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Predicting the future for people with lung cancer

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Abstract

A large multicenter study shows that lung adenocarcinomas have messenger RNA expression signatures that greatly add to the use of clinical data in predicting an individual's survival (pages 822–827).

A major goal of 'personalized' medicine for cancer is to develop the tools to sample a patient's tumor and then perform molecular analyses to identify the tumor type, its behavior in the patient, the patient's prognosis and the best treatment. The study by Shedden *et al*.[1] in this issue of *Nature Medicine* provides an important step in this direction.

The authors addressed the problems plaguing studies that attempt to systematically compile such molecular information: the small number of tumor samples, inconsistent and variable clinical data, and sample collection and processing that do not translate well to the real world environment[1].

In this study, the authors used common protocols at several different institutions to analyze more than 440 lung cancer samples, collected from six major clinical centers, for global mRNA expression. The researchers compared different ways of analyzing the mRNA data, emerging with several tumor-derived molecular signatures that reproducibly and robustly predicted the survival of individual human subjects when used in combination with standard clinical data. The study highlights the importance of collaboration between multiple groups to generate a large number of high-quality tumor specimens, with accurate clinical annotation, and the commitment of the US National Cancer Institute to fund and coordinate such an important enterprise.

Lung cancer is the biggest cancer killer in the US and in most parts of the world, with only 15% of all affected individuals surviving five years or more[2]. As Shedden *et al*.[1] point out, multiple studies show improved survival in individuals with lung adenocarcinoma given aggressive chemotherapy after surgical resection for cure. However, this benefit, although statistically significant, is quantitatively small. Additionally, the chemotherapy has major side effects, can lead to death and is expensive. Tumor gene expression profiles indicating which individuals have good prognoses and which have bad prognoses will be a great help in recommending such therapy.

The samples studied were all obtained as part of standard clinical practice and were not fractionated, and thus they contained both the tumor and its microenvironment. This is exactly the way lung cancer samples will be collected in the real world. The authors used a variety of statistical approaches to generate the signatures1, and they tested their results against other predictive signatures from the literature3,4. They found that only a few signatures consistently predicted survival, particularly in the group of subjects with the smallest amount of cancer to begin with (stage 1 tumors) 1. They also found that, in all cases, the molecular predictors were

improved by adding in standard clinical information1. They found that subjects with stage 1 tumors that had a 'bad' signature were more than twice as likely to die from from lung cancer (hazard ratio) compared to subjects whose tumors had the 'good' signature. These numbers represent a very big difference in predicted clinical outcome1.

In the current analysis, the researchers performed mRNA profiling, but investigators working in this field will be extending predictive signatures to protein expression, microRNA profiling, DNA copy number profiling and germ line DNA polymorphism analysis—along with genomic sequencing, tests for circulating tumor cells, quantification of cancer stem cells (cancer-initiating cells) in a tumor, and serum proteomic and antibody profiling[5–9]. In the future, combining such analyses could help clinicians make decisions about prognosis, response to therapy and susceptibility to toxic side effects.

The current study focused on prognosis—determining whether a subject was likely to survive1. Several preliminary studies suggest that such an approach will also help guide therapy, for instance by determining whether a tumor will respond to a specific drug or targeted therapy[10,11]. What's needed now are prospective studies testing the idea that survival can be predicted by molecular signatures indicating the use of specific therapies (for example, carboplatin plus paclitaxel or cisplatin plus gemcitabine chemotherapy given as adjuvant therapy to subjects with lung adenocarcinoma). The current study provides key baseline mRNA data for untreated individuals and will serve as a framework for the large collaborative effort required for such studies.

The tumor microenvironment may also contain clues about prognosis and appropriate therapy[12]. Future analyses will surely parse out the components of the mRNA signature that originate with the tumor or its microenvironment or that reflect the interaction between the tumor and the microenvironment, such as paracrine growth regulation, tumor angiogenesis and immune responses. The Shedden *et al.*[1] data will also be mined with bioinformatics combined with functional tests in the laboratory (for example, small interfering RNA gene knock-down and exogenous gene expression studies) to determine whether the genes in the signatures have any functional consequences for tumor biologic behavior.

Ultimately, all of the clinical information and tumor molecular data, combined with germline polymorphism information, will be integrated into an algorithm to develop an optimal treatment and prognosis plan for each individual afflicted with cancer (Fig. 1). This goal may be obtainable in the next few years.

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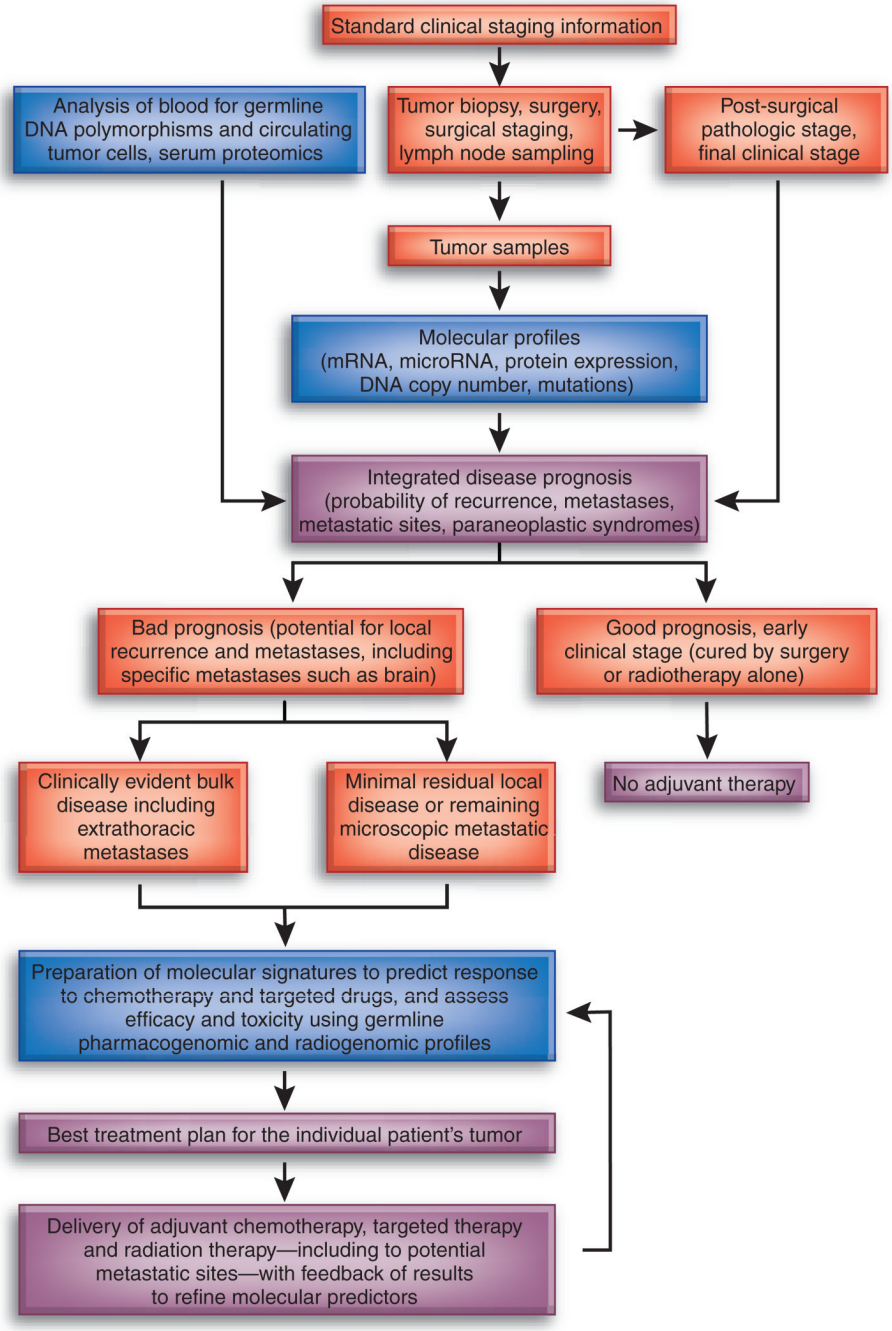

Figure 1.

Personalized medicine for lung cancer in the future. Integration of various molecular markers with clinical data will be used to develop prognosis and treatment plans for each individual patient. Standard clinical data will be integrated with tumor molecular markers, as well as germ line polymorphism differences and other potential biomarkers (such as circulating tumor cells). These data will feed into an integrated clinical and molecular predictor of prognosis, which could reveal the propensity of specific sites to develop metastases and the probability of tumor response to specific types of chemotherapy or to targeted agents and radiation therapy.