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PERCEPTA BRONCHIAL GENOMIC SEQUENCING CLASSIFIER FOR LUNG CANCER SCREENING

Keywords: lung nodule, screening, ribonucleic acid (RNA), field of injury

SUMMARY OF TECHNOLOGY

Percepta Bronchial Genomic Sequencing Classifier (GSC) is a medical device to improve the diagnosis of lung cancer patients by reducing the need for invasive procedures following detection of potentially cancerous lung nodules or lesions found on CT scans. It was developed by Veracyte partnered with Johnson and Johnson.

The 23-gene classifier identifies patients with lung nodules who are at low risk of cancer following an inconclusive bronchoscopy result, making it possible to monitor these patients with CT scans in lieu of invasive diagnostic procedures. The device uses proprietary genomic technology to measure gene expression alterations in bronchial epithelial cells collected from two brushings of the main stem airway of current or former smokers. These changes can be detected in cells obtained from standard brushings taken during bronchoscopy from the mainstem bronchus and indicate the presence of malignancy or disease processes from distant sites in the lung. Thus the test is designed to determine a lung nodule's or lesion's likelihood of cancer, without the need to sample the nodule or lesion directly.

The device is built using Veracyte's Ribonucleic acid (RNA) whole-transcriptome sequencing and machine-learning platform. The test uses novel "field of injury" science to identify genomic changes associated with lung cancer in current or former smokers by using a simple brushing of the person's airway. [1]

The field of injury stated that molecular changes occur throughout the tissue that are exposed to certain carcinogen. It reflects the host response from the carcinogen which may or may not be a precursor to premalignant lesions and frank malignancy. In other words, the normal-looking tissue which has been exposed to carcinogen repetitively may have some changes genomically.

The cytology samples can be obtained using fine-needle aspiration (FNA) biopsies, washings, brushings, lavages or from bronchoscopy biopsies, to diagnose the disease. The company is currently studying the efficacy of nasal swab to be used as sample collection.

Following sample collection, the cytology brushes are cut and placed in an RNA preservative immediately and stored at 4ºC. Specimens are then shipped at 4-20 ºC to laboratory. RNA are then isolated by phenol/chloroform extractions and purified. Total RNA (200nanograms) is converted to sense strand cDNA and undergoes microarray processing.

The technology has not been approved by any regulatory bodies for the proposed indications.

INNOVATIVENESS

Novel, completely new	√
Incremental improvement of the existing technology	
New indication of an existing technology	

DISEASE BURDEN

According to the International Agency for Research on Cancer (IARC) lung cancer has the highest percentages of new cases being diagnosed (11.6% of all new cases) and it was the leading cause of death (18.4%) of all cancers globally in 2018.[2]

The incidence is expected to continuously rising. The American Cancer Society's estimates that in 2019, about 228,150 new cases of lung cancer (116,440 in men and 111,710 in women) will be diagnosed and about 142,670 will die from lung cancer (76,650 in men and 66,020 in women). [3]

Early detection is the key to reduce lung cancer deaths and typically begins with identification of lung nodules on CT scans either through screening or incidentally.

The U.S. Preventive Services Task Force recommends yearly lung cancer screening with low-dose CT scan for people between the age of 55 and 80 years old who smokes more than 10 pack years, or an ex-smoker who quitted within the past 15 years.[4]

CURRENT OPTIONS FOR PATIENTS

Currently, annual screening with low-dose computed tomography (LDCT) is the only recommended screening strategy for lung cancer in some countries.[4, 5] However in Malaysia, due to its high cost and low specificity, it is recommended only for screening among high risk group or in research environment.[6] In diagnosing lung cancer, the preferred approach uses imaging (chest Xray, CT scan) as a road map and invasive biopsy as a tool to confirm both the histopathological diagnosis and the stage of disease.

According to National Institute for Health and Care Excellence (NICE), the criteria for suspected cancer pathway referral (for an appointment within two weeks) includes if they have chest X-ray findings that suggest lung cancer or are aged 40 and over with unexplained haemoptysis. An urgent chest X-ray (should be performed within two weeks) is offered for people aged 40 and over who have two or more of the following symptoms; or if they have ever smoked with one or more of the following symptoms: cough, fatigue, shortness of breath, chest pain, weight loss, appetite loss. An urgent chest X-ray is also considered for people aged 40 and over with any of the following such as recurrent chest infection, finger clubbing, supraclavicular lymphadenopathy or persistent cervical lymphadenopathy, chest signs consistent with lung cancer or thrombocytosis. A contrast-enhanced chest CT scan is offered for those with known disease or suspected lung cancer to further confirm the diagnosis and stage the disease. It includes the liver, adrenals and lower neck. PET-CT is the preferred choice for patient with a low probability of nodal malignancy (lymph nodes below 10 mm maximum short axis on CT), for people with lung cancer who could potentially have treatment with curative intent.[5]

Location of the lesion or the node is an important factor in choosing the test for diagnostic pathology. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is offered for biopsy of paratracheal and peri-bronchial intra-parenchymal lung lesions.[5]

POTENTIAL IMPACT OF TECHNOLOGY

Systematic search from MEDLINE, Embase, Cochrane Library and EUROScan database identifies three clinical trials and one cost-effectiveness study.

One prospective phase 3 clinical trial recruited 639 patients which consisted of smokers and former smokers suspected to have lung cancer undergoing

bronchoscopy. The patients were enrolled in the Airway Epithelial Gene Expression in the Diagnosis of Lung Cancer (AEGIS) trials (AEGIS-1 and AEGIS-2), two independent, prospective, multicenter, observational studies. A gene-expression classifier was measured in epithelial cells collected from the normal-appearing mainstem bronchus to assess the probability of lung cancer. Patients were followed until a diagnosis was established or until 12 months after bronchoscopy. A diagnosis of lung cancer was established at the time of bronchoscopy or subsequently by means of biopsy with the use of a transthoracic needle, a surgical biopsy, a second bronchoscopic examination, or another invasive procedure. The prevalence of lung cancer was 74% and 78% in the AEGIS-1 and AEGIS-2 cohorts, respectively. In AEGIS-1 (n=298), the classifier had an AUC of 0.78 (95% CI: 0.73, 0.83) and accurately identified 194 of 220 patients with cancer (sensitivity, 88%; 95% CI: 83, 92) and 37 of 78 patients without cancer (specificity, 47%; 95% CI: 37, 58). In AEGIS-2 (n=341, the classifier had an AUC of 0.74 (95% CI: 0.68, 0.80) and correctly identified 237 of 267 patients with cancer (sensitivity, 89%; 95% CI: 84, 92) and 35 of 74 patients without cancer (specificity, 47%; 95%: 36, 59). The combination of the classifier plus bronchoscopy increased the sensitivity to 96% (95% CI: 93, 98) and 98% (95% CI: 96, 99) in AEGIS-1 and AEGIS-2, respectively, as compared with 74% and 76% for bronchoscopy alone (P<0.001 for both comparisons). In patients with a nondiagnostic bronchoscopic examination, the classifier accurately identified cancer in 49 of 57 patients in AEGIS-1 (sensitivity, 86%; 95% CI: 74, 94) and in 58 of 63 patients in AEGIS-2 (sensitivity, 92%; 95% CI: 82, 97). Because there was no significant difference between the two cohorts with regard to the classifier AUC either among all patients (P=0.32) or among those with a nondiagnostic bronchoscopic examination (P=0.61), subsequent subgroup analyses by combining the cohorts were done and showed that the sensitivity of bronchoscopy was lower (75% CI: 71, 79) for lesions that were smaller than 3 cm in diameter (P<0.001) or peripherally located (P<0.001) as well as in patients without hilar or mediastinal adenopathy (P<0.001). In contrast, the sensitivity of the classifier (89%; 95% CI: 82, 94) and of the classifier combined with bronchoscopy were consistently high (97%; 95% CI: 95, 99) and not significantly associated with the size or location of the lesion, cancer stage, histologic type of the cancer, or presence of adenopathy. The combination of the classifier plus bronchoscopy had a sensitivity of 96% among patients without hilar or mediastinal adenopathy (285 patients). Bronchoscopy was nondiagnostic for cancer in 83% of patients with an intermediate pretest probability (101 patients), despite a cancer prevalence rate of 41% (95% CI: 31, 51). In this subgroup, the classifier achieved a negative predictive value of 91% (95% CI: 75, 98) and a positive predictive value of 40% (95% CI: 27, 55).[7]

Another validation accuracy study was done recruiting cohorts from AEGIS I, AEGIS II and Percepta Registry. The training set included 1611 patients from four cohorts and the validation set included 412 patients from three independent cohorts. The

inclusion criteria for this study included smoker or former smoker undergoing bronchoscopy who aged more than 21 years old with history of smoking more than 100 cigarettes in a lifetime with a pulmonary nodule on Chest CT scan. Patients were followed up until diagnosis was established or for 12 months after bronchoscopy. Two bronchial brushings were obtained during the initial bronchoscopy from cytologically normal appearing bronchial epithelial cells in the mainstem bronchus. The machine-learning algorithms inputting RNA sequencing results and clinical factors were used from more than 1600 patients to train the new Percepta Genomic Sequencing Classifier. The final classifier is an ensemble of four models which combine genomic and clinical features. The primary outcome measured are positive predictive value (PPV), negative predictive value (NPV), specificity and sensitivity in each pre-test risk category. The results showed the percepta GSC down-classified intermediate-risk patient to low-risk with 91% NPV and up-classified the intermediate-risk patients to high risk with PPV more than 65%.[8]

A clinical utility study was done among AEGIS trials participants to evaluate the potential of the classifier to reduce invasive procedure utilisation in patients with suspected lung cancer. The study recruited 222 patients with a low or intermediate pretest probability of cancer and 188 (85%) had an inconclusive bronchoscopy and follow-up procedure data available for analysis. Seventy-seven (41%) patients underwent an additional 99 invasive procedures, which included surgical lung biopsy in 40 (52%) patients. Seventy-seven (41%) patients underwent an additional 99 invasive procedures, which included surgical lung biopsy in 40 (52%) patients. Benign and malignant diseases were ultimately diagnosed in 62 (81%) and 15 (19%) patients, respectively. Among those undergoing surgical biopsy, 20 (50%) were performed in patients with benign disease. If the classifier had been used to guide decision making, procedures could have been avoided in 50% (21 of 42) of patients undergoing further invasive testing. Further, among 35 patients with an inconclusive index bronchoscopy who were diagnosed with lung cancer, the sensitivity of the classifier was 89%, with four (11%) patients having a false-negative classifier result.[9]

A study was conducted to assess the cost-effectiveness of bronchoscopy plus a genomic classifier versus bronchoscopy alone in the diagnostic work-up of patients at intermediate risk for lung cancer. A decision-analytic Markov model was developed to project the costs and effects of two competing strategies by using test performance from the Airway Epithelial Gene Expression in the Diagnosis of Lung Cancer–1 and Airway Epithelial Gene Expression in the Diagnosis of Lung Cancer–2 studies. A follow-up time horizon of two years was chosen in this study. The patients with an inconclusive result (either bronchoscopy alone or bronchoscopy plus a genomic classifer) would be followed up with either a second bronchoscopy, a TTNA procedure, or a surgical biopsy through VATS or thoracotomy. The option for noninvasive imaging follow-up were either computed tomography (CT) or positron emission tomography (PET) scan. The results showed that the use of the genomic

classifier reduced invasive procedures by 28% at one month and 18% at two years, respectively. Total costs and QALY gain were similar with classifier use ($27,221 versus $27,183 and 1.512 versus 1.509, respectively), resulting in an incremental cost-effectiveness ratio of $15,052 (about RM63069) per QALY GAIN.[10]

In conclusion, Percepta GSC has potential in diagnostic work-up of patient with intermediate risk of suspected lung cancer by avoiding unnecessary invasive surgical procedure following inconclusive bronchoscopy. It was proven to be cost-efective in United State of America.

EVIDENCE

Silvestri GA, Vachani A, Whitney D et al. A Bronchial Genomic Classifier for the Diagnostic Evaluation of Lung Cancer. New England Journal of Medicine. 2015;373(3):243-251.

Bhorade S, Bernstein M, Dotson TL et al. Accuracy of the Next Generation Percepta Genomic Sequencing Classifier (GSC) for the Diagnosis of Suspicious Intermediate Pulmonary Nodules. 2019.

Vachani A, Whitney DH, Parsons EC et al. Clinical Utility of a Bronchial Genomic Classifier in Patients With Suspected Lung Cancer. CHEST. 2016;150(1):210-218.

Feller-Kopman D, Liu S, Geisler BP et al. Cost-Effectiveness of a Bronchial Genomic Classifier for the Diagnostic Evaluation of Lung Cancer. Journal of Thoracic Oncology. 2017;12(8):1223-1232.

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