

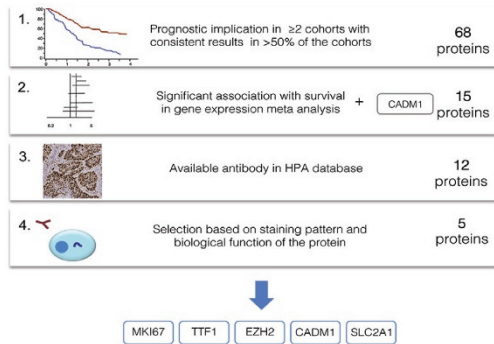
# INSIDE THE USCAP JOURNALS

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## MODERN PATHOLOGY

### Prognostication in NSCLC

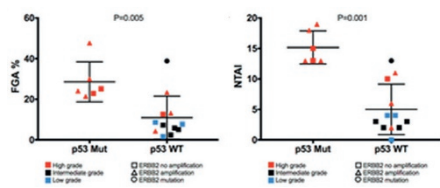
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Grinberg *et al* sought to determine whether there was room in the clinical setting for a prognostic model of protein biomarkers in non-small cell lung cancer (NSCLC). Developing prognostication tools to support clinical decisions in subgroups of patients who may not see benefit from adjuvant chemotherapy would be of significance. Despite stringent selection of the confirmed prognostic biomarkers MKI67, EZH2, SLC2A1, CADM1, and NKX2-1 (TTF1) for immunohistochemistry on tissue microarrays of 326 NSCLC patients, the combination of clinical and protein markers did not correctly classify a significantly greater number of patients as long- or short-term survivors beyond 2, 3, or 4 years. Although the authors acknowledge that marker selection might be responsible, they remain convinced that clinical practice will be better supported by further developing the parameters that are currently used for prognostication in these patients, TNM staging and accurate assessment of patient performance status being two such methods.

### Mutation analysis of ductal carcinoma *in situ*

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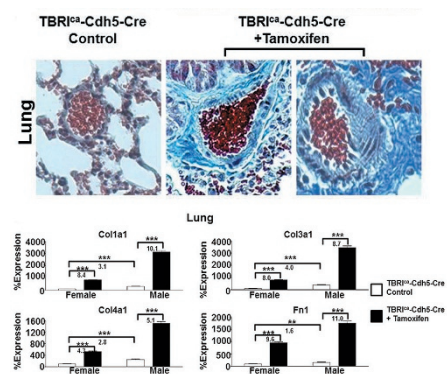
Massively parallel sequencing of a targeted panel of 107 cancer-related genes was used to identify mutations and copy number alterations in 20 ductal carcinoma *in situ* (DCIS) cases of various phenotypes. Mutations in genes involved in DNA

repair and cell cycle control, as well as transcription factors and other tumor suppressor genes, were identified. The novel findings were *RUNX1* mutations and *MAP2K4* copy number loss, not previously known in DCIS. The authors propose that *GATA3* mutations could be a marker for less aggressive behavior, as opposed to *TP53* mutations, which are associated with adverse tumor characteristics. Although they note that an increased panel of tissue matched to outcome data would be required to learn more about these potentially prognostic markers, the expanded sequencing shows promise and possible clinical efficacy in predicting the severity of genotypes present in these tumors.

## LABORATORY INVESTIGATION

### Endothelial cell-specific TGF- $\beta$ activation

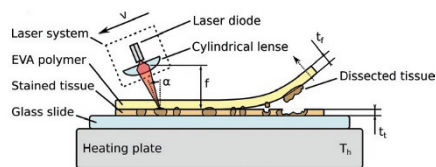
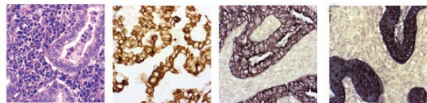
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Little is known about the pathogenesis or etiology of systemic sclerosis (SSc). Recent data indicate that this autoimmune disorder is a vascular disease, resulting from infiltration and downstream effects of infiltrating inflammatory cells. Transforming growth factor- $\beta$  (TGF- $\beta$ ) has been shown to be worthy of further investigation as a possible signaling pathway for SSc pathogenesis. In a mouse model of constitutive TGF- $\beta$  signaling, tissue fibrosis was accompanied by severe fibroproliferative vasculopathy. Increased collagen deposition in the visceral organs as well as marked fibrotic changes in the lung, heart, liver, and kidneys were observed. The authors express confidence that their model will become a valuable tool not only in further elucidating the etiology of SSc but, just as significantly, in the development of therapeutic agents that might halt its progression.

## Optimized dissection of lung cancer tissue

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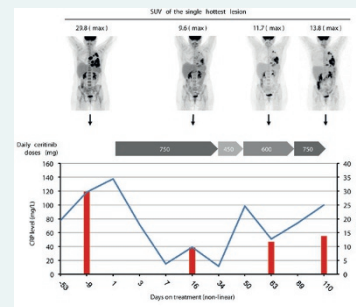
Grafen *et al* sought to develop a technique for assessing DNA alterations in tissue samples that demonstrate high cellular heterogeneity, as is sometimes encountered in lung cancer. The group developed an optimized method for expression-based microdissection, aiming to remove operator-dependent selection bias in selecting regions of interest. Whole-slide irradiation resulted in the removal of membranes where staining was most intensive, thus allowing the cells to be isolated without altering DNA quality. The authors observed that the amount of DNA extracted from ethylene-vinyl-acetate (EVA) membranes was lower than that from undissected control. This was understandable owing to the stroma and immune cells excluded by microdissection. The smaller DNA amount did not alter its quality, which indicated that neither the immunostaining nor laser irradiation of the EVA membrane adversely affected the use of the extracted analyte. Their technique is a rapid and reproducible microdissection method, and they believe it could be used in both diagnostic and scientific contexts.

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## nature.com/pathology

### ALK-rearranged inflammatory myofibroblastic tumor

ALK gene rearrangements are the most common derangements in inflammatory myofibroblastic tumors (IMTs). Several ALK inhibitors have been developed and used successfully in these tumors; however, resistance builds. The authors describe the treatment of a 36-year-old woman who was diagnosed with an IMT in 2009. Crizotinib treatment started in 2011 resulted in a good radiologic response until March of 2014. Next-generation sequencing revealed the acquisition of an *ALK<sup>G1269A</sup>* mutation as a mechanism of resistance. Ceritinib treatment was initiated in June 2014 and the patient showed a renewed response. However, disease progression was evident at day 110, and the patient died in February 2015. The authors propose that the next-generation ALK inhibitors have the capacity to overcome *ALK<sup>G1269A</sup>*-derived resistance. C-reactive protein levels were shown to correlate inversely with tumor response. They could be a potential serum marker of treatment response in future evaluations of ALK-inhibitor resistance, perhaps in other tumors and a wider patient population.



*npj Precision Oncology* 2017;1:4; doi:10.1038/s41698-017-0004-3

### Germline *ABL1* and congenital heart and skeletal defects



Wang *et al* report how *ABL1* germline variants such as c.734A>G cosegregate with an autosomal dominant disorder characterized by congenital heart disease, skeletal abnormalities, and failure to thrive. Looking at both isoforms of the *ABL* gene, the group identified affected families and showed informative pedigrees in four families. By transfecting HEK293T cells with plasmid constructs encoding c-terminal tagged wild-type and mutant proteins using complementary DNA, they were able to investigate downstream consequences of overexpression of the mutant variants, namely, an increase in overall phosphotyrosine levels as well as in phosphorylation of specific *ABL1* substrates. These results potentially connect to findings of congenital

malformations reported in fetuses exposed to the tyrosine kinase inhibitor imatinib, which is used in cancer treatment. The group proposes the identification of a novel genetic syndrome caused by constitutional *ABL1* variants. *ABL1* should be included in the growing list of genes involved in both cancer development and human developmental disorders.

*Nature Genetics* 2017;49:613–617; doi:10.1038/ng.3815

### Deep imaging of living tissue

A couple of years ago, we produced a special issue of *Laboratory Investigation* dedicated to novel imaging methods in pathology using fixed tissues. This included technologies potentially applicable to diagnostic pathology as well as novel research tools. Now, *Nature Methods* has produced a Focus issue on optical *in vivo* imaging—modalities that can be used in living tissues, even in a living animal. Owing to interactions of light sources and tissue that produce scattering and absorption, imaging deep within living tissues has been a challenge. The reviews and research papers in the Focus issue discuss new methods to image more deeply in a variety of animals, from model genetic organisms such as flies and worms to mice. It is possible that one day pathology itself might rely to some degree on diagnostic imaging of live tissues. The issue presents a wealth of methods of interest to researchers in this area as well as pathologists wanting to know what might be coming next.

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Emma Judson contributed to these reviews.

