Blood test can differentiate between benign lung nodules and early stage lung cancer, study suggest

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Indi (Integrated Diagnostics), an emerging leader in molecular diagnostics, today announced the results of a major study which suggests that quantifying a combination of blood proteins can distinguish between benign lung nodules and early-stage lung cancer with high probability. The study, which was published today in *Science Translational Medicine* (STM), suggests that when this group of proteins (or 'classifier') is detected, and their relative concentrations are used to identify a patient's lung nodule (a round lesion of up to three cm) as benign, the classifier result is correct more than 90 percent of the time. This multiple protein expression classifier, which is intended to assist physicians with the early diagnosis of lung nodules, uses a highly sensitive analytic technique called multiple reaction monitoring mass spectroscopy (MRM-mass spec). This laboratory-based analytical method – combined with sophisticated bioinformatics and systems-biology approaches – allowed the researchers to assess the diagnostic power of 371 potential lung cancer biomarkers in millions of different combinations before settling on the diagnostic classifier (set of biomarkers) that these data indicate is most effective.

"These studies suggest that Indi's technology is capable of detecting the molecular signature of lung cancer by measuring the presence of multiple proteins in a patient's blood," said Paul Kearney, Ph.D., president and chief science officer, Indi and senior author of the STM paper. "We are very pleased that these data suggest we have achieved a

90 percent probability with this diagnostic classifier. Doing so required performing an unbiased search for biomarkers involved in early-stage lung cancer, considering all potential disease pathways. Using MRM-mass spec as the platform was essential because it makes it feasible to simultaneously measure hundreds of proteins at once. Conducting the broadest possible search for biomarkers allowed us to find the group with the greatest diagnostic value."

The proteins that make up the molecular signature of lung cancer are associated with several disease pathways, such as cell growth and proliferation, lung inflammation, and oxidative stress responses. Rather than look for a single biomarker – as is common among traditional diagnostics – the researchers looked for groups of 'cooperative' proteins – the ones that these data suggest have the most accurate diagnostic performance in combination rather than individually. In the paper, researchers describe how this was a crucial insight, as the cooperative proteins were often not the ones with the best individual performance for assessing lung nodules.

"Physicians often find managing their patient's lung nodules problematic because of the difficulty of differentiating which nodules have a lower or higher probability of lung cancer," said Kenneth C. Fang, M.D., chief medical officer, Indi; board certified pulmonologist and co-author of the STM paper. "Given the relative frequency with which physicians use invasive procedures like biopsy and surgery – and their associated risks – there is a high unmet need for a non-invasive test that provides clinicians with an additional, objective parameter for assessing lung nodules."

Indi researchers collected plasma samples from 143 patients from three sites to study the diagnostic value of various combinations of biomarkers. They came from patients with either benign nodules or Stage IA lung cancer, matched for nodule size, age, gender and clinical site. The sample matching strategy yielded a classifier whose results are

independent of a patient's age, smoking history or nodule size. Therefore the resulting classifier has the potential to complement each of these risk factors that are currently used in the clinical assessment of lung nodules.

"This study suggests the tremendous power of using systems biology and bioinformatics to better understand health and disease," said Lee Hood, M.D., Ph.D., co-author of the study; co-founder and board member of Indi; and co-founder of the Institute for Systems Biology (ISB), which collaborated with Indi on the study. "These systems approaches convert blood into a window that will readily allow us to distinguish health from disease—and if disease, which disease. This is just the beginning. The principles used to develop this classifier should be applicable to a range of unmet diagnostic medical needs."

The final group of proteins was validated in a second study that utilized an independent set of 104 plasma samples (52 with cancer; 52 benign), including successful validation of the classifier at a completely new hospital site. As with the earlier study, each malignant sample was matched with a benign sample of the same age, gender, nodule size and participating clinical site. In this study, the classifier was found to have a negative predictive value (NPV) of 90% – meaning that patients whose test results identify protein markers at concentrations suggesting that their nodule is "likely benign" may have a high probability of that classification being correct.

"We believe this technology, when applied to a commercial protein expression test, will be of tremendous interest to pulmonologists," said Albert A. Luderer, Ph.D., chief executive officer, Indi. "Clinicians encounter patients with lung nodules in their practices on a regular basis, which often lead to invasive procedures. We expect that a non-invasive test based on Indi's technology may be able to assist physicians in determining which nodules do not require risky and costly clinical interventions. Eliminating those invasive procedures on benign patients

should lead to significant savings in the healthcare system."

The STM paper is titled "A Blood-Based Proteomic Classifier for the Molecular Characterization of Pulmonary Nodules" and included the participation and/or the provision of clinical specimens from investigators and collaborators at Caprion Proteomics, the British Columbia Cancer Agency, ISB, the Institut Universitaire de Cardiologie et de Pneumologie de Quebec, the New York University Langone Medical Center and School of Medicine, the Perelman School of Medicine at the University of Pennsylvania, and the Vanderbilt University Medical Center.

Current Procedure for Managing Lung Nodules

Each year millions of patients undergoing CT scans are found to have pulmonary nodules. Patients whose nodules are initially deemed likely to be benign are generally followed up by CT scans performed over a two-year interval. If the clinician's initial assessment of the patient's lung nodule is later found to be incorrect, then the cancers are usually discovered early in the follow up period and remain at an early enough stage for therapeutic intervention.

In contrast, when physicians initially assess their patient's nodule to have a higher probability of lung cancer, they often undergo biopsies or surgeries to identify cancer. However, these invasive procedures often end up identifying the nodules as benign or turn out to be non-diagnostic, meaning that many patients may undergo costly, invasive procedures that turn out to be unnecessary.

More information: "A Blood-Based Proteomic Classifier for the Molecular Characterization of Pulmonary Nodules," by X. Li et al. *Science Translational Medicine*, 2013.

Provided by Indi (Integrated Diagnostics)