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PERSPECTIVE

Breath analysis: clinical research to the end-user market

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Abstract
Breath research is now well established and is solving some of the applications in the area of identifying volatiles for medical diagnosis. This paper looks at how this research has been taken to an end-user market. It is not intended to be an indepth study of the science but simply to draw attention to the role of the commercial link between the researcher and end-user. This market is not only in research but exists in hospitals, clinics, sports medicine and even homecare. The link between research and the end-user market is a vital one to avoid breath analysis being the tool of researchers only. The ubiquitous use of breath analysis depends upon it. This is a review of some of the success stories in commercializing the important breath analysis research that has been conducted over the last few decades. In order to make breath analysis the new blood test, products that have end-user appeal need to be developed and routes to market established.

Background

Breath analysis research has been a cornerstone of university practice for several decades [1].

There is a need to take this research from academics into sustainable commercial applications.

Any healthcare article that starts off by talking about Hippocrates is at risk of being a cliché. However, breath analysis is an ancient art of diagnosis, simply by smelling the breath of patients. But for many years breath analysis has been largely ignored as a tool suitable for use by health professionals. Indeed it has only been over the last few decades that breath analysis has started to become an accepted part of everyday life. The best example of this is the use of the alcohol breathalyser to establish whether drivers are legally intoxicated or not.

Since the 1960s a simple breath test has been employed by the police and the legal system to establish the capability of drivers to drive their cars safely. These days it is quite acceptable for breath analysis to be used as a substitute for blood analysis; in this case there is a direct relationship between the amount of alcohol in the blood and how much can be found in the breath. This technique has pioneered the acceptance of breath analysis as a serious clinical tool.

Nowadays there are a number of breath tests which are used in clinical research and other healthcare environments. The benefits of moving from blood analysis to breath monitoring are numerous and are listed below.

- Non-invasive.
- Breath testing provides quick results.
- Can be carried out anywhere and is not subject to laboratory conditions.
- Lower cost per test than a blood test.
- Can be carried out patient side and has a greater acceptance from patients.
- Could be done at home remotely from a clinic or surgery.

As with most new techniques their use is pioneered by clinical research. First of all the relevant gaseous biomarkers need to be identified and then the possible clinical application researched. This may take several years. In order to make the application truly clinically useful a route to market needs to be established.

There are a number of settings where breath analysis can be used which include clinical research, hospitals, clinics, GP and physician's surgeries, pharmacies, corporate wellness facilities, sports medicine facilities, commercial fitness centres and homecare. Products for breath analysis in clinical research tend to be more sophisticated and flexible analysis systems. Additionally these types of products tend to be more expensive often costing more than € 100 000. For example SIFT-MS which has been used extensively in breath research but usually at only those centres of excellence that can afford one. To take breath analysis to the other markets mentioned here the cost of ownership and therefore the return on investment needs to diminish as we move further down the list to the consumer market.

Once the breath biomarker has been identified and the application established, an appropriate sensor technology needs to be chosen. Then a suitable breath entrapment system needs to be developed in order to present the chosen sensor with a sample under conditions it enjoys. The development of an appropriate format is then necessary in order to provide the health professional with the correct method of interfacing with the patient. Once the product is proven and regulatory affairs satisfied a route to market needs to be established. The danger of not applying this routine to market is that breath analysis will remain a research tool and the number of patients benefitting from the technology diminished.

The scope of this paper is not to review the different techniques used in breath gas analysis but simply to draw attention to the need for the appropriate product development in order to take the applications to market. Techniques such as mass spectrometry and absorption spectroscopy are high powered and versatile gas analysis techniques. However, they come at a high cost and therefore are usually only found in research environments. Lower cost gas monitoring equipment usually utilizes less expensive gas sensing technology such as electrochemistry. These products are normally hand-held, patient side and low cost. They normally provide a focus application and are not normally used for multi-gas analysis like the research tools are. These types of devices are finding a route to clinical market with mass appeal.

In 1985 I personally was involved in researching and subsequently taking to market a breath analysis technique. At this time, the measurement of breath carbon monoxide (CO) was little known by practising health professionals. Its main use was as a diagnostic alternative to blood analysis for CO poisoning mainly subsequent to smoke inhalation in fires [2].

The equipment used at this time was mainly bench top and had other primary intended uses normally in environmental analysis. This meant that these analysers had drawbacks in use such as impractical breath collection, interference from other breath gases such as hydrogen (H_2) and not patient side not to forget quite expensive (between € 15–25 k by today's standards).

My company Bedfont Scientific Limited had at this time limited resources. We set forth, however, to work with researchers to develop an accurate, low cost and practical breath CO analyser but directed at the smoking cessation market rather than the diagnostic market. The use of electrochemical gas sensor technology was at the centre of our development project. These types of sensor were commonly used in environmental and safety applications and as a result the first sensor we had to work with had drawbacks. Its relatively slow response and cross sensitivity to H_2 (another commonly encountered breath consistent [3]) made it impractical.

We first worked closely with the manufacturer to develop a new sensor that was more appropriate, at the same time developing a breath entrapment system that ensured end-tidal lung gas was presented to the sensor for analysis. These two elements were then connected to a simple electronic device that displayed breath CO in parts per million (ppm). This measurement has been shown to directly reflect blood carboxyhaemoglobin (COhb) normally shown as a percentage [4]. This device was sold for less than € 1000 to health professionals who used it to demonstrate the dangers of smoking to educate and motivate smokers to quit smoking [5].

However, in 1985 almost no health professionals knew such a tool had become available. Without determined, long term and resolute marketing this would have remained the case for some years. The brand Smokerlyzer® was created and commercially presented to health professionals worldwide. Today it forms the centre piece of many stop smoking clinics' activities and is frequently used in conjunction with an array of pharmacotherapies to treat nicotine addiction [6].

It is true to say that the development of sensor technology is normally emerging from industrial applications such as environmental pollution analysis and health and safety applications. In order to make these sensors appropriate for breath analysis further research and development has to take place, as breath gas is a complex sample containing many components at elevated temperature and saturated with water. Pressure changes during breath sampling also have to be allowed for when presenting the sample to the sensors.

If we look at a global situation, the number of companies taking breath analysis to market successfully are few and far between. They tend to be niche marketeers, and focused on one particular application. These companies can be presented with a number of obstacles; these are listed below.

- Absence of technically or commercially viable sensors, for example tuneable lasers.
- Appropriate format.
- Breath entrapment system.
- Ability to satisfy clinical guidelines.
- Availability of clinical research.
- Availability of appropriate products to satisfy needs of clinical research.
- Timescales.
- Cost of appropriate technology.
- Regulatory approvals.

Taking breath analysis to a homecare market must be the 'Holy Grail'. This is the way that a larger percentage of the population can benefit from this easy technique. Breath analysis is the most convenient expleted analyte that the human body can provide. Breath biomarkers can be used to diagnose, monitor, demonstrate and educate patients as to what is going on in their metabolism. It can be envisaged that some time in the future a black box on the bathroom cabinet could be used daily to assess any emerging health problems for an individual. Early warnings of changes could indicate that further investigation is required.

Breath analysis can be a powerful tool. In order for it to take its rightful place in a global healthcare system further efforts and investment need to be made. It is possible to say at present that breath analysis has been recognized as a serious clinical tool but its growth in world markets is relatively slow.

Breath analysers are not simply gadget, but regulated medical devices and clinical tools. Smaller more affordable products have appeared on the market over the last 10 years. A good example is breath nitric oxide (eNO), formerly solved using expensive (€ 25–40 k) chemiluminescence analysers but now utilizes well-correlated electrochemical technology (€ 2–4 k). The market here is asthma care. The provision of an appropriate homecare device may significantly help control this disease which is developing as an international pandemic [7].

Conclusion

What can our dream for future breath analysis be? Maybe, a black box on the bathroom shelf that alerts us to metabolic changes that may need further investigation? I see no reason why a partnership between researchers, health professionals and entrepreneurs cannot make this happen.

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