What the nose knows: Trends in biomimetic sensor technology

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Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication Dec 29, 2017; accepted for publication Jan 10, 2018; available ahead of print Feb 16, 2018.

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J Thorac Cardiovasc Surg 2018;155:2626-7

0022-5223/\$0.00

Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2018.01.031>

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Central Message

Electronic nose breath analysis is a promising technology for translation to a clinically useful lung cancer biomarker platform, but not before collaborative efforts address standardization issues.

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The early diagnosis of non–small cell lung cancer (NSCLC) via an accurate, reliable, noninvasive, zero-risk (to the patient) methodology remains an elusive reality in the clinic. This current paradigm of the lack of a widely adopted, clinically useful diagnostic NSCLC biomarker^{1,2} may change in the near future with ongoing development of e-nose technology, as highlighted by Dr Rocco and colleagues³ in this issue of the *Journal*.

Exhaled breath analysis for diagnostics is underpinned by recognition of diseases from unique combinations of metabolites, some of which are volatile organic compounds (VOCs) as by-products of oxidative stress⁴ entering air through alveolar-capillary membrane gas exchange. The e-nose is a new class of biomedical device inspired by the mammalian olfactory system that mimics odor discrimination by combining an array of sensors interacting with multiple vapor analytes, a signal transduction mechanism, and pattern recognition algorithm (computer software) into a measurement platform. Breath-collection methods occur by the entire expired air volume or just the alveolar air volume (where the concentration of VOC is highest and contaminants are lowest, but is technically more challenging to isolate).

Early platforms relied on quantitative analysis using gas chromatography–mass spectrometry identification of specific VOCs in exhaled breath compared with metabolite reference libraries of known standards. A great amount of expense, sophisticated equipment, specialized personnel, and numerous other factors such as lung washout, diet, exogenous exposures, and breath sample collection practices/hardware, to mention a few, impede widespread adoption of this technology for large-scale use. To overcome the multitude technical limitations inherent in this type of breath analysis, many groups have refined qualitative, pattern-based “breathprint” systems as discussed here.⁵ Thus, the e-nose is trained to build a database for recognition that is subsequently applied to classifying unknown samples. Aside from the discriminant performance of the

recognition computational algorithm, the size of the training set, how well the samples represent the target population, and the internal versus external validation are crucial factors of meaningful pattern recognition.

Dr Rocco and colleagues⁶ tested their BIONOTE breath analyzer platform in a high-risk patient group in whom the e-nose technology is based on gravimetric sensors (ie, oscillation frequency as the sensing parameter) that characterize analytes by mass. Of note, the Pneumopipe device circumvents many problems encountered with the breath sample collection technique, storage, and logistics of specimen processing/data acquisition because VOC are captured onto a cartridge, which can be analyzed at a more convenient time later. Furthermore, the BIONOTE platform has been refined to enable low-cost disposable materials for each breathprint test. In contrast, the technology used by Shlomi and colleagues⁷ is based on proprietary electrical type sensors (nanomaterial chemiresistors) arranged in an array ($n = 40$). Alveolar air from patients was collected during a slow exhalation protocol into a specialized plastic bag, and the air contents were finally trapped on a sorbent tube. These authors sought to extend the utility of breathprint analysis by detection of epidermal growth factor receptor (EGFR) mutation in patients with NSCLC. However, there are many missing details such as patient factors in breath exhalation, logistics of breath collection, and

sorbent tube properties, which VOCs were identified by nanosensors, the specific type of EGFR mutation (exons 18, 19, 20, or 21), as well as study design limitations (ie, small size sampled). Further, it is not intuitive that EGFR mutants would necessarily exhibit a unique VOC breathprint versus non-EGFR NSCLC.

With ongoing technologic progress, the prospect that an e-nose could provide highly accurate vapor component analysis in a clinically practical manner seems within reach eventually. Both of the aforementioned technologies are intrinsically plagued by peculiar limitations due to nonuniformity of surface coatings, humidity, or ambient temperature requiring frequent recalibrations. Optimistically, e-nose systems using optical sensors characterizing analytes by electron/photon properties surmount many of these shortcomings while maintaining high accuracy and specificity.⁸ These technologic milestones notwithstanding, there are current needs for standardization of breath collection, sample storage/logistics, data analysis, and validation criteria. Hopefully, with collaborative efforts across institutions and timely leadership from pioneering

groups such as Dr Rocco and colleagues,³ this reality can be achieved.

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