Bridging the Collaborative Gap: Realizing the Clinical Potential of Breath Analysis for Disease Diagnosis and Monitoring–Tutorial

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***Abstract*— Exhaled breath analysis holds great promise for the development of noninvasive, frequently repeatable diagnostic and monitoring tools. For clinical breath analysis to advance beyond its current state, however, much closer multidisciplinary collaboration needs to be not only recognized but also effected. Therefore, this paper reviews the current state of clinical breath analysis from the perspective of the challenges the field faces medically (biomarker uncertainties, sampling methods, dynamics of exogenous compounds within the body, and standardization), technologically (the need for an affordable, user-friendly, real-time, point-of-care instrument for accurate identification of breath volatiles and their concentrations), biochemically (the need to link exhaled compounds with specific diseases by understanding the volatile products particular to relevant pathogenic processes), and in terms of data interpretation (quality, quantity, and complexity of data), collaboration (the need for a more integrated approach to breath analysis, including public health input), and development from research to accepted clinical use (funding challenges peculiar to the medical/technological interface, achieving standards of effectiveness and cost-effectiveness). Having thus increased awareness and aligned expectations among relevant disciplines, this paper provides a course of action for closer collaboration, better understanding, and more productive dialogue between these disciplines, including an iterative sensor development process that is integrated with clinical trials, formation of goals that transcend individual disciplines, creation of multidisciplinary research teams and a cross-disciplinary student exchange program, and collaborative funding options.**

***Index Terms*— Breath analysis, collaboration, diagnostics, trace gas sensing.**

I. Introduction

BREATH analysis represents an exciting new approach to medical diagnostics and monitoring. It has, potentially, at least two great advantages over other means of diagnosis, including blood, urine, biopsy, endoscopy, and imaging: complete non-invasiveness and virtually limitless repeatability with respect to frequency, access, and cost (cf. Table I).

The use of exhaled breath to detect disease has, in some form, been in use since ancient times. For instance, Hippocrates reports that distinct odors are associated with particular diseases [1]. Modern breath analysis is generally acknowledged to have begun with Pauling's 1971 study of exhaled breath using gas chromatography, which identified some 250 volatile organic compounds (VOCs) in the breath [2]. More recently, great interest in the clinical potential of breath analysis began with studies in the 1990s that found a correlation between nitric oxide and asthma [3]–[5]. Since then researchers have made many attempts to correlate diseases, from renal failure to cancer, with particular VOCs or patterns of compounds [6]–[9]. However, there remain a number of medical obstacles that prevent breath analysis from having wider application in a clinical setting; these problems will be further discussed in Section II.

Additionally, while breath analysis is inherently non-invasive, its practical repeatability is limited by factors such as access, cost, user-friendliness, and real-time measurement capability. For instance, one potential application of breath analysis is diabetes monitoring [10], where a breath test replaces the current invasive method of blood testing. However, even if a reliable breath test could be developed, there remain questions regarding practical implementation; clearly, a diabetic cannot come to a clinic daily to have their breath analyzed, as this would no doubt be prohibitively inconvenient and expensive in comparison to the existing alternative. A successful diabetes monitoring program using breath analysis would require an inexpensive, in-home, self-administered test.

Developing this test, or similar tests for the monitoring and screening (cf. Fig. 1) of a variety of diseases, including certain cancers, is nearly as dependent on sensor technology as it is on clinical ability to link detected compounds with specific diseases. This is a crucial realization which should guide the field of clinical breath analysis as it advances.

Indeed, it is widely agreed that clinical breath analysis needs, perhaps more than anything, a strong multidisciplinary effort in order to realize its potential. There have been numerous, but underdeveloped, calls for such an effort (e.g., [11]–[17]); recognition of a need for close collaboration is

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TABLE I

CURRENT WIDELY-USED MEDICAL DIAGNOSTIC TECHNIQUES, ALL OF WHICH SUFFER FROM INVASIVENESS AND/OR PRACTICAL RESTRICTIONS ON REPEATABILITY. BREATH ANALYSIS, IF IT FULLY REALIZES ITS POTENTIAL, WILL SUFFER FROM NEITHER, ENABLING REVOLUTIONARY DIAGNOSTIC APPLICATIONS.

	Blood	Urine	Biopsy	Endoscopy	Examples of imaging			Breath Analysis
					X-ray/CT scan	MRI	Sonography	
Non-invasive?	✗	✓	✗	✗	✗	●	✓	✓
Limitlessly repeatable?	✗	✗	✗	✗	✗	✗	✗	✓
Reason	Invasive: painful Non-repeatable: finite, expense, logistics	Non-repeatable: finite, timing, expense, logistics	Highly invasive Non-repeatable: major procedure, expense	Invasive procedure Non-repeatable: major procedure, expense	Invasive: ionizing radiation Non-repeatable: radiation exposure, expense, logistics	Possibly invasive: injected dyes Non-repeatable: expense, logistics	Non-repeatable: expense, logistics	

Key: ✓ = meets requirement ✗ = fails to meet requirement ● = may meet requirement

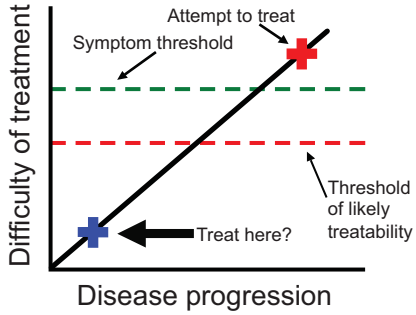

Fig. 1. Novel approach to disease treatment, one potentially revolutionary application of an ideal breath sensor. Equipped with such sensors, clinicians may be able to detect and treat some diseases, such as certain types of cancer, at the blue cross, rather than the red cross, through screening and early detection.

not the same as effecting close collaboration. While multidisciplinarity is the right idea, actual levels of communication and integrated research among participating disciplines remain underwhelming; nobody has devised a plan to put the calls into action, which is due in part to a lack of awareness and understanding between collaborating disciplines. This paper attempts to address this matter with a comprehensive yet accessible assessment of the current state of clinical breath analysis, particularly the challenges facing the field, and by providing recommendations for resolving these challenges. Here, effective collaboration will be the focus, rather than a hopeful, vague suggestion, as found in many papers.

II. MEDICAL CHALLENGES

The medical challenges which serve as major impediments to the achievement of clinical breath analysis may be grouped into two general categories: 1) identification of biomarkers, defined as measurable characteristics which indicate either normal or pathogenic processes [18], and 2) confounding factors.

Uncertainty in regard to exhaled breath biomarkers, i.e., a lack of understanding about how detectable compounds in exhaled breath relate to specific diseases, is the most significant obstacle clinical breath analysis faces at this time. Even assuming that engineers can develop sensors that can detect a great variety of compounds in the parts per trillion (ppt) range, their achievement would be far more effective if stronger links between exhaled breath compounds and the pathobiology of specific diseases were already established.

The search for a biomarker of lung cancer, which remains inconclusive [19], is a representative example. Some researchers recently suspected that ethane might be indicative of lung cancer, since it seems to be derived ultimately from oxidative stress (OS), which can indicate DNA malfunction, and therefore potentially cancerous processes [20]–[26]. Ethane seemed attractive as a potential biomarker because, unlike other products of lipid peroxidation, which is thought to be caused by OS, it is insoluble in tissue and highly volatile [6], [24], [26], [27]. However, researchers have since concluded that OS is far too general a cell process to be a biomarker for lung cancer, or anything else; it has been linked to breast cancer, heart transplant rejection, HIV, bronchial asthma, and arthritis, among other things [6], [20], [22], [26]. The "weak link" between ethane and lung cancer is typical of the types of uncertainties involved in attempts to correlate specific diseases with concentrations of a single compound. The body is an immensely complex system, and it has proven difficult to find isolated pathological sources for particular volatile compounds. Simultaneous detection of multiple compounds (VOC profiles or patterns) has met with some success, and may be the approach of the future [10], [28]–[32]; however, identification of those compounds may be very difficult or impossible, as in the case of pattern-recognition sensors like the electronic nose [7], [19], [33]–[35]. Even in cases where some multi-compound identification is possible (e.g., alkanes and monomethylated alkanes

[25]; acetone and isoprene [36]), the true sources of detected volatiles, and therefore a fundamental understanding of the relationship between these compounds and specific diseases, remain largely elusive [37].

There is both a top-down and a bottom-up approach to overcoming the biomarker challenge; both should be pursued in parallel and ultimately used for cross-reference.

The top-down approach attempts to determine biomarkers by identification of compounds, using appropriate sensing technology and careful experimental design, which differ in a statistically significant manner between diseased and healthy individuals. It must be noted, however, that there is no single, comprehensive top-down methodology, because sampling and analytical technique and instrumentation will determine the subset of breath analytes that can be measured, i.e., every possibly relevant breath analyte cannot be measured using the same experimental setup. For instance, pre-concentrating fibers are better at adsorbing some compounds than others (cf. discussion in Section IV); likewise, instrumentation that has difficulty with water vapor interference will be less than useful for measuring compounds affected by this interference. In short, selection of any measurement technique entails selection of a particular subset of measurable breath analytes. Therefore, various techniques should be employed in complementary fashion in order to investigate a broader range of analytes, and thus potential biomarkers, though at this stage of clinical breath analysis this effort is hindered by a lack of standardization and means of inter-group comparison, as discussed later in this Section. To minimize these difficulties, development of standards as well as novel sampling and instrumentation techniques that can satisfactorily measure ever-broader sets of breath analytes is encouraged.

Once measurement technique has been selected, the top-down approach involves a number of steps. Initially, summary statistics on a population, regardless of disease state, must be established to develop an appreciation with respect to range and distribution of as many compounds as possible [30]. Then, intra- and inter-subject variability must be understood in order to assess the value of any individual measurement in the context of the population. Next, the total population statistic must be organized into stratified groups based on meta-data (age, ethnicity, gender, etc.); afterward, disease and control subject breath data must be collected and compared according to meta-data categories. With sufficient data, specific trends in disease group concentrations become apparent, assuming that disease group concentrations are significantly distinct from those of the control group (see, e.g., Fig. 2). However, this assumption may not hold for all target diseases. When it does hold, those concentrations of compounds which seem to differ significantly between disease and control groups can be given closer attention and possibly, using spectral database, library, and/or external standard referencing, identified as specific biomarkers of a particular disease, provided that correlations between disease subjects and specific compounds are validated (or even discovered) by thorough statistical analysis.

Heatmaps (as in Fig. 2), which present three axes of information (e.g., subject, suspected compound identity, concentration), often have been found useful for quick, qualitative interpretation of breath data [38], [39], although in some cases this method and other qualitative pattern recognition schemes can be misleading [37]. Data should be subjected to further or alternative analysis; methods that have been used in breath studies include regression analysis, principle component analysis, cluster analysis, discriminant analysis, random forest analysis, and factor analysis [25], [30], [32], [39]–[42]. Dimension reduction is a key concept in many of these techniques, whereby data complexity can be decreased with minimal loss of integrity.

Statistical analysis is playing an increasingly important role in clinical breath analysis. Not only can it confirm and discover relevant correlations, assess reproducibility of measurement techniques, and eliminate artifacts (e.g., due to sampling method) from data, but it is also needed to process the immense amount of data produced by the latest breath biomarker discovery instruments, like 2D gas chromatography time of flight mass spectrometry (GC $\times$ GC-ToF) [37], [43], which may be difficult to interpret even qualitatively without advanced chemometric analysis. Even as measurement methodologies are improving, breath analysts still encounter great difficulty distinguishing true effects from random correlations, and identifying measured compounds with certainty [37], [44]. Fortunately, this need for more powerful statistical and data processing techniques is widely recognized within the breath community [32], [37]. The broader participation and assistance of dedicated statisticians would significantly contribute to the advancement of the field.

Finally, the top-down approach subjects any apparent links between compounds and biomarkers to a rigorous validation process before clinically useful conclusions are drawn.

Though it has been proposed that the top-down approach is sufficient for biomarker discovery [44], at best it is analogous to logical induction, where a conclusion is supported, though not entailed, by premises or "evidence"; the top-down approach can only provide suggestions, not certainty, about connections between measured compounds and disease—and at the current state of clinical breath analysis, the connection between measured compounds and disease is, in most cases, tenuous. This is not to say that the top-down approach cannot by itself establish strong, statistically robust suggestions about compound-disease linkages, but an understanding of the underlying physiology of the disease in question as it relates to exhaled breath—at its best, a deductive process—will always increase (or reduce, if physiology does not corroborate measurements) degree of confidence in these linkages. Establishment of causal explanations for top-down observations (e.g., one measures elevated compounds Y and Z in the breath of a subject with disease C, which makes sense because disease C is known to elevate levels of Y and Z) in particular will permit more robust conclusions about disease-compound correlations.

The bottom-up approach, then, involves an investigation of disease metabolomics; specifically, determining the disease-specific products of individual pathologies which are subsequently excreted in breath. This approach would not only serve to confirm correlations found by the top-down approach,

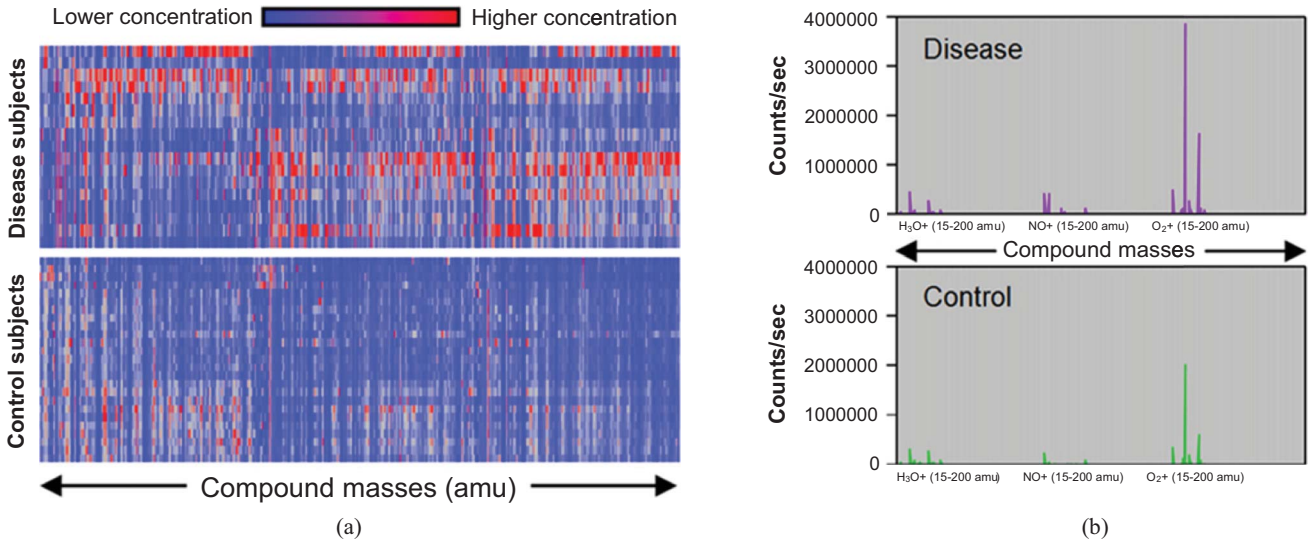

Fig. 2. Examples from the top-down biomarker investigation process. (a) Clear differences in compound concentrations between healthy controls and disease subjects using mass spectrometry. (b) Noticeable differences in compound concentrations between healthy controls and patients with a different disease. Both data sets must be placed in proper statistical context and subjected to statistical validation. (Source: selected ion flow tube mass spectrometry data from the Dweik group.)

but also to inform the top-down approach about which compounds are known to correlate with specific diseases, and therefore which compounds to target during measurement. Absence or presence of such compounds, or most likely, an alteration in their concentration, would provide information about the absence, presence, and potentially severity of a correlated disease. Ideally, a database of disease pathways through products exhaled in breath, in format not unlike metabolomic databases already available [45]–[48], should be developed.

Despite the importance of this approach for the success of clinical breath analysis [37], to our knowledge no research group has undertaken it in a dedicated fashion, although investigations of the volatile products of microbes and cell lines [19], [32], [49] are a step in the right direction. This therefore serves as an invitation to biochemists, who can assist and enrich the breath analysis community by tracing the pathways from disease to exhaled compounds, even as clinicians and sensor groups try to trace exhaled compounds back to disease.

The second general category of medical challenges is confounding factors. These factors include sampling method, pharmacokinetics, and standardization.

Correct sampling and measurement method is difficult to achieve primarily due to the minuteness of measured VOC concentrations. Thus, even a small error in method may cause great variations in measured concentration, resulting in misleading data. This means that even assuming a perfectly specific biomarker and adequate measurement capability, poor sampling method can ruin a study, making it draw incorrect conclusions. Sampling method should be designed to minimize the alteration of relevant VOC concentrations. For instance, if a certain biomarker is only detectable in alveolar air, and is diluted by proximal air from the airways [50] or the gut micro-biome [51], then a sampling method must be implemented that measures alveolar air to the extent possible. Likewise, non-alveolar exhaled biomarkers that are produced in the airway and the gut must be measured using methods tailored to these biomarkers. If a biomarker is flow rate dependent, or altered by diet or compounds originating in the mouth [16], these dependencies must be reflected, respectively, in sampling method. If a compound is "sticky" and adheres to surfaces, a sampling method must be implemented for that compound to minimize adhesion, if adhesion interferes with its usefulness as a biomarker.

Pharmacokinetics, the dynamics of exogenous compounds within the body [29], can further confound data by introducing exogenous artifacts which, though measured as part of the breath sample, indicate little about current state of health. These artifacts may be impossible to eliminate entirely [32]: though attempts have been made to control their introduction into a breath sample by pre-test preparations such as the avoidance of smoking, breathing purified air, background subtraction, or maintaining a tight seal at the collection interface [6], [16], [29], [50], [52], certain exogenous VOCs may be detected in a breath test which were inhaled hours, days, or weeks ago from various environments [15], [16], [29], [53].

The absence of standardization among breath studies is also problematic. Currently, there are little means of comparing them [15], [16], [29], [32]. Commendably, there has been widespread recognition of this problem, and consistent, urgent calls for standardization (e.g., [16], [19], [44], [54]), but progress in this regard has been slow. However, this is not surprising: sampling technique and instrumentation are still very much in development at this stage; efficacy must first be soundly demonstrated, then the merits of each effectual methodology compared in an optimization process; only at this point does standardization seem likely.

Large databases need to be established to determine ranges of "healthy" concentrations for various VOCs; currently there seems to be a great range of what might be considered "normal" or "healthy" [6], [15], [16], [53], [55]. Indeed, healthy breath standards may vary from person to person based on physical condition, general health, diet, age, environmental

exposures, lifestyle, weight, rate of metabolism, and possibly even ethnicity [6], [15], [16], [25], [29]. Until a more concrete sense of normalcy is established, a continued effort should be made to minimize and account for variables by age, gender, ethnicity, etc. matching healthy subjects with confirmed disease subjects, and by carefully controlled experimental design. Also, while establishing ranges of normalcy by measuring healthy controls is important, it is also essential that the breath of confirmed disease subjects is studied. Biomarkers of disease will never be found by exclusive measurement of a control group, and it is only slightly more likely that they will be found by exclusive measurement of a disease group. The key to biomarker identification, using this top-down approach, is comparison of the two groups. Thus, the immediate focus should be on this comparison to find "cut points" [56], [57], or thresholds, in compound concentration which indicate, in a statistically and clinically significant way, departure from normal (control group) physiology.

III. Reasons for Medical Optimism

While these medical challenges are formidable, they are not insurmountable. Though specific biomarkers or sets of biomarkers often remain unknown, many studies have observed a significant difference between the breath of controls and that of disease subjects (e.g., [7], [34]); this strongly suggests that biomarkers are present, even if breath analysts have thus far not been able to identify many of them with great certainty. Some biomarkers, however, have been identified with a good degree of certainty (e.g., NO, H_2) [14], [15], [32], [51], [58], [59]; it is reasonable to expect that this identification process will continue, though it would be greatly expedited and made more certain by advancements in sensing technology and disease metabolomics. The observation of significant differences between the breath of controls and that of disease subjects for particular diseases also suggests that, while establishing standard ranges of normalcy and appropriate sampling method are important, this is not necessarily a precondition for making significant advancements in other areas of clinical breath research. Emphasis should be placed on identification of biomarkers, rather than refinement of sampling method in anticipation of finding or enhancing perception of biomarkers. The latter approach, while it will likely become more useful in the future when fine-tuning measurement of a particular biomarker, may prove an unproductive expenditure of time and resources at the current state of clinical breath analysis. Some sampling issues, like pharmacokinetics and environmental exposures, cannot be fully controlled for, and so it is unhelpful to focus on controlling for them; it must be remembered that, in clinical use, breath tests will have to diagnose and monitor diseases in spite of the environments to which the patient has been exposed, the medications they have been taking, etc. In short, breath analysts should focus on identification of biomarkers before they begin perfecting the sampling method to measure these biomarkers. Proper sampling method is important, but so is awareness and discovery of biomarkers; researchers cannot fully understand the "big picture" of clinical breath analysis without paying attention to details, but they also cannot focus too closely on details lest they overlook the "big picture".

Both the biomarker discovery challenge and the pharmacokinetic challenge can be partially addressed by drawing upon approaches and expertise from the environmental exposure discipline (EE) within public health studies. While EE does not investigate disease metabolomics per se, in comparison to clinical breath analysis it has a well-developed understanding of the kinetics of many breath-related compounds in the body [40]. The inevitable presence of exogenous compounds in breath that might otherwise be confounders may be able to be accounted for using EE models or modeling methodologies, including classical absorption, distribution, metabolism, and elimination (ADME) models and physiologically-based models (pharmacokinetic and toxicokinetic, PBPK and PBTK, respectively) [40], [60]–[62]. These are developed through carefully controlled studies that attempt to determine locations, quantities, and rates of exposure; absorption and elimination routes and rates; residence times in various locations using detailed compartment models (e.g., fat, particular organs, gas exchange mechanism); and interaction with body metabolism [60], [61]. Such public health studies have been conducted on several substances that have implications for public health, including jet fuel, benzene, toluene, MTBE, tetracholoroethylene, polycyclic aromatic hydrocarbons, ozone, automotive fumes, cigarette smoke, trihalomethanes, and vinyl chloride [30], [54], [60], [63]–[65]. Predictably, EE studies and models tend to focus on substances which are suspected or known to be harmful and to which populations are exposed, in order to predict, e.g., risks and allowable exposures [61], [62]. Clinical breath analysis would require a much broader range of modeled substances, since it is concerned less with harmful exposures than with any exposure that interferes with potential disease biomarkers. Construction of such models would be a step forward, albeit a complex and time-consuming process, as kinetic models often must be tailored to individual compounds, which have, e.g., different rates of absorption and residence times, and are highly dependent on the characteristics of the affected person [60]–[62], [66]. Furthermore, while models of exogenous substances are often well developed, an understanding of the even more complex metabolic processes and metabolites induced by particular exposures is needed [61], [62]. This is closely related to the disease metabolomics research characteristic of the bottom-up approach to biomarker discovery, especially as exposure can be tightly linked to pathogenesis, even if the mechanism by which this occurs is often unknown [54], [67]; thus, EE scientists, biochemists, and clinicians in particular should collaborate closely on this research, drawing upon the experience and expertise of each discipline.

While clinical breath analysis does indeed hold great promise, this must not translate into inflated, unrealistic expectations. Even if breath analysis proves revolutionary, it is highly unlikely to become a "holy grail" for diagnosing disease; it should probably not be envisioned, for instance, that people could use breath-based personal diagnostic devices to determine their general state of health. This simply is not the nature of diagnostic testing; excepting occasional exam-

inations, healthy people do not visit physicians; they do not receive MRI or ultrasound scans (and would not, even if costs were negligible) if they are asymptomatic and not considered at risk in some way or another. While breath analysis does have great potential for disease screening, interpretation of results will depend on context, as other diagnostic tests depend on context (cf. discussion in [57]). For instance, low blood cell counts may indicate one problem in one person, and a different problem in another person, depending upon factors like age, medical history, symptoms, etc.

It is helpful to keep this connection between breath and blood in mind, especially since blood is considered a gold standard for medical diagnostics. Volatiles in the blood are excreted into the lung via the alveoli, and then exhaled through the airway and nose and/or mouth (cf. Fig. 3). While most of the constituents of blood that currently yield crucial diagnostic information are absent in breath (blood cells, proteins, etc.), the link between blood and breath remains strong, not only in terms of physiology, but also, perhaps, historically. Blood faced—and overcame—the types of medical challenges breath analysis currently faces. Despite the fact that levels of blood constituents, like volatiles in breath, may depend strongly on "sampling method" (e.g., fasting, pre-analysis preparation) as well as factors like age, ethnicity, etc., that blood is susceptible to exogenous contamination, and that indicators of disease long remained unknown, blood has become the most pervasive and useful tool for medical diagnostics. But this did not happen rapidly, it took decades: widespread syphilis testing began in the 1930s, hepatitis testing in the 1970s, and AIDS testing in the 1980s; many other blood tests were developed during and after these times, and much remains to be understood about blood [68], [69]. Breath analysis has received serious clinical attention for less than twenty years, and is very much in its infancy. With patience and persistence, breath analysis may very well experience a similar ascent to diagnostic prominence.

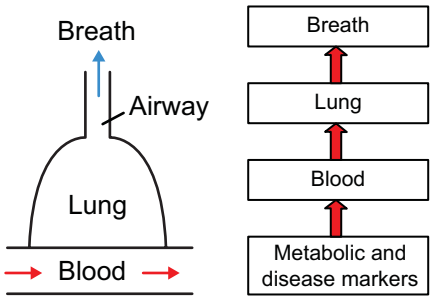

Fig. 3. Two schematics illustrating the close physiological link between breath and blood.

IV. Technological Challenges

The need for clinical breath analysis and sensing technology to grow together in a mutually enabling way—sensors to support point-of-care breath diagnostics and monitoring, and clinical practice to provide novel, useful applications for sensors—is reflected in the parallel between the current state of medical diagnostics and the current state of sensor technology. Both medical diagnostics and sensor technology have gold standards, blood and mass spectrometry, respectively, that, while known for their utility and reliability, could still be greatly improved, viz., diagnostics could become less invasive and more repeatable, and sensors could become more affordable, portable, user-friendly, and oriented toward point-of-care measurement.

Indeed, an ideal sensor for clinical breath analysis needs to be compact, portable, room-temperature operable, user-friendly, highly sensitive (ppt ideal), highly selective, robust, precise, accurate, capable of real-time measurement, and inexpensive. Conveniently, these needs are often closely interrelated, such that meeting one need often meets others; for instance, a sensor that is room-temperature operable can be more compact and portable than a system which requires cryogenics or heating; a more robust and well-packaged system is more likely to be consistently accurate. Breath systems must be able to be brought to inpatients, who might be immobilized, not vice versa; they should also be able to be given to patients for self-administered tests at home. A comparison of several available and developing sensor technologies is shown in Table II. Gas chromatography-mass spectrometry (GC-MS) techniques have highly-developed—although not entirely comprehensive, especially in the analysis complex biological mixtures [52], [70]—libraries (e.g., NIST) [33], and increase likelihood of compound identification using external standards [71], [72]. In general, there is a commendable (and predictable) trend towards instrumentation that can collect data of higher dimensionalities. Multi-dimensional data enables (assuming management of processing and statistical complications) more confident compound identification, since each dimension provides additional criteria by which to distinguish compounds from one another. For instance, two compounds may have the same nominal masses, but different retention times, or different velocities to a detector. A prime example of higher-dimensional data instrumentation is GC $\times$ GC-ToF, mentioned previously (Section II), which many breath analysts consider the gold standard for biomarker discovery [44], [73]. In the case of GC $\times$ GC-ToF, bands with overlapping peaks from the first GC column are sent to a second column for further separation, followed by ToF-MS [73].

While they may have a role as lab instruments, such devices are both expensive and relatively immobile. Efforts have been made to miniaturize (components of) GC-MS and related systems (e.g., chip-based GC separation) [74]–[78], but the development of an ultra-portable product will remain a challenge.

Furthermore, all of these mentioned technologies require analyte preconcentration, thermal desorption, or other significant delays between breath collection and measurement (offline sampling). This is a concern not only for clinical implementation, but also for biomarker discovery. The notion of delivering simplicity amid complexity in breath analysis [79] can be applied here; specifically, sampling method and instrumentation should be as simple and require as few sampling steps as possible, provided that desired effectiveness is achieved, because there is the potential for introduction of confounding variables and error with each additional step or layer of complexity, especially since the concentration

TABLE II

COMPARISON OF THE CURRENT STATE OF SELECTED BREATH ANALYSIS SENSOR TECHNOLOGIES. FOR MORE ON GC/MS, SEE [9], [19], [32], [35], [72]; GC × GC-ToF, SEE [43], [44], [73]; MINI GC-MS, SEE [74]–[78]; REAL-TIME MS, SEE [29], [33], [59], [71], [72], [80], [86]–[88]; CHEMILUMINESCENCE, SEE [99]; SENSOR ARRAY/e-NOSE, SEE [7], [19], [33]–[35]; SOLID-STATE/MEMS, SEE [99]; DIODE LASER SPECTROSCOPY, SEE [90], [93]; MID-IR LASER SPECTROSCOPY, SEE [89], [94], [95]

		Requirements for Ideal Breath Analysis Applications								
		Adequately selective	Adequately sensitive	Robust/low maintenance	Real-time operation	Self-administration	Adequately portable	Inexpensive	Adequate compound identification abilities†	Multi-species detection*
Technologies	GC-MS	◡	●	●	○	○	○	○	◡	●
	GC x GC-ToF	◡	●	●	○	○	○	○	◡	●
	Mini GC-MS	◡	◡	◡	○	○	◡	○	◡	●
	Real-time MS (SIFT, PTR/PTR-ToF, IMS)	◡	●	●	●	○	○	○	◡	●
	Chemiluminescence	◡	◡	◡	●	◡	◡	○	N/A**	○
	Sensor Array/ E-nose	◡	◡	●	●	●	●	●	N/A**	●
	Solid-state/MEMS‡	◡	◡	●	●	●	●	●	N/A**	◡
	Diode laser spectroscopy	◡	◡	●	●	◡	○	○	N/A**	◡
	Mid-IR laser spectroscopy	◡	◡	●	●	●	●	●	◡	●

Key: ● = meets requirement; ● = is likely to meet requirement; ◡ = may meet requirement in some cases or in the future; ○ = fails to meet requirement

† Useful for discovery phase
* May be a requirement for some applications
‡ Micro-electromechanical systems (MEMS)
** Not useful for discovery phase

of potential biomarkers is so minute. Indeed, it has been noted that, with instrumentation requiring a more complex sampling method and multiple stages of analysis, incorrect procedure at any stage can ruin a study [54], [73]. The complexities of offline measurement ultimately risk greater sample contamination and compound loss, especially through the rapid degradation of unstable compounds, permeation, leaking, condensation, and surface adhesion [31], [54], [72], [80], a risk that cannot be taken when those lost compounds could be biomarkers. Bag collection (Tedlar is commonly used) can introduce impurities from outgassing, and results in limited or uncertain sample stability and integrity [36], [71], [81], [82]. Adsorbent traps (e.g., SPME, needle trap devices, polymer films) have raised concerns about reliability and, when adsorption/desorption dynamics are even well understood, tend to be quite selective in the compounds they can adsorb, retain, and desorb effectively [8], [71]–[73], [76], [78], [81], which excludes potential biomarkers (as mentioned in Section II, all analytical methods for biomarker discovery have their limitations in this regard, but preference should be given when possible to methods that can measure a broader range of analytes). From an extra-methodological perspective, delays and processing requirements make ideal clinical implementation (e.g., frequent, affordable screening programs) unlikely.

None of these difficulties are presented to discourage offline approaches to breath analysis, but, all else being equal, it is always preferable [83] to use an online sampling instrument; if online sampling can perform adequately, there is no need to introduce additional methodological and extra-methodological complexity and potential sources of error. This is the same reasoning behind favoring direct analysis of exhaled breath over techniques like collection of exhaled breath condensate (EBC), which, in addition to uncertain clinical effectiveness [84], [85], requires collection and handling by a skilled technician and laboratory analysis; due to its likely expense and offline methodology, it does not meet the requirements for the kind of clinical implementation that would make breath analysis the diagnostic and monitoring breakthrough (cf. Table I) it has the potential to become. Indeed, some breath analysts have been cautious about pursuing EBC on account of a recognition that the future of breath analysis is in real-time sensing [84].

MS-based systems that can perform ultra-sensitive, real-time, online breath measurements, like selected ion flow tube mass spectrometry (SIFT-MS) or proton transfer reaction mass spectrometry (PTR-MS), are a major improvement. Historically, they have had difficulties with relatively incomplete libraries or mass overlaps, which can interfere with compound identification [29], [33], [35], [71], so recent work

has focused on addressing these issues. SIFT-MS currently uses three different precursor ions whose product masses can be compared, enabling enhanced compound distinction [32], [59], [71]. However, this technology has difficulty measuring compounds with low proton affinities and high ionization energies, and libraries are still very much in development; often mass overlaps remain unresolved [71]. PTR-MS for breath analysis has replaced its quadrupole system, which required switching between mass channels, with a time-of-flight (ToF) spectrometer, enabling simultaneous measurement of the complete mass spectrum and higher resolution, which in turn enables discrimination between isobaric compounds; isomeric discrimination is more difficult [80], [86]. The combination of ion mobility spectrometry with real-time MS (IMS-MS) is another promising MS-based technology; it can potentially resolve compound identification difficulties by providing information on compound shape and size, in addition to compound mass, and thus additional criteria by which to distinguish compounds [87], [88]. However, as all of these instruments rely on MS technology, they may not be able to meet the degree of compactness and portability, nor the inexpensiveness, required for an ideal clinical breath analysis instrument. The limitations of MS in these respects is a general concern in the breath analysis community [44]. Indeed, while MS will continue to have an important role in biomarker discovery, its use for clinical sampling, especially of seriously diseased subjects and those in monitoring programs, is limited, even if the instrument is capable of real-time analysis. Breath analysis research, even at the discovery phase, needs to move towards online measurement that enables point-of-care sampling and eliminates many of the confounding variables introduced by breath collection, concentration, and storage. But this transition is unlikely to happen without novel, highly portable real-time sensing systems.

One class of sensors that seems especially promising in this regard is based on mid-infrared (mid-IR) spectroscopy, using both direct and indirect (e.g., photoacoustic effect [89]) absorption techniques. Many VOCs have strong characteristic absorbance signatures in the mid-IR (up to 100 times stronger than the near-IR [90]), and spectral databases for the purpose of compound identification are well-established (e.g., HITRAN [91], PNNL IR database [92]). High-powered laser-based systems, like those utilizing Quantum Cascade lasers (QCLs), have demonstrated an ability to achieve sensitivity levels ideal for measurement of the often minute (ppb-ppt) concentrations of exhaled breath VOCs, as well as impressive compound selectivity via tuning abilities and narrow emission linewidths [11], [89], [90]. However, the measurement of larger molecules tends to be more challenging due to their typically congested spectral signatures, as opposed to the strong, relatively interference-free absorption peaks which often characterize smaller molecules with resolved rotational structure [11], [53], [93]. For applications which focus on a single, small compound known to be a biomarker, wide tunability may not be critical, but for applications that depend upon measurement of multiple or larger compounds, broad tunability over a range of wavelengths, and therefore potentially useful molecular absorption peaks, will be useful. Broad tunability may also be effective in biomarker exploration applications [94], [95], although it is possible that mid-IR laser-based sensors would be more useful in validation and clinical application phases, rather than in the discovery phase [16], [96], since they would be competing with well-established techniques capable of reliable multi-compound detection and concentration determination, like mass spectrometry. Additionally, mid-IR technologies hold great potential for inexpensiveness and portability [89]. While still larger than ideal, many laser-based systems are still in prototype stages and at this point demonstrate no fundamental limitation to becoming handheld devices. Because mid-IR sensors are based largely on semiconductor technology and fabrication methods, they also demonstrate no fundamental limitation to affordability, assuming they will be mass-produced.

While some technologies may seem more promising than others at this point, clinical breath analysts will ultimately have little preference for the means by which the ideal sensing requirements are met; what is important is that they are met by some technology or another. Thus, development of diverse sensing approaches is strongly encouraged. One sensing approach that seems to have less potential now may, by some breakthrough, become a frontrunner in the development of an ideal breath analysis instrument. It is also possible that, depending upon respective characteristics and capabilities, some sensing technologies may be better suited for some applications (e.g., biomarker discovery or monitoring condition X), and other technologies for other applications (e.g., frequent clinical measurement or diagnosis of disease Y).

As with any medical diagnostic tool, a successful breath analysis system must undergo a thorough validation process before it sees clinical use. As it transitions from the research-discovery phase to the clinical utility phase, the instrument must increasingly realize the requirements listed above, especially user-friendliness, compactness, and inexpensiveness.

V. Toward Transdisciplinarity

Despite implications by device engineers that such technology is ready for clinical deployment, and that various groups and companies have breath analysis instruments ready for clinical use, there are in fact very few prototypes available for trial in a clinical environment. Perhaps the principle reason for this is apparent from risk analysis: engineering groups have, quite sensibly, allocated limited resources towards the development of environmental, industrial, defense, and security applications, which are generally less complex to implement and offer more immediate and certain benefits. In many respects clinical applications like breath analysis face more difficult obstacles to implementation (cf. Section II), and more uncertain benefits. For example, environmental systems can be tested in any number of settings, e.g., in a lab, out of doors, or at a pollution source, whereas there is no substitute for sensor deployment in a clinical setting with large and diverse groups of disease subjects, and the interpretation of results by both clinical experts in breath analysis and clinical experts in the diseases being studied, not clinicians unfamiliar with these areas; breath is a particularly complex mixture to analyze, especially in regard

to high concentrations of potentially interfering species, like water vapor and carbon dioxide; in environmental, industrial, defense, and security monitoring, generally the relevance of the target species is known, whereas in clinical breath analysis this may not always be the case due to biomarker uncertainty or confounding factors; environmental, industrial, defense, and security studies do not have to be concerned with the stringent administrative processes involved in approving and carrying out human research.

However, the success of sensitive, potentially portable and inexpensive trace gas sensing systems in other applications [97]–[102] suggests that some of these technologies are mature enough to meet the challenges clinical breath analysis presents. In principle, it should not be very difficult to adapt environmental systems for clinical use, because most of the underlying sensor infrastructure would be similar or identical. There is a need for some group or company to undertake this task, to focus on interfacing existing systems for clinical breath analysis. The other option would be to build dedicated breath systems, but this would come at a higher cost. Instruments need not be optimized before they are deployed in clinics; on the contrary, deployment of a prototype in a clinic and with clinical input is likely necessary for optimization. A user-friendly interface and maintenance-free operation, while eventually necessary, are not requirements at this stage of sensor development, as long as knowledgeable technicians are available to assist with system operation. The priority is testing of prototypes in clinics sooner than later.

One of the greatest obstacles at the intersection of breath analysis and sensing technology is a less than optimally effective approach to collaboration, due in large part to a lack of awareness and understanding between disciplines, and the fact that each discipline has separate expectations and goals.

A typical example of this lack of awareness, at least from the clinical perspective, is the distance between EE scientists and clinicians with respect to breath analysis. The goals of each are distinct, and yet there is clearly a convergence at some points; EE attempts to link the external environment to internal dose and biomarker levels, and at this endpoint health effects science begins [103] (cf. also [39], [40]). Not only can exposure science inform medical research and practice, but, as mentioned in Section III, there are certain areas of research (e.g., pharmacokinetics, pathogenesis, metabolite/biomarker formation and pathways) where similar or common approaches are or can be employed. Thus, with this awareness, EE scientists and clinicians (and biochemists, upon further involvement) should be natural partners in close collaboration.

Other examples of lack of awareness and understanding as well as divergent expectations and goals may be found in the distance between clinicians and engineers. For instance, it is typical for an engineering group to state that compound A may have a clinical relevance B, then measure the concentration of the compound, with more or less success. While these "show and tell" studies are commendable in their intention to branch from device engineering to breath analysis application, they actually have little immediate clinical relevance, because they lack follow-through [16]. Not much clinically useful information can derived simply from measurement of the concentration of a suspected biomarker. Is that suspected biomarker, in fact, a biomarker? Determining compound concentration may be an impressive feat, but what does that concentration mean? Can it be used to determine whether a patient is diseased or healthy?

Such studies are not poorly designed or executed; rather, their goals are limited by disciplinary expectations. It is often considered a success and end-goal for an engineering group to design, fabricate, and demonstrate a functional device. While this is an important incremental goal, it is not enough for the success of clinical breath analysis. Engineers, EE scientists, and clinical breath experts need to target goals that transcend the standards of success typical for their respective disciplines.

Fortunately, the obstacle of suboptimal collaboration is the easiest to overcome. This paper has thus far clarified the status and challenges of clinical breath analysis for all scientific disciplines involved. Starting with such a common understanding, the breath analysis community needs to focus on transitioning from interdisciplinarity, a loose association of collaborating disciplines in which each discipline's research is more or less self-contained, to transdisciplinarity and translational research, a much tighter collaborative effort in which multidisciplinary teams work together towards shared goals, resulting in heightened cross-disciplinary awareness and communication. Specifically, clinical breath analysis would benefit both from integrated research with EE scientists and from a sensor development process that is both integrated and iterative: integrated in that development would occur partially in a clinical setting, with input from clinical team members, and iterative in that there should be frequent clinical testing as well as feedback among clinicians and engineers, so as to align expectations and minimize any unproductive developments.

One of the most productive ways to foster transdisciplinarity would be to seek funding for and implement an exchange program in which young engineers (especially graduate students and post-doctoral researchers) would spend part of their training in breath analysis laboratories, to become familiar with and have the opportunity to take an interest in breath analysis, as well as to develop and test instruments in a clinical setting and with clinical input. Furthermore, environmental exposure researchers, clinicians, and their mentees should hold conferences and offer visiting positions and internships specifically to address research overlaps and synergistic opportunities. Not only would these programs create, in a very concrete way, transdisciplinary teams and resolve misunderstandings and communication issues between disciplines, but they would also expose and educate the next generation of scientists, who can help clinical breath analysis become the next generation of medical diagnostics and monitoring.

VI. Other Considerations

Translational research beyond one's own compartmentalized discipline has proven challenging enough; researchers, whether clinical, biochemical, public health, or engineering, may also be inclined to forget the regulatory, financial, etc. considerations involved in bringing any novel technology or technique to commercial maturity or acceptance within a field

TABLE III
SUMMARY OF ACTION ITEMS FOR THE ADVANCEMENT OF CLINICAL BREATH ANALYSIS

Clinicians	Biochemists	Public Health	Engineers	Statisticians	Business
Use top-down approach for biomarker discovery; search for cut points Refine sampling methods and work towards standardization Test sensor technologies with focus on disease/ control subject comparison Integrate more closely with exposure science Educate, expose, encourage with respect to clinical breath analysis Seek funding options	Use bottom-up approach for biomarker discovery Explore further what biochemistry can achieve for clinical breath analysis Seek funding options	Provide expertise to the clinical breath community, including biochemists, on kinetics of exogenous and endogenous substances Pursue synergistic research, especially on pathogenesis and the bottom-up approach Seek opportunities to incorporate aspects of clinical breath analysis into current and prospective programs Seek funding options	Develop sensors that approach ideal breath analysis requirements, with frequent clinical consultation and involvement Increased education and involvement with respect to clinical breath analysis Seek funding options	Work with breath measurement and instrumentation teams to process and interpret complex data Seek funding options	Become more familiar with clinical and non-clinical breath analysis and iteratively assess its commercial potential as the field advances Assess funding strategies and viability Manage commercial logistics
Seek collaborative funding options					
Transdisciplinary collaboration and communication					

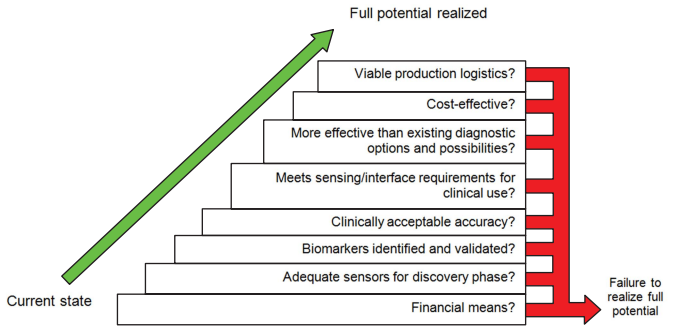

Fig. 4. One model suggesting steps clinical breath analysis must take in order to realize its full potential. Green arrow: affirmative response to the question posed. Red arrow: negative response.

(cf. Fig. 4). For instance, breath analysis is not guaranteed to see widespread clinical application if it seems like it is falling short of its diagnostic potential; resources may be diverted elsewhere. Fortunately, recent papers (e.g., [17], [28]) suggest that researchers are beginning to grapple with commercialization and production issues. It is particularly important, when considering these matters, to have knowledgeable investors, business liaisons, and relevant federal agencies involved [16]; ideally, they, too, participate in the development process in a transdisciplinary way, so that they are very familiar with the strengths and weaknesses of breath analysis technologies and approaches as they look to commercial and practical clinical application. Importantly, private developers will have to balance the desire for expedited commercialization, and therefore a competitive advantage on the market, with technological maturity, i.e., recognizing when a technology is truly prepared for effective and robust clinical use.

The obstacle of funding must also be overcome. At the moment, it is difficult to secure federal funding for the type of transdisciplinary research suggested in this paper: in addition to a sagging economy, different agencies tend to function in different spheres, human research and technologies, respectively. Grant-writers and those who work with funding need to research ways of securing financial support for this translational research, which may involve an effort to seek joint NIH/EPA/NSF funding, perhaps by proposing a combined clinical-public health-engineering breath research center that would serve as a nexus for transdisciplinary collaboration, or reaching out to a wide variety of investors. It is particularly worth noting that clinical breath research could benefit from EE stakes and programs already underway in related breath research, which open up new avenues of federal funding (e.g., DoD [44], EPA, CDC, NIOSH, NIEHS, HUD).

VII. FUTURE DIRECTIONS: GATEWAYS AND SYNERGIES

In all of these considerations, it is important to keep an open mind; the ideas, approaches, and innovations that provide sparks for major progress and new directions in the field often come from fresh perspectives that see solutions and opportunities which a single individual, research group, or discipline do not. Environmental breath applications have been emphasized throughout this paper for this purpose; they can aid the advancement of clinical breath analysis both through direct pursuit of synergistic research and by providing an intermediary platform through which public health funding and environmental sensing systems might make appropriate transitions toward clinical breath applications.

There are many other examples. For instance, recent breath analysis research has focused on biomarkers of disease via direct analysis of VOCs. This focus will remain important, but perhaps clinical breath researchers should borrow an approach from nuclear medicine; the use of tracers or challenges during the biomarker discovery phase may prove highly effective. Or perhaps breath analysis should find inspiration in the world of sports and fitness and law enforcement by searching

for markers of performance-enhancing or otherwise illegal drug use in exhaled breath [17], [29], [59], [71], [104], [105]; this pursuit seems especially promising as such markers, derived from the metabolized products of these drugs, have the potential to be binary indicators (i.e., simply a matter of compound presence or absence) of illicit drug usage, eliminating the ambiguities introduced by the concentration dependence characteristic of endogenously-produced VOCs (cf. Section II). The intelligence and forensics communities would also welcome effective, portable, inexpensive breath-based drug tests, as well as compact, widely-deployable (e.g., in cell phones) breath monitors for dangerous (potentially explosives-related) substances and radiological poisoning [39], [105]. Breath analysis could be useful in the regulation of artificial environments (e.g., submarines, spacecraft) [9], [14], [83]. Personal metabolism and exhaled contaminant (e.g., particulate matter, ozone) monitoring are also attractive options. If these approaches prove promising—most of them certainly have an enormous potential market—they may not only be valuable in themselves but also serve as a gateway, especially financially and in terms of general interest, to further disease biomarker research. Significantly, they will also emphasize the need for and drive the commercial development of user-friendly, ultra-portable, inexpensive sensors.

VIII. Conclusion

Clinical breath analysis is a broad concept with immense potential; a large, complex, collaborative system (cf. Table III), and a commensurately large and open perspective, are required to explore this potential. This paper has progressed beyond the frequent "calls to action" found in much breath analysis literature by actually developing a course of transdisciplinary action. Significantly, this paper has also attempted to provide the cross-disciplinary foundations of understanding required to effect this action by emphasizing clarity and multi-discipline accessibility, without compromising comprehensiveness. It has considered current medical, biochemical, technological, collaborative, and commercial statuses and challenges in regard to the advancement of clinical breath analysis, and proposed ways of addressing these challenges, beginning with increased transdisciplinary communication, education, exchange, and exposure.

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