collapse recognized as an ex vivo artifact.\(^2\)

Parenthetically, one must consider that MIP pattern
in airspaces may represent a retraction artifact, a
recognized phenomenon in poorly fixed resection
specimens.\(^3\)

Not surprisingly, the authors report a frequent as-
sociation of both “filigree” and “classical” patterns in
their cases and a lack of significant prognostic differ-
ences between the two patterns. More necroses and
fewer psammoma bodies in the “filigree pattern” may be
an orientation-dependent interpretation of the same
lesion and a statistical type I error.

A diagnosis of surgical pathology is, in large part, a
pattern recognition exercise; however, it only works
when it follows logical morphologic observations.
Perhaps, this is why reproducibility values are low for
most adenocarcinoma subtypes and the notation of mi-
nor subtypes in 5% increments.\(^4,5\) Adding another
pseudopattern masquerading as a new concept will not
aid diagnosis or reproducibility.

As thoracic oncology has entered the era of tar-
geted therapy, morphologic subclassi-
cations are not
nearly as important as they once were. Perhaps the
authors should consider the widely held and generally
accepted notion that simple rather than complex
morphologic classification schemes are more repro-
ducible and of far greater utility to our clinical
colleagues.

The Newly Described Filigree Pattern Is an
Expansion of the Micropapillary
Adenocarcinoma Concept
Rather Than a Proposed
New Subtype

To the Editor:
We appreciate the opportunity provided by the letter
from Thunnissen and Flieder to clarify any misunder-
standing regarding our recent publication, which
described the filigree micropapillary (MIP) pattern of
lung adenocarcinoma.\(^1\)

We described the filigree MIP pattern as tumor cells
growing in delicate, lacelike, narrow stacks of cells
without fibrovascular cores, with attachments to alve-
olar walls that are frequently visible when the cross-
section is cut.

First, we would like to correct Thunnissen et al.’s
misunderstanding of our article’s goal, which was not to
define a new subtype but rather to expand the concept of
the MIP subtype to include the filigree pattern. This is on
the basis of supportive data that exhibit similar de-
mographics, clinical behavior, and histologic features of
filigree versus classical MIP patterns. Even though
numerous clinicopathologic studies have consistently
reported that the MIP pattern is associated with poor
prognosis,\(^2-7\) the MIP pattern is the most
underrecognized histologic subtype of lung
adenocarcinoma. We postulated that the lack of
appreciation of the filigree pattern may be one of the
reasons that the MIP pattern is overlooked. Supported
by our data from the analysis of a large cohort of
patients, we proposed that the filigree pattern should be
categorized as an MIP pattern. Our proposal to

References
of micropapillary adenocarcinoma to include a newly
recognized Filigree pattern as well as the classical
pattern based on 1468 stage I lung adenocarcinomas.
2. Thunnissen E, Blauwgeers HJ, de Cuba EM, Yick CY,
Flieder DB. Ex vivo artifacts and histopathologic pitfalls in
Thunnissen E. Gross handling of pulmonary resection
specimen: maintaining the 3-dimensional orientation.
4. Thunnissen E, Beasley MB, Borczuk AC, et al. Reproduc-
ibility of histopathological subtypes and invasion in pul-
monary adenocarcinoma. An international interobserver
5. Wright J, Churg A, Kitaichi M, Yang HM, Hyde D, Yi E.
Reproducibility of visual estimation of lung adenocarcinoma
recognize two patterns as one category serves to simplify the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society and European Respiratory Society classification, and also the 2015 WHO classification,[8,9] and at the same time expanding the role of pathologists in aiding clinicians to identify patients with poor prognosis. The criticism that our cartoon and microscopic images are two-dimensional overlooks the point that these figures were intended for, which was to educate pathologists who practice their clinical work by reviewing images in two dimensions. Although some filigree cellular structure could result from tangential cuts of classical MIP, there are cases in which this is unlikely owing to a large number of filigree structures in the absence of classical MIP areas nearby.

The statement that reproducibility values are low for most adenocarcinoma subtypes and also further questioning the reproducibility of the recorded 5% increments in the patterns ignores other published data and implementation of these recommendations in multiple institutions worldwide. We take this opportunity to educate and remind the readers that the 2015 WHO classification encourages the use of comprehensive histologic typing to determine the predominant pattern in 5% increments for two reasons. First, allow for greater flexibility in choosing a predominant pattern for cases in which there are two patterns with similar percentages (e.g., one can choose 55% versus 45% for the two patterns rather than 60% versus 40% using 10% increments or 50% and 25% using 25% increments), or for cases in which there are four to five patterns present. Second, facilitate the recording of small amounts of poor prognostic patterns, such as MIP or solid, as multiple publications have documented that even in small amounts of 5%, these patterns are associated with poor outcome.[7] Of course, reproducibility for percentages of adenocarcinoma patterns will be better when using larger percentage cutoffs, such as 10% to 25%, given that reproducibility improves with fewer categories; but this practice could result in the overlooking of the minor 5% poor prognostic patterns, which are highly relevant clinically. Also, this could make it more difficult to choose a predominant pattern for cases in which four to five patterns are present, or for cases in which two patterns have similar percentages. Recording of minor components at 5% amounts may be also important for the upcoming IASLC grading recommendations for lung adenocarcinoma, in which the recording of minor amounts of high-grade patterns is critical.[10]

Reproducibility results based on typical patterns or representative cohorts from routine clinical practice exhibit reproducibility that is moderate to substantial,[11-14] and it can improve after a training session.[15] The fact that studies based on difficult patterns exhibited poorer reproducibility (moderate to fair),[16,17] was precisely the reason for our efforts to identify, define, validate and educate pathologists regarding the filigree pattern and to further simplify adenocarcinoma classification by recognizing both filigree and the MIP pattern together. We hope that the abovementioned data directly answer the criticism of Thunnissen et al. that our article adds "another pseudopattern masquerading as a new concept (that) will not aid diagnosis or reproducibility."

We are pleased that the authors have raised the issue that MIP in airspaces may represent a retraction artifact that can be seen in fixed resection specimens. Although this may be true in some cases, three-dimensional imaging studies have revealed that MIP clusters in airspaces within the main tumor are actually attached to surrounding alveolar walls and not free-floating as they seem in two-dimensional imaging (Y. Yagi, unpublished observations).[18-20]

We would also like to comment on the statement that "as thoracic oncology has entered the era of targeted therapy, morphologic subclassifications are not nearly as important as they once were." We agree with the comment that thoracic oncology has entered into the era of targeted therapy, but this is in the context of advanced lung adenocarcinomas; we remind the reader that the focus of our article is surgically resectable stage I adenocarcinomas. We would like to highlight that the guidelines addressing patients with early-stage lung cancer from the IASLC/College of American Pathologists and Association for Molecular Pathology do not recommend mandatory molecular testing for these early-stage tumors.[21] The National Cancer Comprehensive Network does not recommend adjuvant chemotherapy for stage IA cancers and also states that this is optional for some high-risk patients with stage IB cancer.[22] In stage I lung adenocarcinomas with 15% to 25% recurrence after curative surgical resection, we feel obligated to investigate and expand the utility of the morphologic pattern of classification that has already proven to be of great prognostic significance. However, the efficacy of molecular-targeted adjuvant therapy after resection of early-stage lung adenocarcinoma is not established.[23]

Although we agree that targeted therapies and the knowledge of mitogenic drivers have transformed thoracic oncology, we strongly disagree that this renders morphologic classification less relevant. Multiple
The aforementioned studies illustrate the ability of histologic parameters in adenocarcinoma to strongly predict the risk of recurrence of early-stage tumors.\textsuperscript{24–29} In addition, the histologic type was found to predict response to adjuvant therapy\textsuperscript{30} and its association with prognosis in stage IV disease.\textsuperscript{31} The potential of histologic parameters to contribute to treatment decisions is thus immense, and can further advance the care of patients with lung cancer in the era of targeted therapies.

We are pleased to have the opportunity to correct the suggestion by Thunnissen et al. that our article makes the histologic classification of lung adenocarcinoma more complex. In contrast, our efforts in this article were to keep the classification simple by proposing that the filigree and classical patterns be regarded as one MIP pattern. Our study also clarified how morphologic patterns of lung adenocarcinoma, recognized by pathologists (who, in real-life, interpret two-dimensional slides), can provide prognostically significant information that is of great use to our clinical colleagues.

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\textbf{References}


15. Warth A, Cortis J, Fink L, et al. Training increases concordance in classifying pulmonary adenocarcinomas...
Emergence of High Level of MET Amplification as Off-Target Resistance to Selpercatinib Treatment in KIF5B-RET NSCLC

To the Editor:
Solomon et al.1 recently published a series of RET solvent-front mutations and, in some cases, concurrent RET gatekeeper mutations as on-target resistance mechanisms to selpercatinib. We report the case of a 48-year-old female never-smoker who presented with stage IV lung cancer with extensive metastases to the left pelvis with left acetabulum fracture. She received palliative radiation followed by 6 cycles of pembrolizumab by her then treating oncologist owing to a programmed death-ligand 1 (22C3) expression level of 90%. Initial plasma genotyping using Guardant360 (Guardant Health Inc., Redwood City, CA) around the time of diagnosis revealed KIF5B-RET fusion (allele frequency [AF]: 0.3%) and TP53 P190T (AF: 1.8%). Subsequent tumor genotyping revealed KIF5B-RET (K15, R12; AF: 16.10%) and TP53 P190T (AF: 51.05%) through FoundationOne CDx (Foundation Medicine Inc., Cambridge, MA). Of note, a nonreciprocal translocation RET-RPP38 (R11, R1) was noted from the tumor (AF: 17.80%). The patient did not respond to 6 cycles of single-agent pembrolizumab and received one cycle of carboplatin and pemetrexed chemotherapy before enrolling into the phase 2 trial of selpercatinib 160 mg twice daily (NCT03157128).

1. Solomon et al. 1 recently published a series of RET solvent-front mutations and, in some cases, concurrent