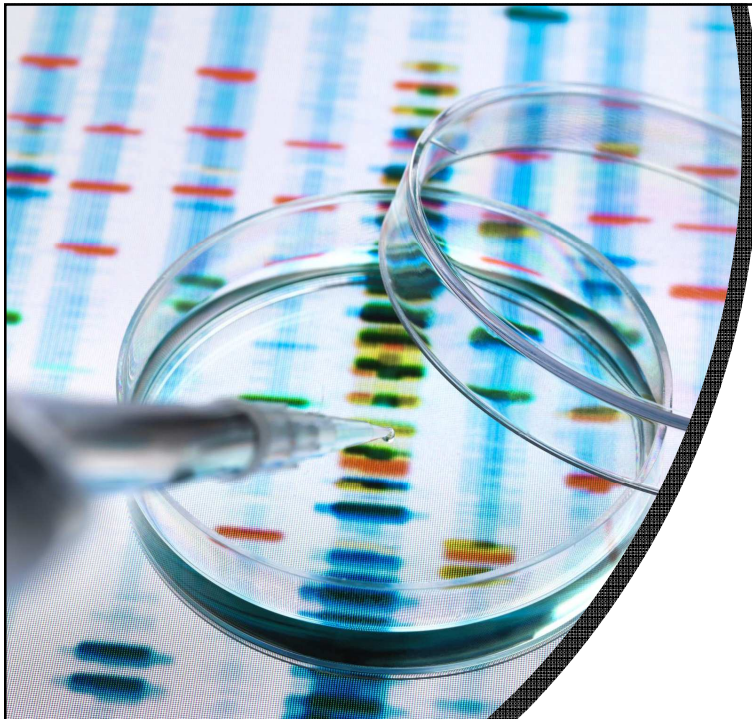
- Historically, tumor subtype:
 - ✓ Directed choice of therapy
 - ✓ Dictated which downstream testing to pursue

-VS-

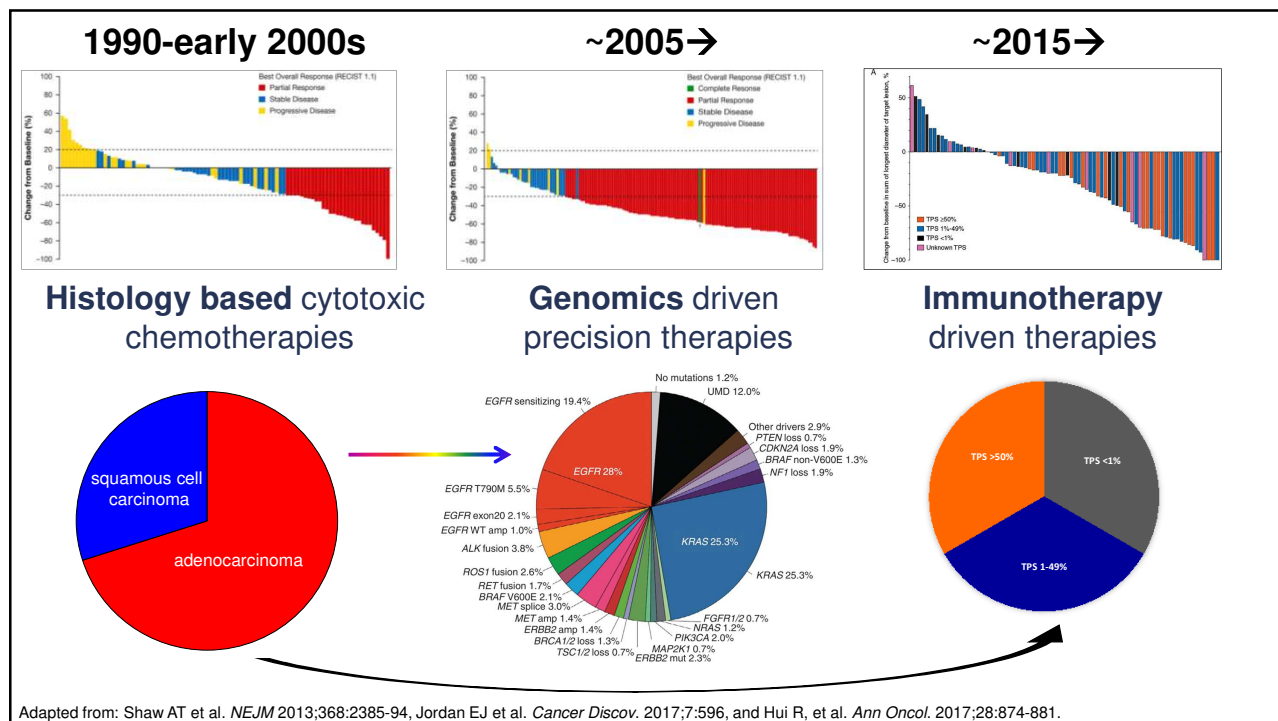
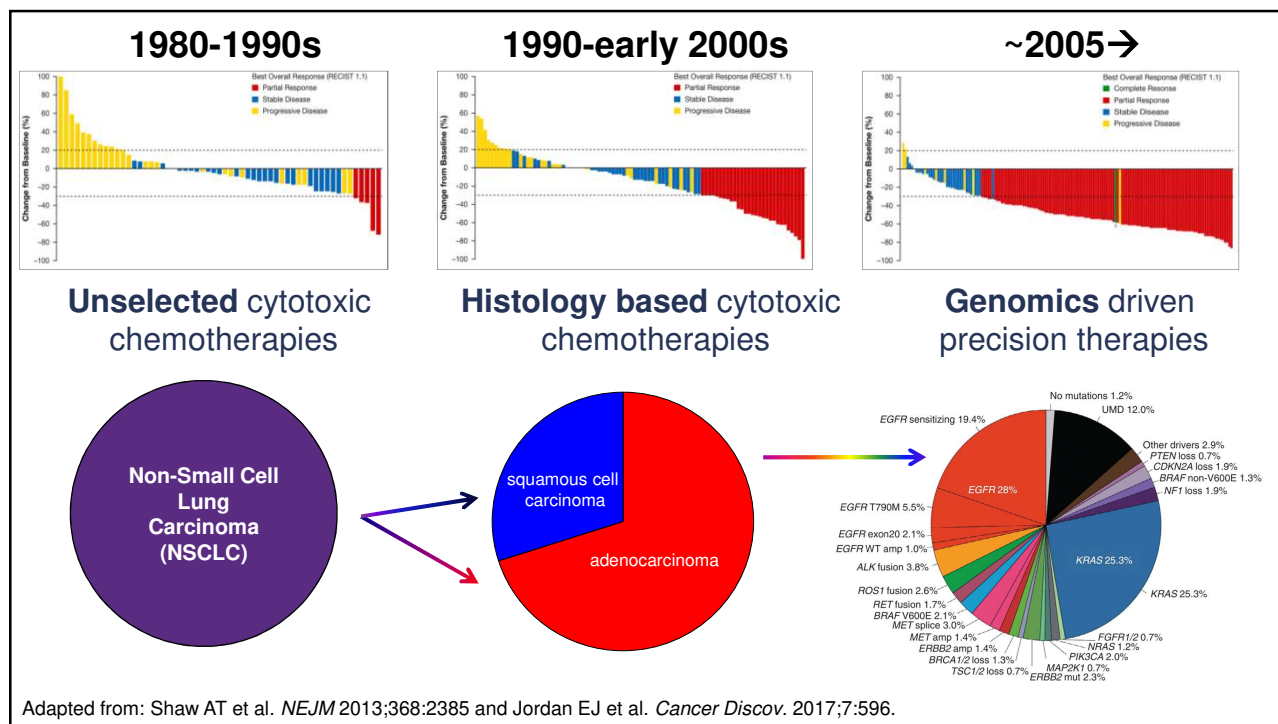
Importance of **minimal tumor utilization**

- Current therapy choices are driven by ancillary testing results
 - ✓ Targetable genomic alterations
 - ✓ PD-L1 (TPS)
 - ✓ MSI status
 - ✓ TMB
 - ✓ Co-mutational profile

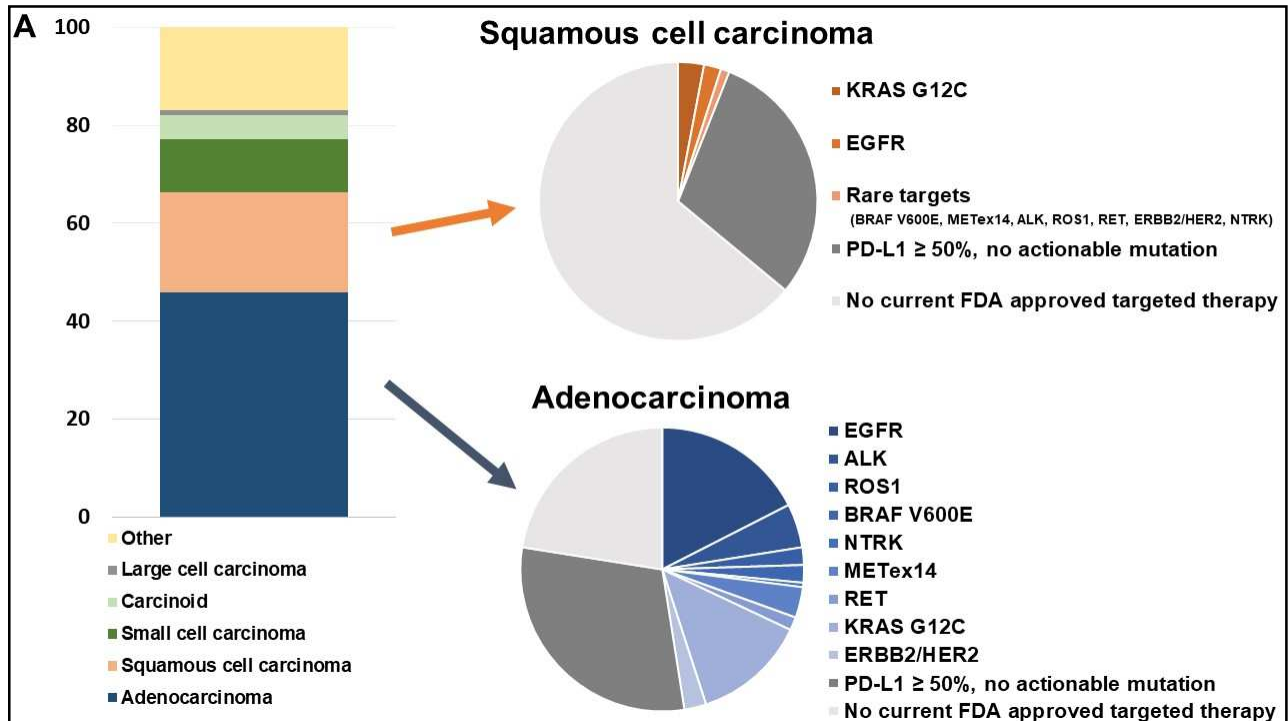
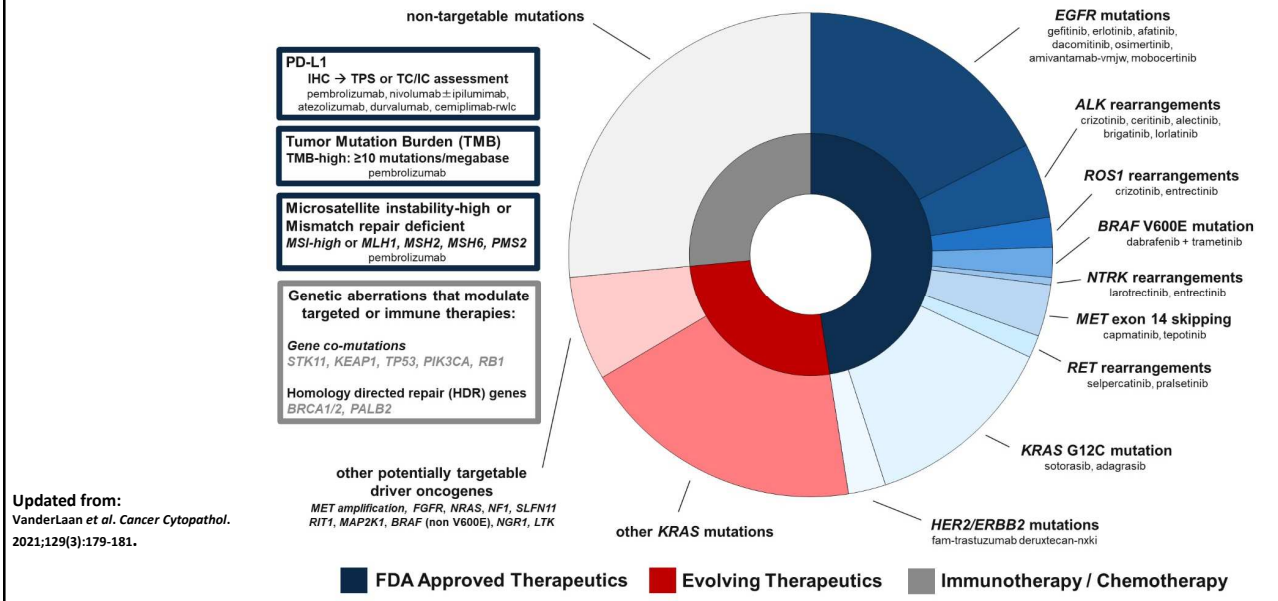
→ ∴ **Need to preserve material for molecular testing!**



Ancillary Testing



Landscape of genomic alterations in NSCLC with corresponding FDA-approved therapeutic options (May 2023)





Original Study

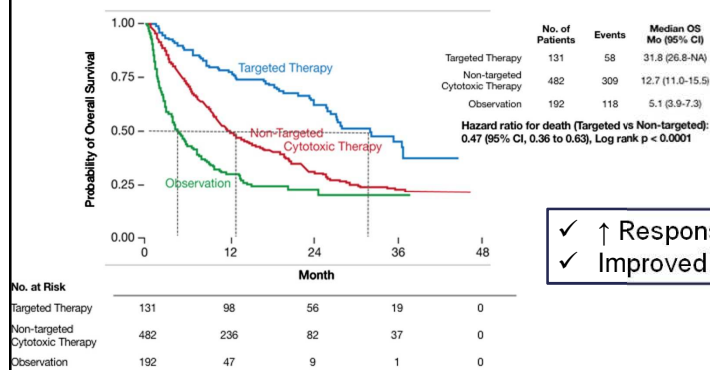
Virchows Arch (2018) 472:581–588
https://doi.org/10.1007/s00428-017-2268-y



Genomic Profiling of Advanced Non–Small Cell Lung Cancer in Community Settings: Gaps and Opportunities

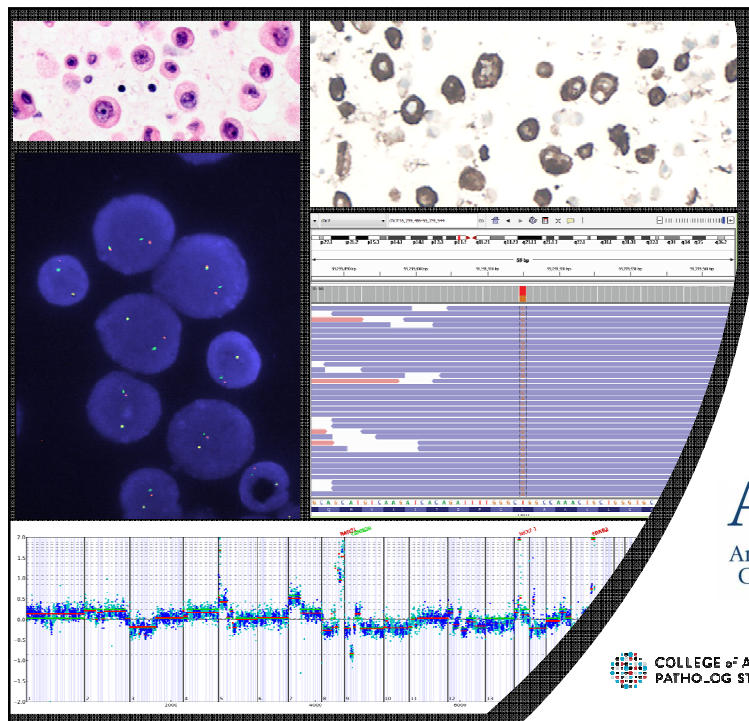
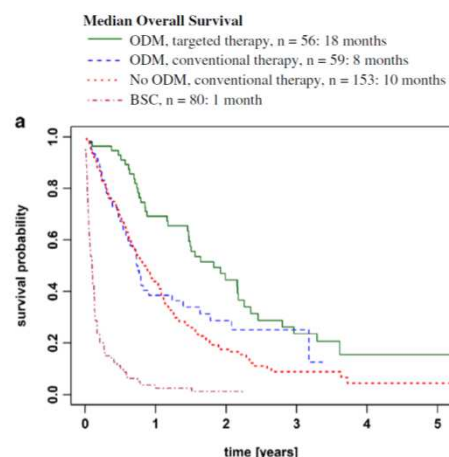
Martin E. Gutierrez,¹ Kelly Choi,² Richard B. Lanman,³ Edward J. Licita,⁴
Stanley M. Skrzypczak,³ Ruth Pe Benito,² Tommy Wu,² Srikesh Arunajadai,²
Sukhi Kaur,² Harry Harper,¹ Andrew L. Pecora,⁴ Eric V. Schultz,²
Stuart L. Goldberg²

Clin Lung Cancer. 2017;18:651–659.



Population-level effect of molecular testing and targeted therapy in patients with advanced pulmonary adenocarcinoma: a prospective cohort study

Christine Schwegler¹ • Dina Kaufmann² • David Pfeiffer^{1,3} • Stefan Aebi⁴ • Joachim Diebold^{1,3} • Oliver Gutschik⁴



NSCLC Testing Guidelines

ASCO[®]
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Clinical Oncology

NCCN
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Comprehensive
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Network[®]

COLLEGE of AMERICAN
PATHOLOGISTS

IASLC
INTERNATIONAL
ASSOCIATION
FOR THE STUDY
OF LUNG CANCER

INTERNATIONAL
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OF LUNG CANCER

AMP
ASSOCIATION
FOR MOLECULAR
PATHOLOGY

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Upcoming CAP Guidelines

Background

The CAP's Pathology and Laboratory Quality Center for Evidence-based Guidelines has several guidelines in various stages of the [Guideline Development Process](#). Learn more about the upcoming evidence-based guidelines that follow the National Academy of Medicine's [Guideline Principles](#).

Evidence-based Guidelines

Topic	Status
Lower Anogenital Squamous Terminology for HPV-associated Lesions (Updating 2010 publication)	Research and Review
PD-L1 Lung Tumors	Complete Recommendations
Principles of Analytic Validation of IHC Assays (Updating 2014 publication)	Complete Recommendations
Workup of Amyloidosis	Determine Scope and Form Panel
HPV Testing in Head & Neck Carcinomas (Updating 2017 publication)	Draft Recommendations
Molecular Testing for the Selection of Lung Cancer Patients for Treatment with TKI (Updating 2018 publication)	Research and Review
Interpretive Diagnostic Error Reduction (Updating 2015 publication)	Research and Review
Gastroenteropancreatic Neuroendocrine Tumors and Ki-67	Determine Scope and Form Panel – submit an application to be

Learn More

Read how we develop evidence-based guidelines and view current guidelines.

Learn about guideline development

View current guidelines

Submit Unpublished Evidence

Let us know about unpublished evidence pertaining to our guidelines in development.

Submit materials

2013

Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology

Neal I. Lindeman, MD; Philip T. Cagle, MD; Mary Beth Beasley, MD; Dharmajit Arun Chitale, MD; Sanjay Dacic, MD, PhD; Giuseppe Giaccone, MD, PhD; Robert Brian Jenkins, MD, PhD; David J. Kwiatkowski, MD, PhD; Jean-Sebastien Labrecque, MD; Jeremy Squire, PhD; Erik Thunnissen, MD, PhD; Marc Ladanyi, MD

2018

Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors

Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

Neal I. Lindeman, MD; Philip T. Cagle, MD; Dara L. Aisner, MD, PhD; Maria E. Arcila, MD; Mary Beth Beasley, MD; Eric H. Bernicker, MD; Carol Colasacco, MEd, SCT(ASCP); Sanja Dacic, MD, PhD; Fred R. Hirsch, MD, PhD; Keith Kerr, MB, ChB; David J. Kwiatkowski, MD, PhD; Marc Ladanyi, MD; Jan A. Nowak, MD, PhD; Lynette Sholl, MD; Robert Temple-Smith, PhD; Benjamin Solomon, MBBS, PhD; Lesley H. Souther, PhD; Erik Thunnissen, MD, PhD; Ming S. Tsai, MD; Christina B. Ventura, MPH, MT(ASCP); Murry W. Wynne, PhD; Yasushi Yatabe, MD, PhD

3rd edition CAP/IASLC/AMP Lung Biomarker Guidelines

✓ ~2024 target publication date

Expert/Advisory panel

Systematic Literature Review

Data extraction

Evidence grading

Drafting recommendations

Open comment period

Revise recommendations

Peer reviewed

Recommendations published

NCCN NSCLC guidelines

✓ 35 updates since 2018 CAP guidelines!

2018
NSCLC Guidelines Ver 3.2018
NSCLC Guidelines Ver 4.2018
NSCLC Guidelines Ver 5.2018
NSCLC Guidelines Ver 6.2018

2019
NSCLC Guidelines Ver 1.2019
NSCLC Guidelines Ver 2.2019
NSCLC Guidelines Ver 3.2019
NSCLC Guidelines Ver 4.2019
NSCLC Guidelines Ver 5.2019
NSCLC Guidelines Ver 6.2019
NSCLC Guidelines Ver 7.2019

2020
NSCLC Guidelines Ver 1.2020
NSCLC Guidelines Ver 2.2020
NSCLC Guidelines Ver 3.2020
NSCLC Guidelines Ver 4.2020
NSCLC Guidelines Ver 5.2020
NSCLC Guidelines Ver 6.2020
NSCLC Guidelines Ver 7.2020
NSCLC Guidelines Ver 8.2020

2021
NSCLC Guidelines Ver 1.2021
NSCLC Guidelines Ver 2.2021
NSCLC Guidelines Ver 3.2021
NSCLC Guidelines Ver 4.2021
NSCLC Guidelines Ver 5.2021
NSCLC Guidelines Ver 6.2021
NSCLC Guidelines Ver 7.2021

2022
NSCLC Guidelines Ver 1.2022
NSCLC Guidelines Ver 2.2022
NSCLC Guidelines Ver 3.2022
NSCLC Guidelines Ver 4.2022
NSCLC Guidelines Ver 5.2022
NSCLC Guidelines Ver 6.2022

2023
NSCLC Guidelines Ver 1.2023
NSCLC Guidelines Ver 2.2023
NSCLC Guidelines Ver 3.2023

National Comprehensive Cancer Network

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

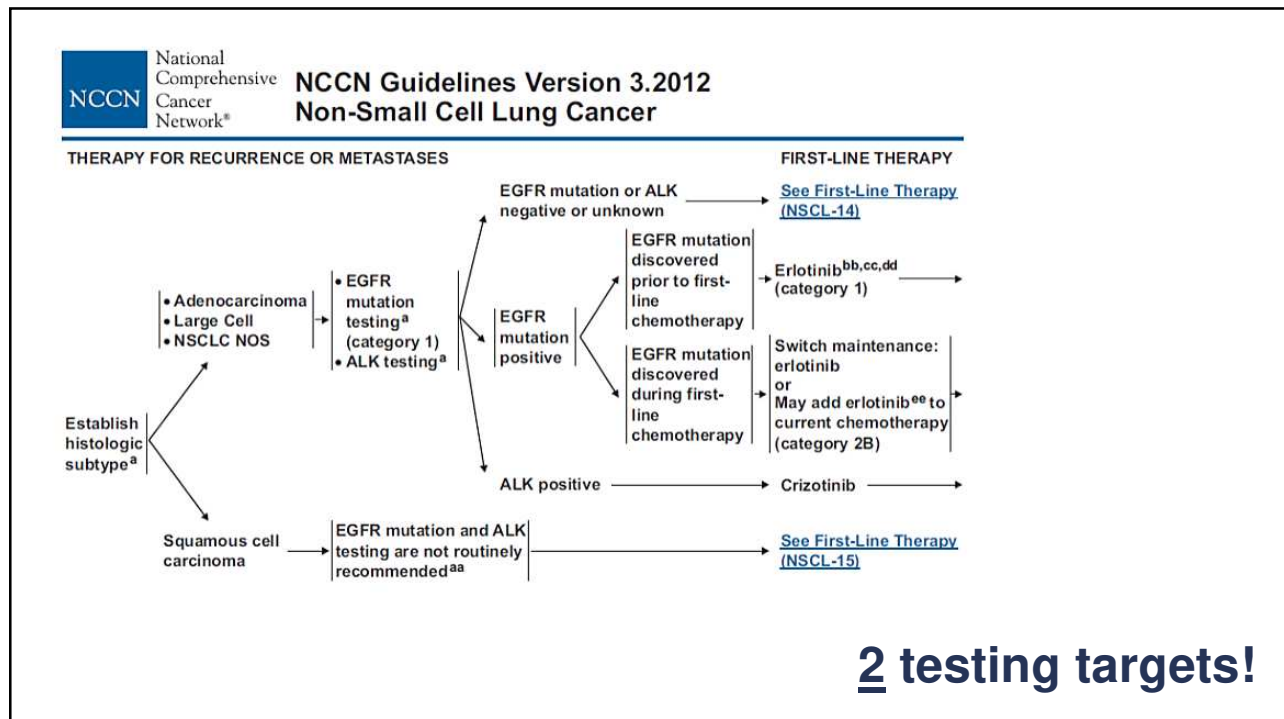
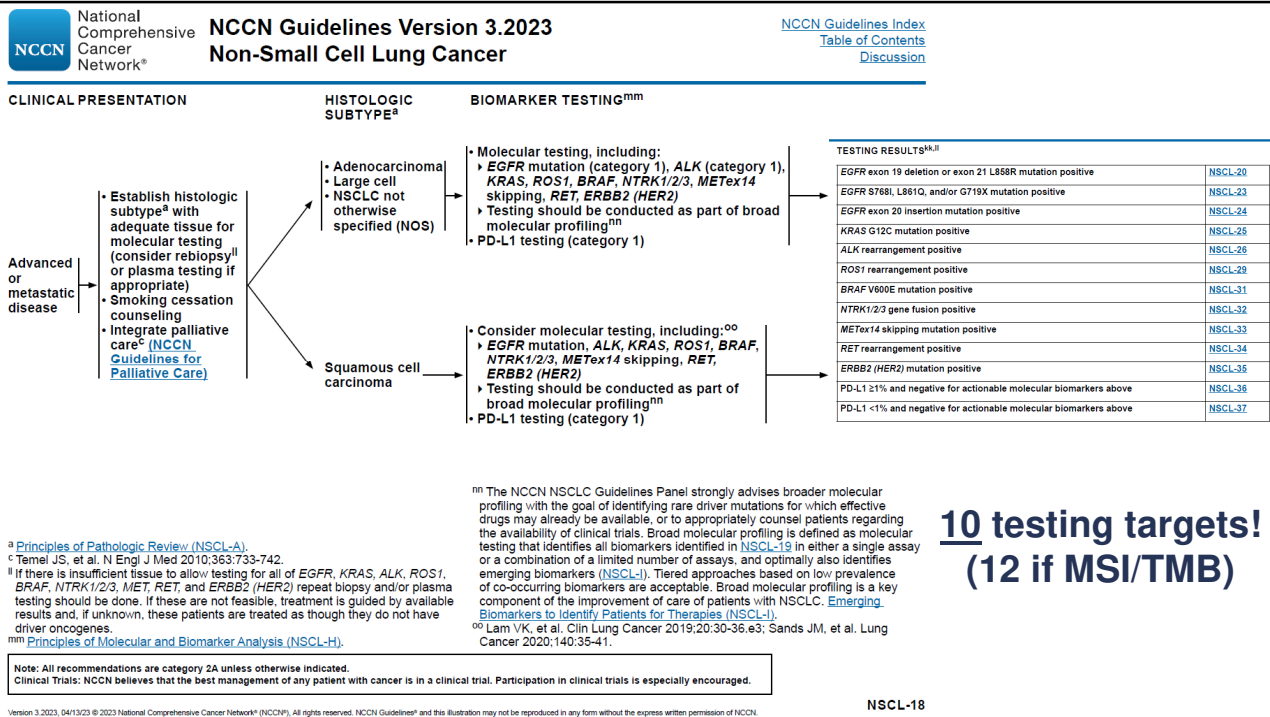
Non-Small Cell Lung Cancer

Version 3.2023 – April 13, 2023

NCCN.org

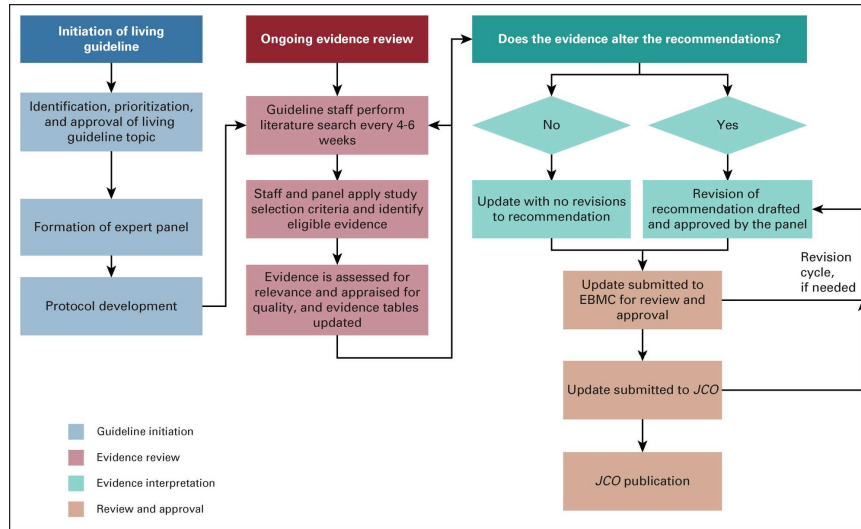
NCCN Guidelines for Patients® available at [nccn.org/patients](#)

Download



ASCO Living Guidelines: The Next Frontier

Veda N. Giri, MD¹; Thomas K. Oliver, BA²; R. Bryan Rumble, MSc²; Jonathan W. Friedberg, MD³; Kathy D. Miller, MD⁴; and Rachel L. Geisel, BS²



Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2022.2

Dwight H. Owen, MD, MS¹; Navneet Singh, MD, DM²; Nofisat Ismaila, MD, MSc³; Elizabeth Blanchard, MD⁴; Paul Celano, MD⁵; Narjust Florez, MD⁶; Dharmvir Jain, MD⁷; Natasha B. Leighl, MD⁸; Hirva Mamdani, MD⁹; Gregory Masters, MD¹⁰; Pamela R. Moffitt¹¹; Jarushka Naidoo, MD¹²; Tanyanika Phillips, MD¹³; Gregory J. Riely, MD, PhD¹⁴; Andrew G. Robinson, MD¹⁵; Erin Schenk, MD¹⁶; Bryan J. Schneider, MD¹⁷; Leticia Sequist, MD¹⁸; David R. Spigel, MD¹⁹; and Ishmael A. Jaiyesimi, MD, MS²⁰

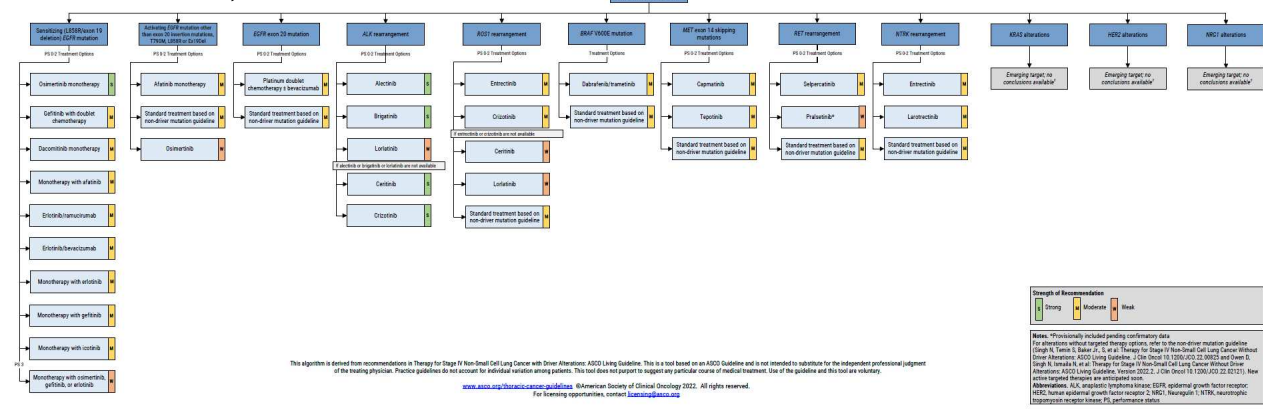
ASCO Guidelines

First-Line Treatment Options for Patients with Stage IV Non-Small Cell Lung Cancer with Driver Alterations

2022.1 Published: July 11, 2022

2022.2 Published: Dec 19, 2022

2022.3 Published: Feb 21, 2023



Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2023.1

Navneet Singh, MD, DM²; Ishmael A. Jaiyesimi, DO, MS²; Nofisat Ismaila, MD, MSc³; Natasha B. Leighl, MD⁸; Hirva Mamdani, MD⁹; Tanyanika Phillips, MD, MPH¹³; and Dwight H. Owen, MD, MS²⁰

Published: April 6, 2023

Lung Cancer Biomarker Testing Modalities

	IHC	FISH	PCR	NGS – DNA	NGS – RNA
EGFR	Limitations / Only specific uses	Not an option	Limitations / Only specific uses	Most common / Optimal modality	Not an option
ALK	Most common / Optimal modality	Most common / Optimal modality	Limitations / Only specific uses	Most common / Optimal modality	Most common / Optimal modality
ROS1	Limitations / Only specific uses	Most common / Optimal modality	Limitations / Only specific uses	Most common / Optimal modality	Most common / Optimal modality
BRAF V600E	Limitations / Only specific uses	Not an option	Most common / Optimal modality	Most common / Optimal modality	Not an option
MET Ex14	Not an option	Most common / Optimal modality	Limitations / Only specific uses	Most common / Optimal modality	Most common / Optimal modality
RET	Not an option	Most common / Optimal modality	Limitations / Only specific uses	Most common / Optimal modality	Most common / Optimal modality
KRAS	Not an option	Not an option	Most common / Optimal modality	Most common / Optimal modality	Not an option
NTRK1/2/3	Most common / Optimal modality	Most common / Optimal modality	Limitations / Only specific uses	Limitations / Only specific uses	Most common / Optimal modality
ERBB2	Not an option	Not an option	Most common / Optimal modality	Most common / Optimal modality	Not an option
TMB	Not an option	Not an option	Limitations / Only specific uses	Most common / Optimal modality	Not an option
MSI/MMR	Most common / Optimal modality	Not an option	Most common / Optimal modality	Most common / Optimal modality	Not an option
PD-L1	Most common / Optimal modality	Not an option	Not an option	Not an option	Not an option

Most common / Optimal modality

Limitations / Only specific uses

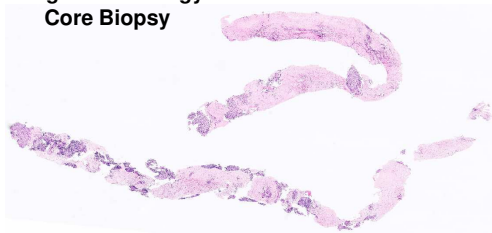
Not an option

∴ No single test will capture every biomarker!

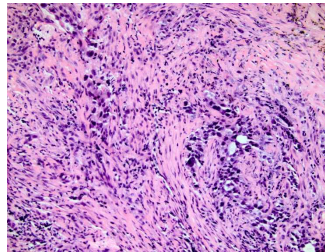
Updated from: VanderLaan et al. / Am Soc Cytopathol. 2022;11(6):403-414.

PD-L1: IHC as the selection biomarker

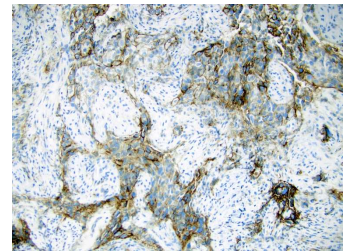
Surgical Pathology
Core Biopsy



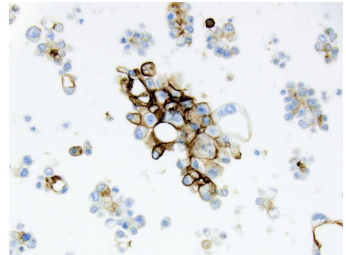
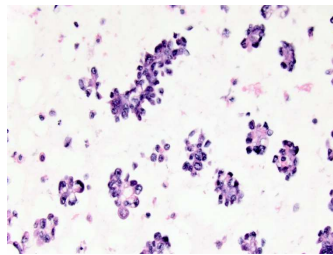
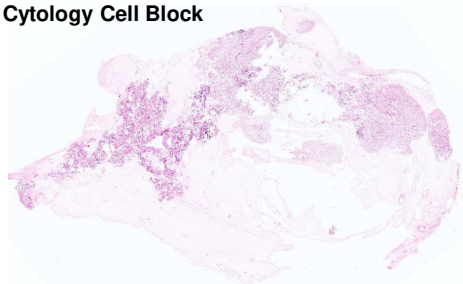
H&E / IHC / Molecular testing



PD-L1 IHC (22C3)



Cytology Cell Block



Current BIDMC NSCLC NGS Testing

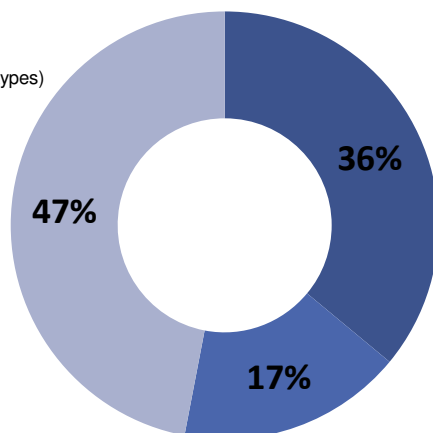
2021 stats:

NSCLC n=230

- 33% of all solid tumor NGS testing
- ~93+% success rate (no Δ across specimen types)
- Testing phase: 10 calendar day TAT

Liquid Biopsy n=50

- 61% of all solid tumor NGS liquid bx
- ~82% success rate
- Testing phase: 10 calendar day TAT



■ Cytology Cell Block

■ Surgical resection

■ Small Biopsy

Specimen Handling

CAP Laboratory Improvement Programs

Collection and Handling of Thoracic Small Biopsy and Cytology Specimens for Ancillary Studies

Guideline From the College of American Pathologists in Collaboration With the American College of Chest Physicians, Association for Molecular Pathology, American Society of Cytopathology, American Thoracic Society, Pulmonary Pathology Society, Papanicolaou Society of Cytopathology, Society of Interventional Radiology, and Society of Thoracic Radiology

Sinchita Roy-Chowdhuri, MD, PhD; Sanja Dacic, MD, PhD; Mohiudeen Chofrani, MD, MBA; Peter B. Illei, MD; Lester J. Layfield, MD; Christopher Lee, MD; Claire W. Michael, MD; Ross A. Miller, MD; Jason W. Mitchell, MD, MPH, MBA; Boris Nikolic, MD, MBA; Jan A. Nowak, MD, PhD; Nicholas J. Pastis Jr, MD; Carol Ann Rauch, MD, PhD; Amita Sharma, MD; Lesley Souter, PhD; Brooke L. Billman, MLIS, AHIP; Nicole E. Thomas, MPH, CT(ASCP)^{CM}; Paul A. VanderLaan, MD, PhD; Jesse S. Voss, CT, MB(ASCP)^{CM}; Momen M. Wahidi, MD, MBA; Lonny B. Yarnus, DO, MBA; Christopher R. Gilbert, DO, MS

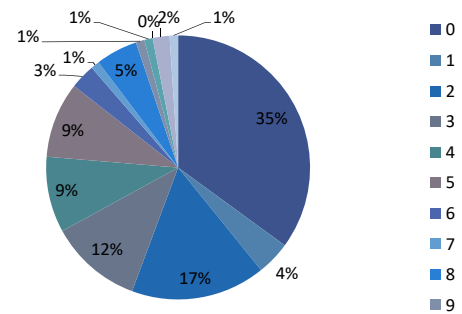
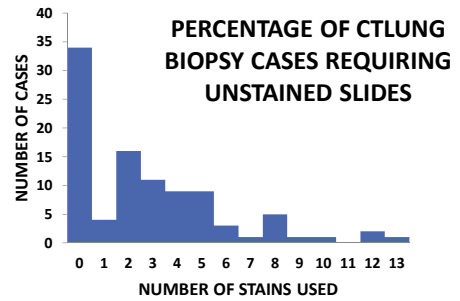
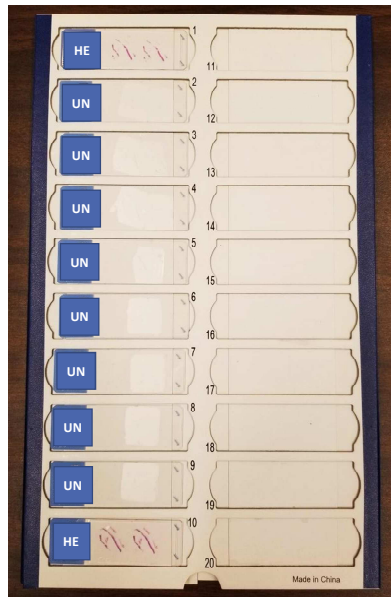
✓ Obtaining adequate material

- Optimal techniques
- Needle gauges
- Number of samples/needle passes

✓ What to collect and how to process

✓ Use of Rapid On-Site Evaluation (ROSE)

CT-guided lung core needle biopsy

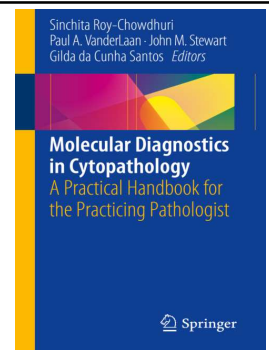
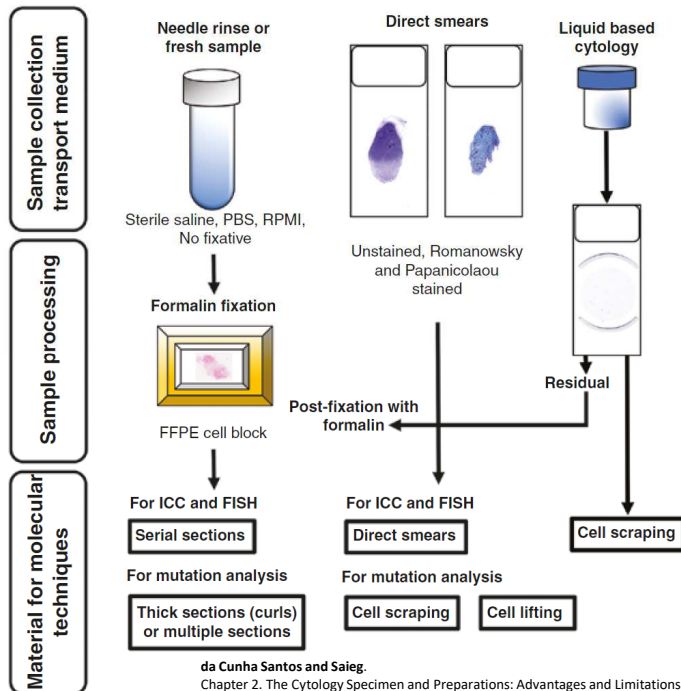


→ 4 unstained slides = 77% of cases

Specimen Triage



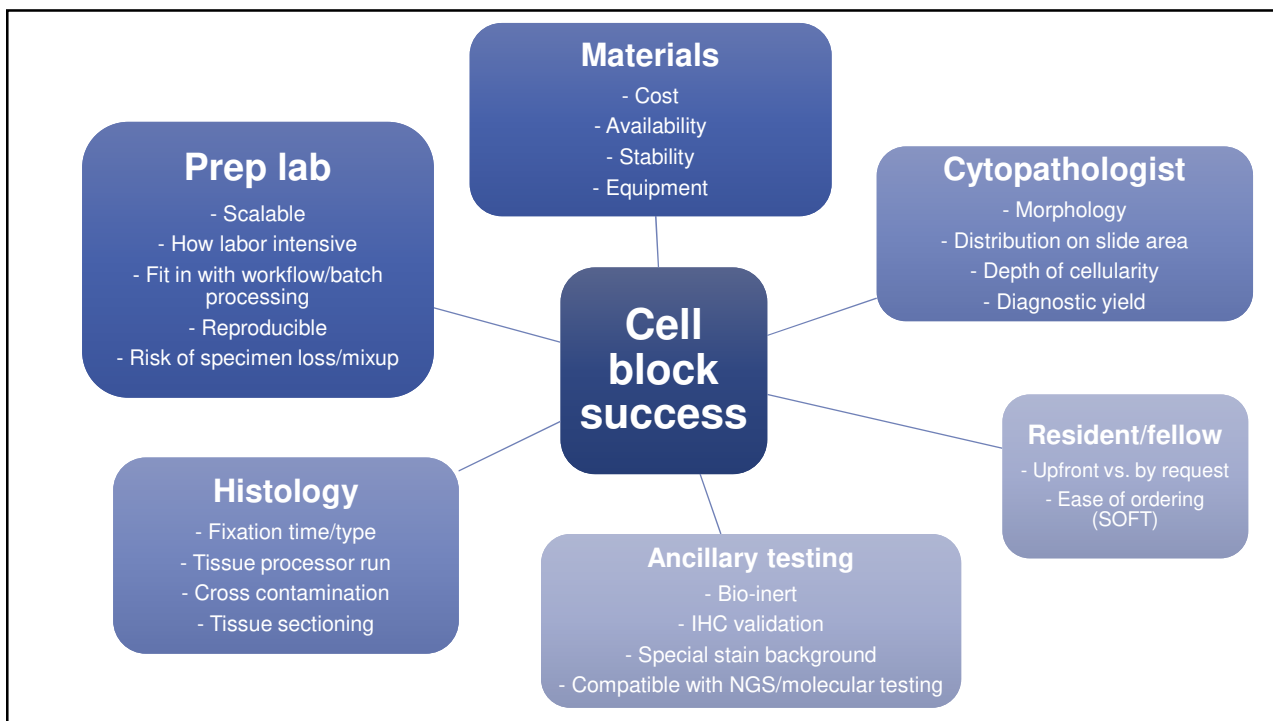
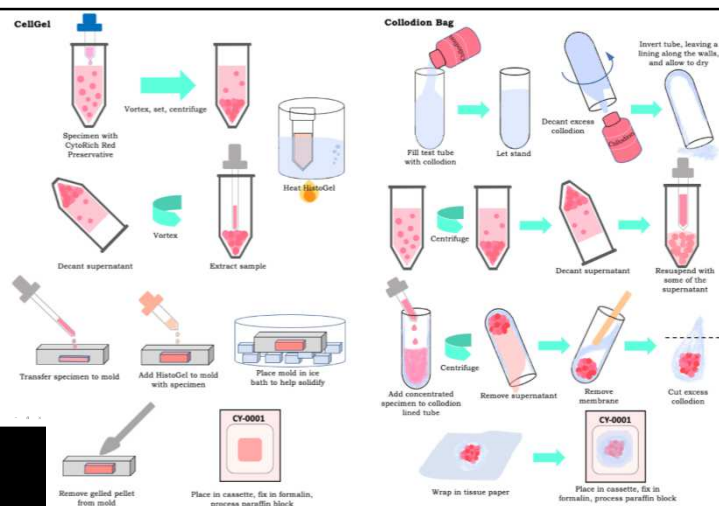
Testing Success



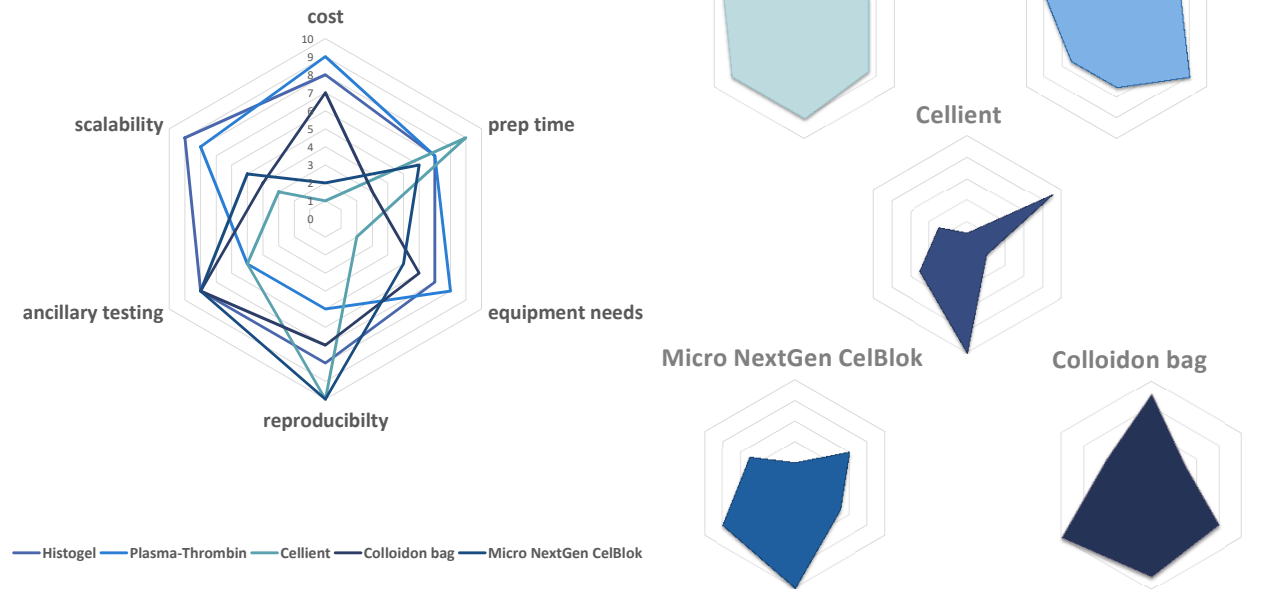
da Cunha Santos and Saieg.
Chapter 2. The Cytology Specimen and Preparations: Advantages and Limitations
in: Molecular Diagnostics in Cytopathology. Springer (2019)

Cell blocks in cytology: review of preparation methods, advantages, and limitations

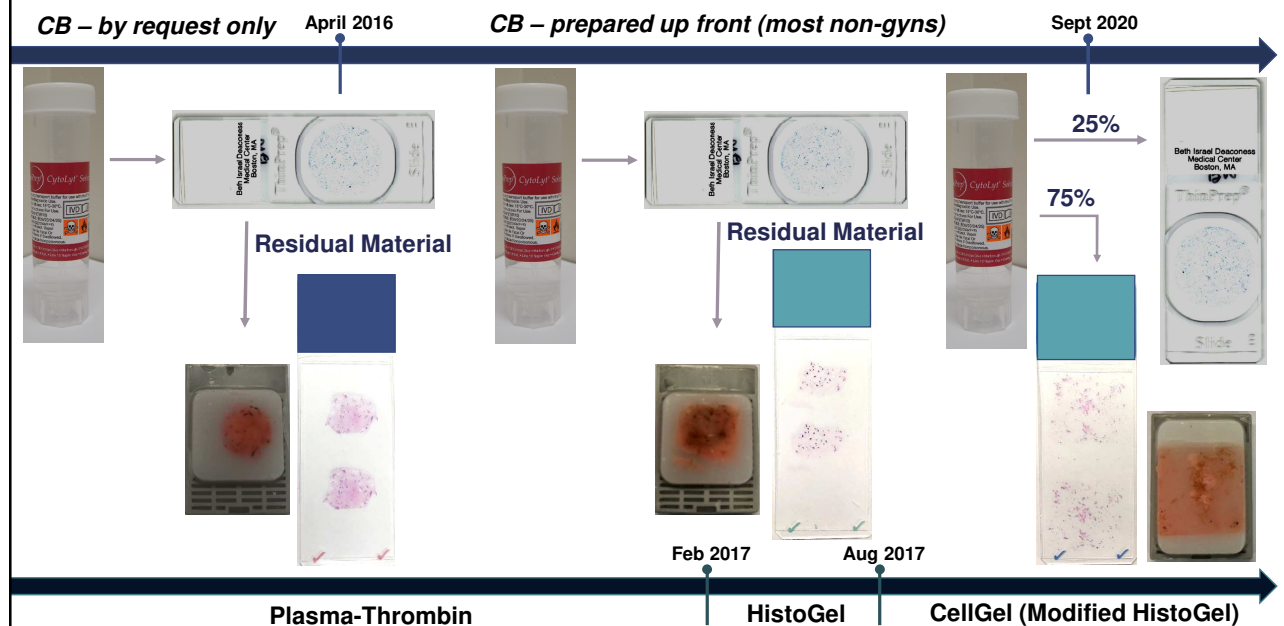
Vanda F. Torous, MD^{a,*}, Jacqueline M. Cuda, BS, SCT (ASCP)^b,
Varsha Manucha, MD^c, Melissa L. Randolph, BS, SCT (ASCP)^d,
Qiuying Shi, MS, MD^e, Christopher J. VandenBussche, MD, PhD^f,
American Society of Cytopathology Clinical Practice Committee



Cell Block Comparison

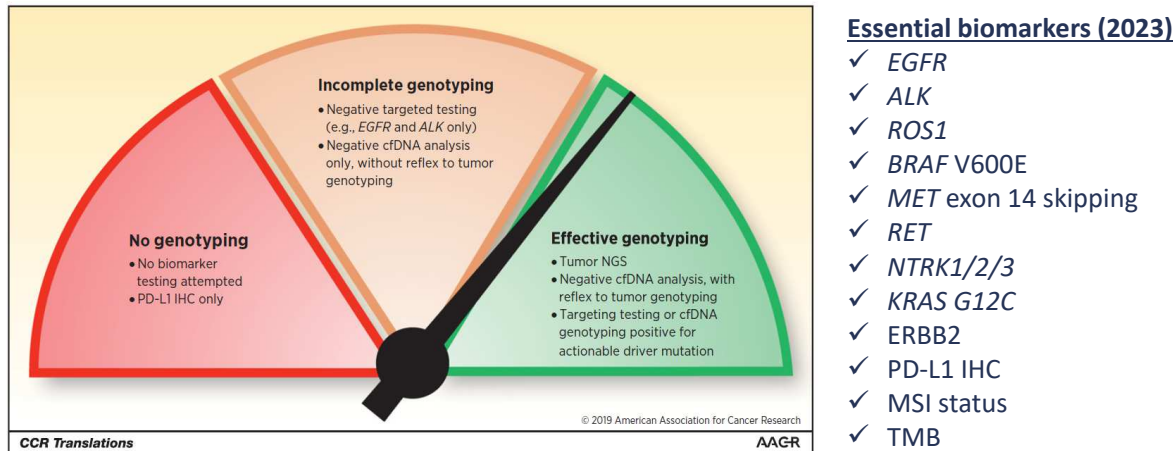


Evolution of Cell Blocks at BIDMC



Pathology:

Must ensure ancillary testing is adequate



Meador and Oxnard. *Clin Cancer Res* 2019;25:4583–5

Conclusions

- Tremendous progress in diagnosis and treatment of patients with NSCLC
- Cytology/small biopsy specimens are the primary diagnostic and ancillary testing modality for most patients with lung cancer.
 - ✓ Multiple objectives for the (cyto)pathologist.
- Oncologists *need* ancillary testing results to guide appropriate therapy.
 - ✓ Number of biomarkers continues to expand.
- **Coordination** and **collaboration** is key to testing success!
 - ✓ Pathology/Cytopathology
 - ✓ Oncology
 - ✓ Molecular lab

**Advances in Cytology and
Small Biopsies**

TUESDAY JUNE 13, 2023

Pulmonary Cytology: Workup of NSCLC on FNA and Small Biopsy



Paul VanderLaan MD, PhD

*Director of Cytopathology, Surgical Pathology, and Thoracic Pathology
Beth Israel Deaconess Medical Center
Associate Professor of Pathology
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