Journal of Medical & Surgical Pathology

Wilson J Med Surg Pathol 2018, 3:4
DOI: 10.4172/2472-4971.1000169

Commentary Open Access

Developing Electronic-nose Technologies for Clinical Practice

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Received date: September 30, 2018; **Accepted date:** October 11, 2018; **Published date:** October 20, 2018

Abstract

The development of relatively simple gas-sensing devices with sensor arrays capable of constructing molecular profiles of complex Volatile Organic Compound (VOC) metabolites from clinical samples, based on production of healthy or disease-specific digital signature patterns, may soon help to revolutionize diagnostic procedures in clinical practice. This mini-review summarizes the development of recent portable electronic-nose (e-nose) technologies as new diagnostic tools with the potential for accelerating clinical procedures to facilitate non-invasive early disease diagnoses, improving the speed and accuracy of Point-Of-Care Testing (POCT); yielding more effective treatments and significantly improving prognoses.

Keywords: Early non-invasive disease detection; Disease biomarker signatures; E-nose VOC profiles

Review

A significant number of conventional diagnostic methods require expensive, time-consuming or invasive medical procedures (e.g., biopsies, colonoscopies, mammograms) that cause pain to patients or delays in diagnoses, resulting in higher healthcare costs, less favorable prognoses and greater incidences of ineffective treatments. Also, invasive or painful procedures often discourage patients from seeking preemptive disease-detection screenings. The recent development of new portable electronic-nose (e-nose) technologies offer earlier disease-detection capabilities with the potential of accelerating the diagnostic cycle, allowing more rapid and accurate disease diagnoses based on non-invasive detection methods that facilitate more timely application of appropriate treatments to significantly improve prognoses [1,2]. This improved approach of early disease detection using e-nose devices moves clinical diagnostics closer to advancing the goals of precision medicine by increasing utilization of non-invasive medical procedures, minimizing the duration of patient hospital stays, and reducing total healthcare costs [3].

Portable e-nose devices useful for clinical applications are lightweight, handheld tools that provide high through-put real-time data. These low-cost instruments have proven potential to detect a wide range of human diseases with diverse etiologies. Numerous types of e-nose devices have been developed, based on different operational mechanisms, offering different capabilities, and having a range of sensitivities, response times, and advantages for various clinical applications [4]. Traditionally defined e-nose technologies, consisting of those with multi-sensor arrays, are most commonly used for clinical practice and include carbon nanofiber (CNF), conducting polymer (CP), gold nanoparticle (GNP), metal oxide semiconductor (MOS), polymer carbon black composite (PCBC), quartz crystal microbalance (QCM), and surface acoustic wave (SAW) device types [4-7]. Electronic-nose operating principles of chemical detection, depending on e-nose type, are based on sensory changes in electrical resistance, current, temperature, resonance frequency, or optical properties that occur when chemical analytes adsorb to sensor surfaces [4,5]. Electronic signals from e-nose sensors are translated by transducers to produce digital data outputs with sensor intensity determined by net sensor sensitivity to all volatile compounds present in the sample analyte. Sensory outputs are interpreted with data analyses software using pattern-recognition algorithms, artificial neural networks (ANNs), application-specific reference libraries, and various statistical analysis methods such as linear discriminant analysis (LDA) and principal component analysis (PCA) [6].

A newer group of more loosely defined e-nose devices include field asymmetric ion mobility spectroscopy (FAIMS), ion molecule reaction-mass spectrometry (IMR-MS), ion mobility spectrometry (IMS), non-dispersive infrared (NDIR) optical devices and photo-ionization detector (PID) [8-10]. These generally single-detector, spectrometry-type devices do not depend on multisensory arrays to create a collective output pattern for sample recognition, but are primarily used to help detect and identify key disease biomarkers, present in complex mixtures of headspace volatiles, derived from clinical samples with methods that are cheaper than conventional metabolomic instruments such as nuclear magnetic resonance (NMR) and gas chromatograph-mass spectrometry (GC-MS).

Electronic-nose devices and methodologies have been developed for the early non-invasive detection of a wide diversity of human diseases in various parts of the body ranging from upper respiratory tract, pulmonary, gastric, intestinal, skin, heart, liver, and kidney diseases [6]. Some diseases successfully diagnosed using e-noses include diseases of the lungs (asthma, aspergillosis, cancer, cystic fibrosis, COPD, tuberculosis), GI-tract (colorectal cancer, irritable bowel syndrome, infectious diarrhea, necrotizing enterocolitis), as well as alcoholic fatty liver disease, chronic hepatitis, diabetes, malaria, late-onset sepsis, renal dysfunction, upper respiratory infections, and ventilator associated pneumonia [1,4,6]. Numerous efficacy studies have revealed the effective performance of e-nose devices for numerous clinical applications, but particularly for clinical and POCT disease diagnoses, often with the accuracy and sensitivity of slower conventional, established gold-standard diagnostic methods [1]. In addition to preventative healthcare applications, e-nose devices also are useful for various therapeutic and patient-recovery applications

such as continuous monitoring of patient recovery, responses to drugs and other treatments, control devices for regulating drug delivery, confirmation of patient identity, post-operative assessments, remote field-based medicine, locating and determining the health status of natural disaster victims, and determining Postmortem Interval (PMI) and cause of death [4,6,11].

The specialized procedures developed for non-invasive early disease detections using e-nose technologies are based on analysis of volatile organic compounds (VOCs) that are relatively low molecular weight (<300 Daltons) metabolites derived from clinical samples [12]. These gaseous sample analytes are primarily derived from either the direct collection of air samples from the lungs (exhaled breath) or from headspace volatiles, generated from the heating of liquids (including biological fluids such as blood serum, urine, sweat, or excretions) or solid clinical samples, placed in a sample-collection chamber from which air with VOCs above the sample are withdrawn for e-nose analyses.

The procedural steps utilized in the electronic-nose diagnostic cycle include acquisition of sample analytes from clinical samples taken from the patient, introduction of VOC-metabolites from the sample into the e-nose instrument to obtain a collective output aroma signature pattern from the sensor array, followed by computer data analyses using pattern-recognition algorithms (for comparing sensor output patterns to known healthy and disease patterns in disease-specific smell print libraries). These steps are followed by interpretation of analysed data to form the basis of a diagnosis, and finally assessments of prognoses and recommendations of appropriate treatments to the patient (Figure 1). The final assessment stage is usually amended with information from other pertinent sources, tests, patient history, symptomology, and other physiological parameters.

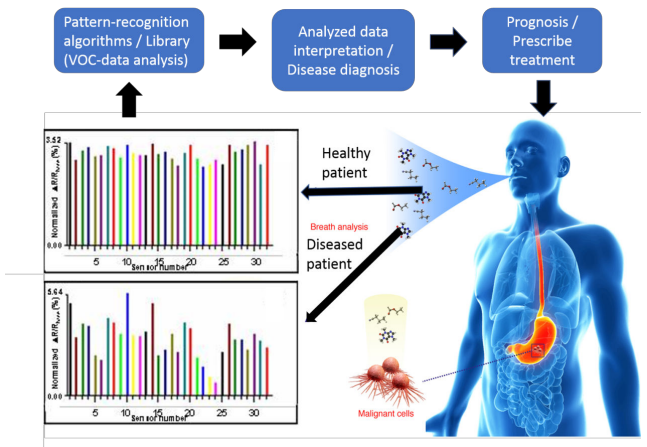

Figure 1: Electronic-nose diagnostic cycle.

Recent advances in the development of new ways to enhance disease-detection theory and practice accordingly have improved the capabilities of e-nose devices to help healthcare providers achieve earlier and more accurate disease diagnoses. Discoveries of connections between the unique biochemical and physiological processes related to specific diseases and associated changes that occur due to effects of early pathogenesis processes on metabolic pathways and the chemical environment of certain tissues has led to the highly useful identification of key VOC-metabolite disease biomarkers.

Different types of diseases have specific effects on a number of important key metabolic pathways and hormone-regulated processes in the body that provide indications of the mechanisms of disease, the precise biochemical nature of a disease, and the most likely volatile target metabolites that have been linked to a particular disease. Thus, the detection and identification of particular volatile metabolites, most associated and correlated with individual diseases, often are the best candidates to potentially serve as effective chemical indicators or biomarkers of disease when consistently produced. Metabolic diseases are perhaps the best examples of human diseases that may be identified by the accumulation of key metabolites that are responsible for disease development [13]. Disease biomarkers associated with key metabolic pathways have been identified for a large number and wide diversity of human diseases [14]. Thus, e-nose devices are particularly useful for detection of unique and often abnormal VOC-biomarker metabolites generated by many different types of diseases.

Bacterial dysbiosis or the alteration of resident commensal microbiome communities in patients due to disease is another recently discovered phenomenon providing additional opportunities for early e-nose detection of diseases by VOC-metabolites [1,15]. Specific changes in microbiome bacteria composition in the gut, due to diseases occurring in the GI-tract and other parts of the body, have provided strong indications of particular diseases. These changes may be detected by e-nose analysis of headspace VOCs derived from fecal samples taken from diseased patients [16]. Dysbiosis also may occur in other parts of the body besides the gut, such as in the oral cavity, lower airways, lungs and kidney where microbiota perturbations have been associated with disease states in other organs and compartments of the body [17-20].

Certain types of multi-sensor e-nose devices are capable of detecting complex mixtures of VOC-biomarkers, associated with particular diseases, by their unique VOC-signature patterns (or VOC profiles). Other e-nose instruments with a small number of chemical-analysis sensors are capable of identifying individual VOC-biomarkers. Examples of putative VOC-biomarkers useful for early detection of specific diseases, (such as butylated hydroxytoluene for amyotrophic lateral sclerosis (ALS), p-menth-1-en-8-ol for cholera, indole for cryptosporidiosis, hypoxanthine for endometriosis) and many others, have been summarized previously [1,13,14,21].

Dual-technology or combination-technology e-nose instruments also are now being developed with the capabilities of both chemical-mixture identification (sample type and source) and analytical-chemistry capabilities. Utilization of both types of e-nose instruments or combination-technology instruments provides complementary information to enhance the accuracy of diagnoses. Disease VOC-biomarker detection *via* metabolomic methods, used individually or in combination with e-nose technologies, are powerful supportive tools for effective disease diagnosis [22].

There are still some important issues and developmental steps that need to be completed before e-nose instruments are fully integrated into routine clinical practice. Universal standardization of methods used for e-nose applications should be developed for sampling protocols, sample transport and sample storage conditions, and analytical methodologies to allow inter-study data comparisons [23]. Additional work also should identify and expand the list of chemical disease biomarkers known for specific diseases and unique VOC profiles, indicative of complex mixtures of specific biomarker metabolites, associated with individual diseases [1].

The author expects the eventual full acceptance of e-nose devices into clinical practice, particularly when used in combination with targeted detection of known disease biomarkers acquired from preliminary prophylactic e-nose disease screenings. The reluctance of physicians to change their use of preferred older diagnostics methods to newer, more rapid and accurate methods will be overcome in time. Additional e-nose clinical trials will contribute to the acceleration of progress in standardization of clinical diagnostic procedures. These improvements ultimately will advance the key goals of precision medicine to increase use of noninvasive medical procedures, improve patient prognoses and treatment effectiveness through early disease detections and treatments, shorten patient hospital stays, and significantly reduce total healthcare costs.

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