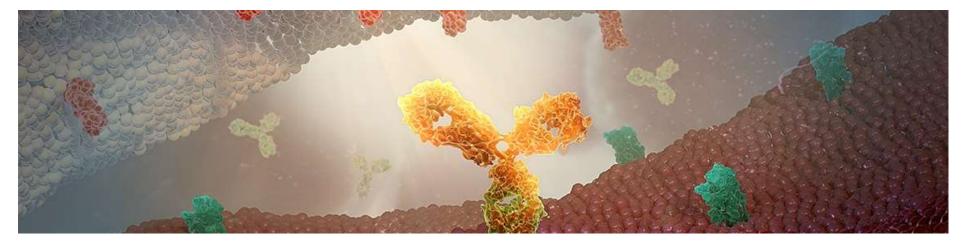


Made to be measured: The revolutions in analytical science for the real time analysis of the human body

Dr Tony Bristow, Principal Scientist Measurement Science, AstraZeneca, Macclesfield FRSC and Associate Visiting Professor, University of Warwick

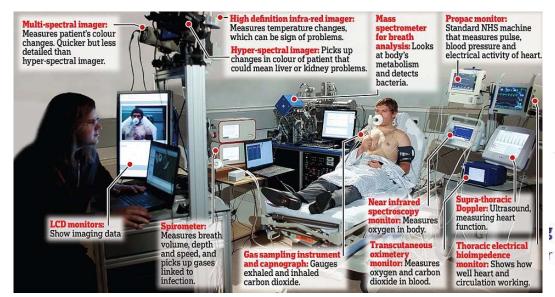
Knutsford SciBar 4 November 2019



All images in this presentation are included unambiguously for educational purposes only as part of public outreach activities



A journey through innovations in analytical science......



Courtesy of Paul Monks – University of Leicester

Courtesy of Abbott Diabetes Care





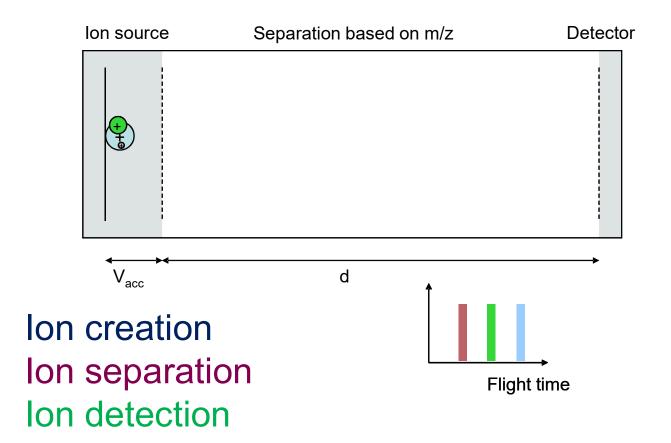
Lets start by thinking big and in the lab

Let's start with mass spectrometry

- Which is a powerful technique used in analytical science that is used to:
 - elucidate the structure and chemical properties of molecules
 - quantify trace levels of compounds in large amounts of other materials (a complex matrix) - as low as one part in 10¹²
- Detection of compounds can be accomplished with very minute quantities of sample
- A mass spectrometer measures the mass-to-charge ratio (m/z) of the ions formed from the molecules (or elements)



Principles of a type of mass spectrometer - Time of Flight

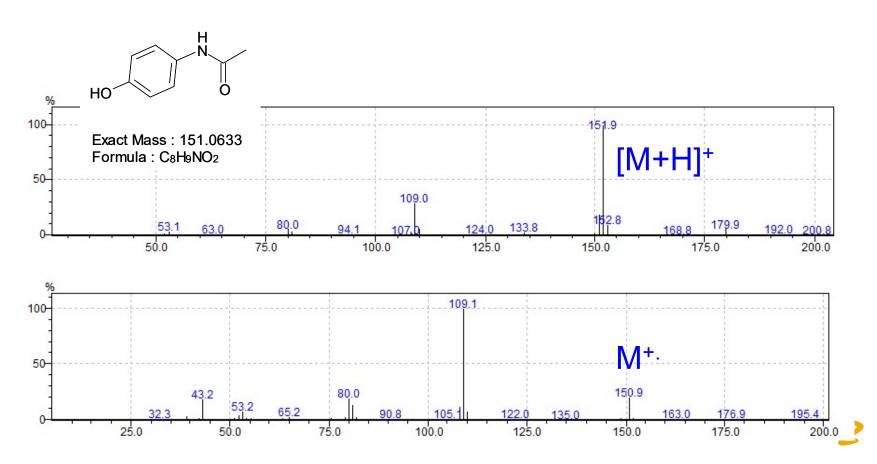




What does a mass spectrum tell you?



Identity – a molecular fingerprint



Fun example of MS – Mobile Environmental Analysis Rack Mounted in Front Seat

- Constant Flow sampling from front of vehicle
- Multiple inlets at different heights





Deep Well Injection - Benzene







How can mass spectrometry be used in disease diagnosis and disease understanding?

Real-time cancer diagnostics by Mass Spectrometry

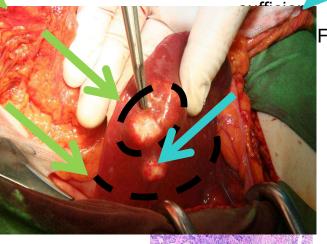
Warning
The Blood and Guts Bit

Courtesy of Zoltan Takats – Imperial College



Where to dissect?

- Intraoper identifica Is it also tumor?
 - Visua information



Frozen section

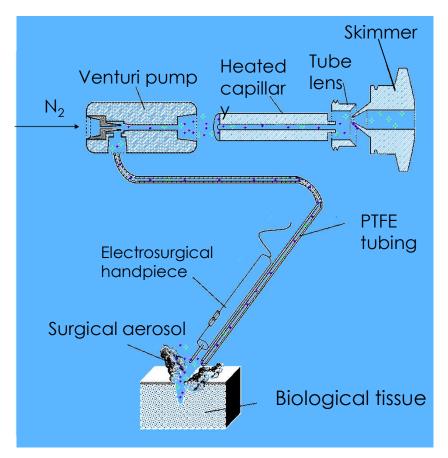
Colon adenocarcinoma liver metastasis

Hematoxylin-Eosin stain ~ 20-30 min

Immunohistochemistry ~ 1 hour

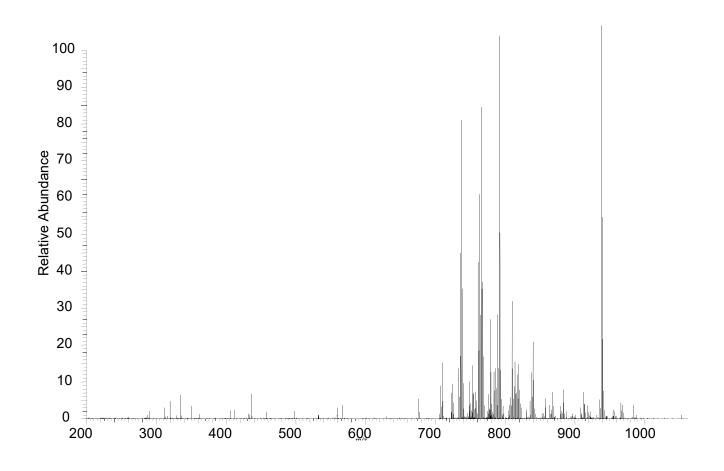


A mass spectrometer in the operating theatre in combination with Electrosurgery





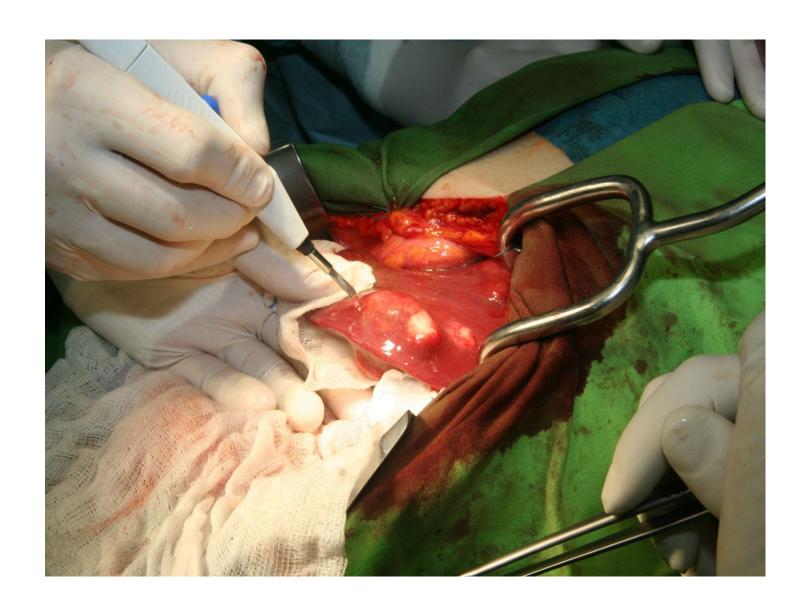
The Tissue Fingerprint – a mass spectrum













Breath-taking research... literally

Prof. Paul S. Monks
PVC and Dept. of Chemistry
University of Leicester

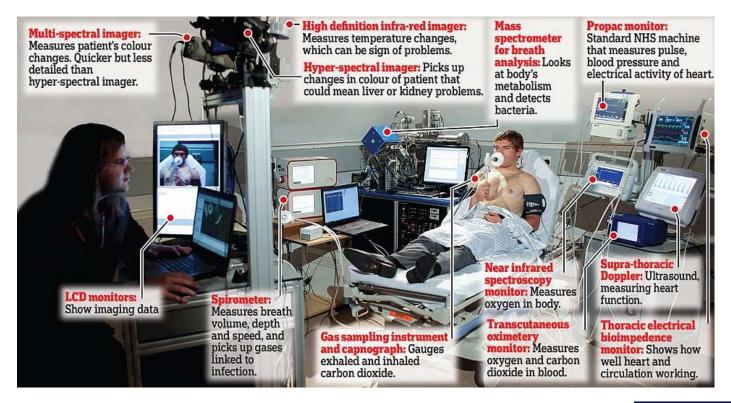








Diagnostic Development Unit - DDU



(Courtesy of the Daily Mail)





Breathomics

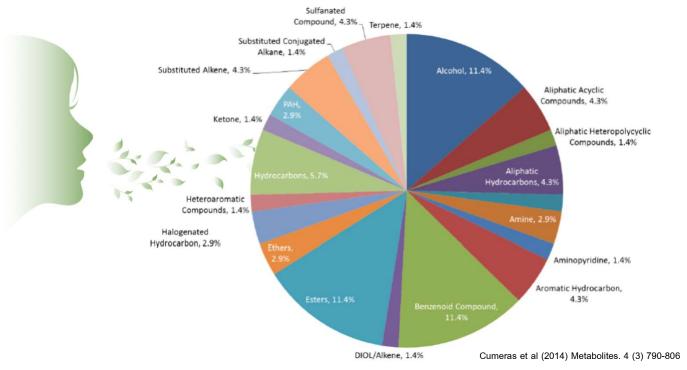








Breathomics



The study of breath as a potential new molecular pathology



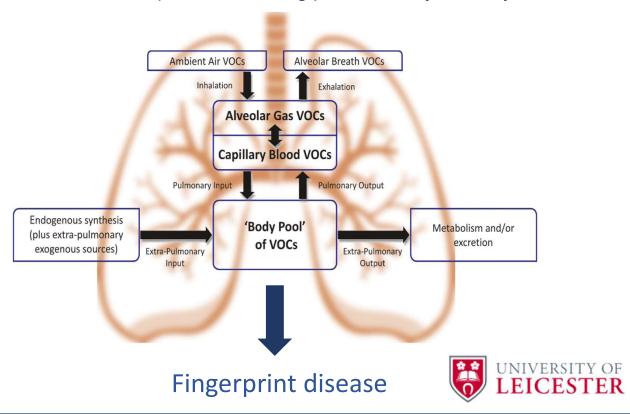
WMJ1

Breath is a wealth of chemical information, it's more than just air (comprised of N2, O2 and CO2). It contains hundreds of chemicals, referred to as volatile organic compounds (VOCs) from within the body. It's this wealth of chemical information that makes a potentially powerful new molecular pathology.

Wilde, Michael J., 02/05/2018

Breathomics

Breath contains hundreds of volatile organic compounds coming from the chemical processes taking place inside your body



WMJ1

Breath contains hundreds to thousands of volatile organic compounds coming from the chemical processes taking place inside your body. Cellular metabolism and reactions release metabolites/VOCs into the bloodstream. When the bloods passes via the lungs to exchange respiratory gases across the alveolar membrane, the VOCs are also exchanged. The VOCs are then exhaled in breath. Therefore, some of the exhaled VOCs represent the processes occurring inside the body.

The air we breathe in also contains exogenous VOCs.

This figure shows the input and output of VOCs in breath, showing why breath contains such a complex mixture of VOCs. Wilde, Michael J., 02/05/2018



Molecular Pathology

Seeks to describe and understand the origins and mechanisms of disease using patient samples (Molecular Pathology Review 2013)



WMJ3 Molecular pathology seeks to describe and understand the origins and mechanisms of disease using patient samples.

We are exploting almost every bodily fluid and cell culture the human body has to offer.

However, most traditional molecular pathologies such as blood are invasive, irreproducible (limited in volume, can't continuously take blood or urine), are biohazardous and require storage.

Wilde, Michael J., 02/05/2018



Molecular Pathology

Seeks to describe and understand the origins and mechanisms of disease using patient samples (Molecular Pathology Review 2013)

✓ Non-invasive procedure

✓ No risk allowing for

repeated use

✓ Suitable for people of all ages and conditions

Quick to perform/immediate results

Advantages of breath



Advantages of breath compared to other molecular pathology technques Wilde, Michael J., 02/05/2018 WMJ3



Analytical technologies



Advances in technology are advancing science



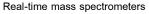
Analytical technologies are advancing Wilde, Michael J., 02/05/2018 WMJ3



Analytical technologies

Range of analytical technologies being developed for various phases of research and applications

Handheld collection device





Ann.



Somewhere in-between

Bedside sampling

Advanced chromatographic instrumentation



Laboratory/
Dedicated clinical room

Laboratory only



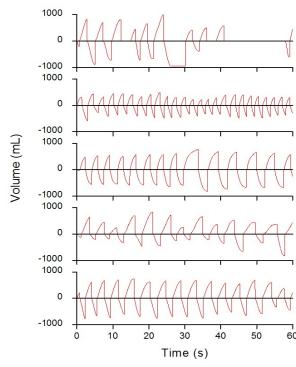
WMJ3

Technologies for analysing breath range from offline laboratory techniques such as GC-MS and GCxGC-MS, real-time chemical ioinsation mass spectrometry such as PTR-MS and APCI-MS, online ion mobility spectrometers and handheld sampling devices for rapid collection of samples which allow bedside sampling in clinic but provide samples for more offline analysis in a laboratory.

Wilde, Michael J., 02/05/2018

Challenges

- Breath is transient
 - Breath cycle
 - Patient variability
- Breath is moist
- Breath composition is inhomogeneous
 - Alveolar air is target
- Breath comes through the oral (and nasal) cavity
 - Potential for contamination (e.g. toothpaste, oral bacteria)
- Breath VOCs are at trace levels
 - pptV to ppbV
 - there are wide variety of compounds



Five different patients undertaking tidal breathing



Despite wealth of information and availability of analytical technologies, breaht analysis is challenging. Wilde, Michael J., 02/05/2018 WMJ3

Real-time analysis

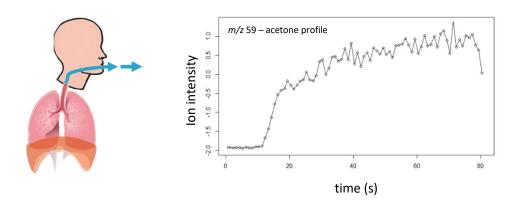
Real-time monitoring of VOCs in clinic

Uses a technology called proton transfer reaction-time of flight-mass spectrometry (PTR-TOF-MS)

Rapid analysis (< 1 min)

Exhaled VOCs as function of time, not just total VOCs

Individual profiles e.g. 'breath fingerprinting' for precision medicine





Real-time analysis

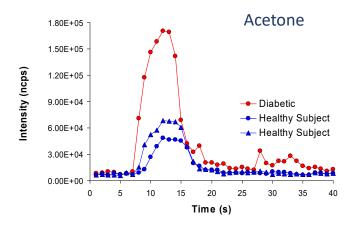


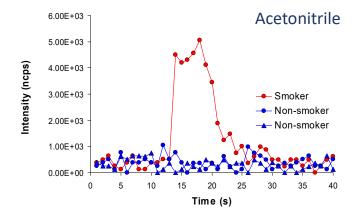
Real-time monitoring of VOCs in clinic





Into the clinic







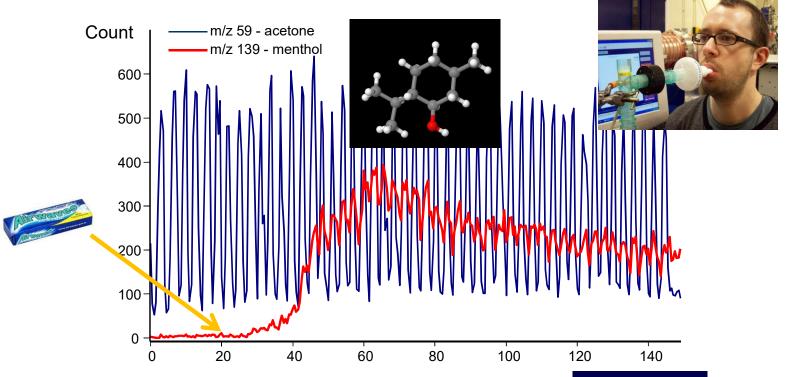
Real-time measurements of breath composition

- a) Acetone simple marker for diabetes
- b) Acetonitrile marker for smokers



WMJ4 Example of real-time analysis of breath in a hospital, couple of different examples of chemicals markers in different groups of patients Wilde, Michael J., 02/05/2018

Specific Applications: Breath Detection of Chewing Gum







Chromatographic separation

Offline analysis of VOCs

Uses a technology called gas chromatography-mass spectrometry (GC-MS) and two-dimensional gas chromatography (GCxGC)

Long analysis time (40+ min)

Separation of individual biomarkers

Chromatographic profile e.g. 'breath fingerprinting' for precision medicine







Offline analysis of VOCs – samples collected at patient bedside and sent to laboratory



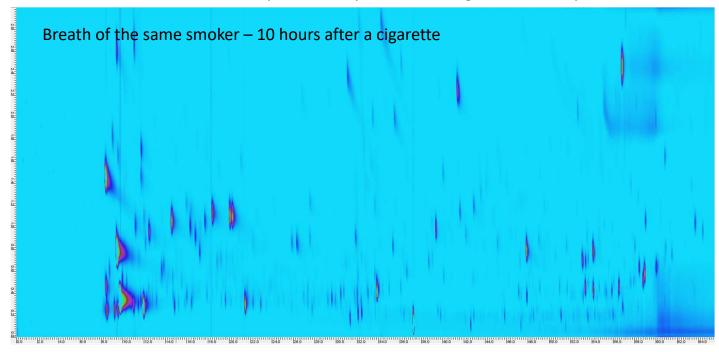
Samples for offline analysis are collected in clinic. Wilde, Michael J., 02/05/2018 WMJ9



Into the clinic

Effects of smoking

Even after 10 hours, mouth contamination has disappeared (after eating, brushing teeth and sleeping), but additional compounds still present, coming from the body





Graphical portayal of the effects of smoking on the body. After 10 hours, increased complexity due to smoking is still observed, these compounds are in the blood and lungs and still being exhaled from the body.

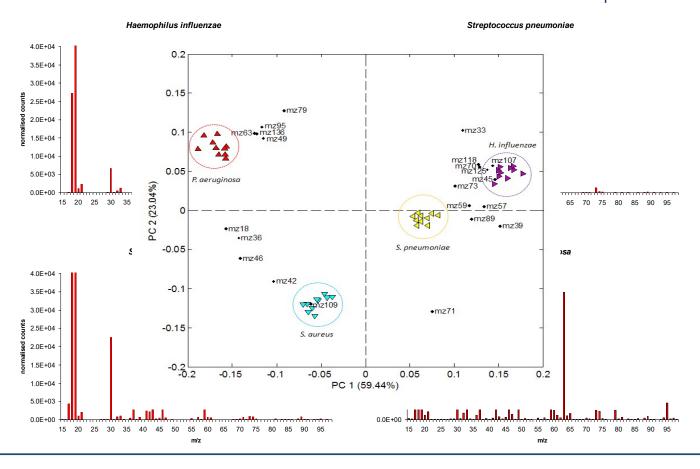
Wilde, Michael J., 02/05/2018



Bacteria headspace analysis White Corporation Bacteria headspace analysis White Corporation White Corp

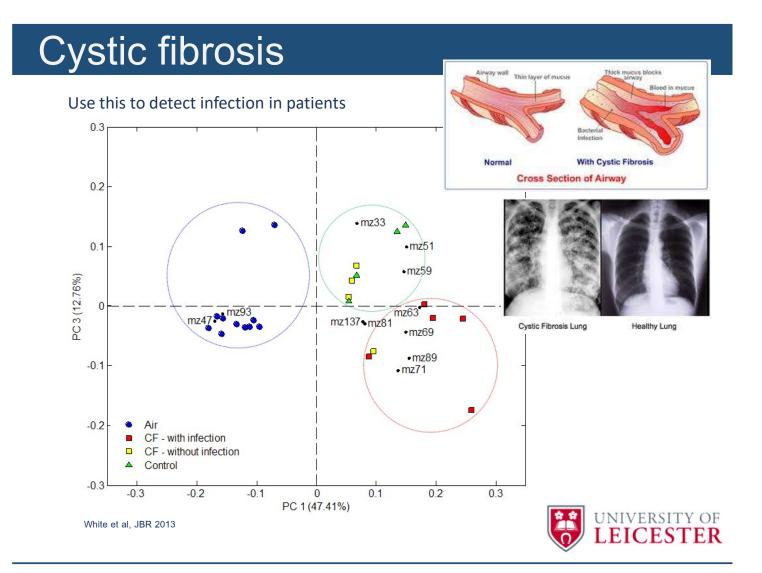


Bacteria release different metabolites and we can differentiate based on this profile



These are four common bacterial infections in the lungs. Analysis of the VOCs they release allows different bacteria to be characterised. Wilde, Michael J., 02/05/2018

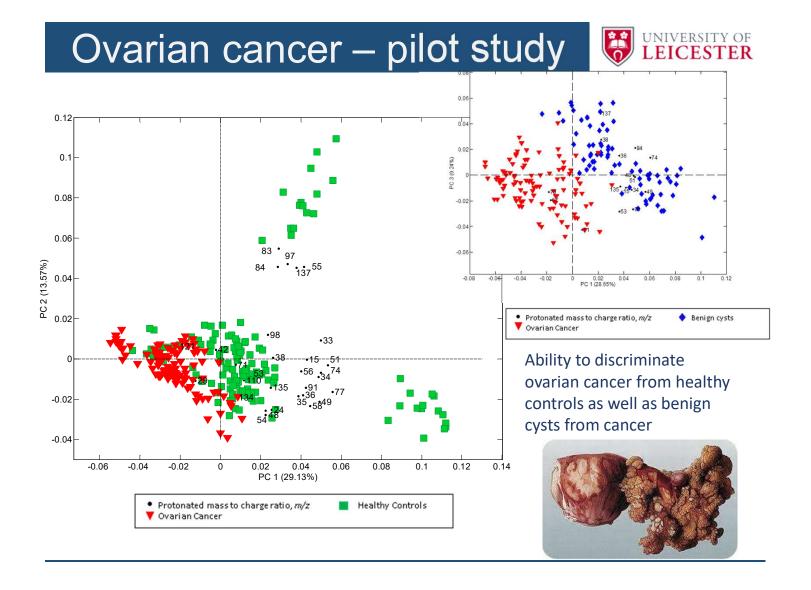




Following on the last slides, as it's possible to differentiate different bacteria, it was possible to differentiate patients suffering cystic fibrosis which had also a lung infection from their breath

Wilde, Michael J., 02/05/2018



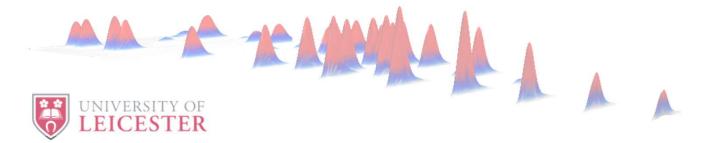


Analysis of different biopsy samples showed it was possible to differentiate cancer cells and healthy cells, if these chemical differences can be detected in breath then it would be a valuable diagnostic tool for clincians.

Wilde, Michael J., 02/05/2018

Future outcomes

- 1) Clinicians- with improved diagnostics and biomarkers
- 2) **Patients-** by improved clinical decision making with near-patient, non-invasive technologies that are widely applicable
- 3) Health care providers- decision making for optimising allocation of resources
- 4) **Pharmaceutical industry-** 'breathomics' as an outcome in early phase development, stratification, companion diagnostic in the clinic
- 5) **Platform technology industries-** improvements in the development of novel devices with clinical applications and the embedding this new molecular pathology in health care.





Decomposition begins approximately 4 minutes after death.

Accumulation of gases causes body to swell.

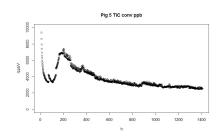
Body deflates, protein is broken down into fatty acids.

Corpse dries. Only remains are skin, hair and bones.

Fingerprinting Air - Applications

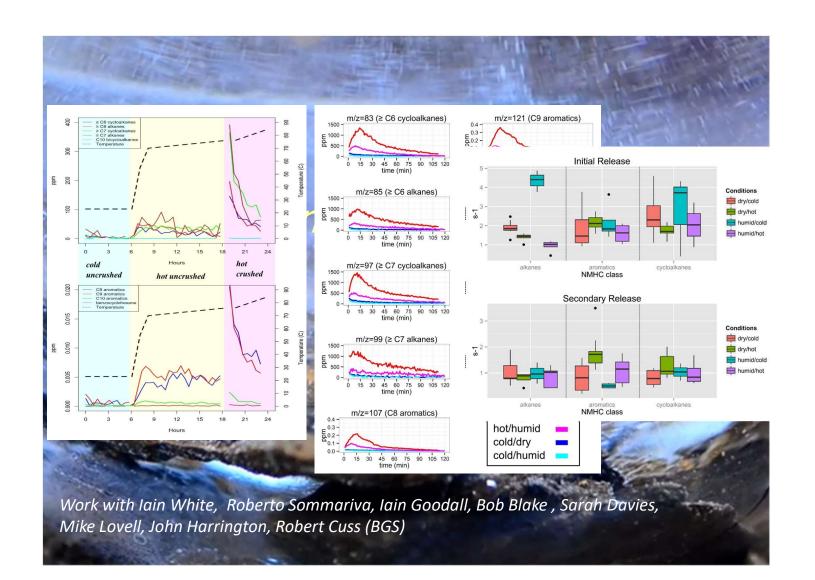


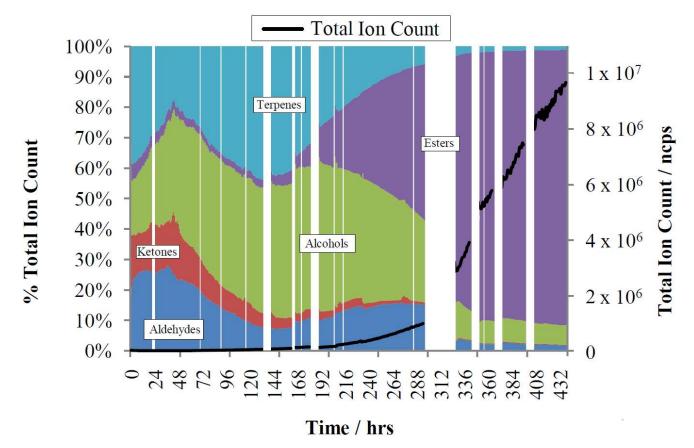
Whiff of Death











Work with Iain White, Bob Blake, Andy Taylor (UNott, MARS)

What have Uni Leicester looked at ...

- Security Chemical Warfare Agents
- Food analysis Is a single malt better?
- Automotive emissions H₂S quantification
- Medical diagnostic or prognostic
 - Breath analysis
- Process monitoring engine emissions
- Consumer Product testing 'Watching Paint Dry'
- Environmental monitoring or measurement
 - Atmospheric Composition, Isobaric Compounds, Secondary Organic Aerosol
- Forensic Science
 - Arson, Bodily fluids, Dead Bodies, DoA





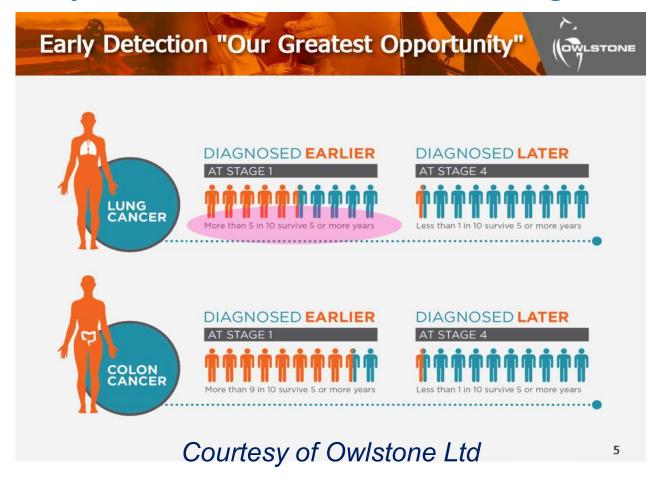




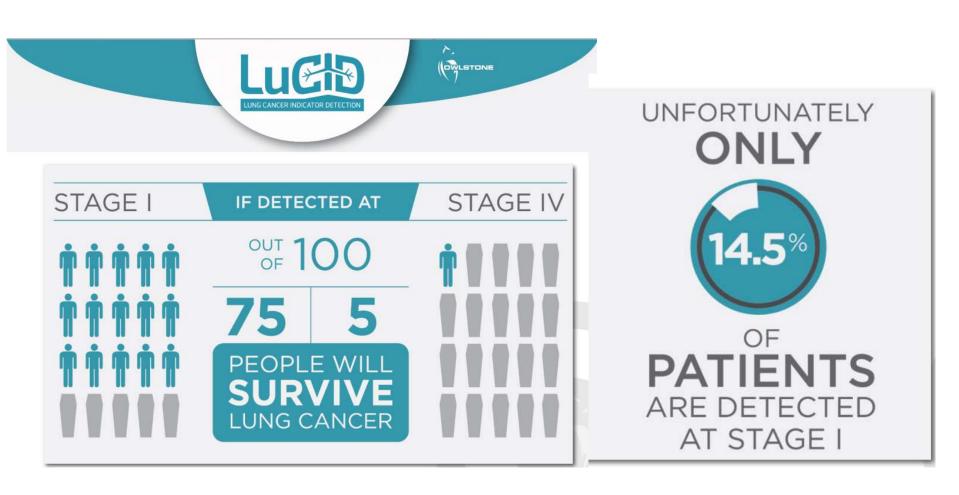


Sampling the patient remotely for disease diagnosis

Early detection for cancer diagnosis





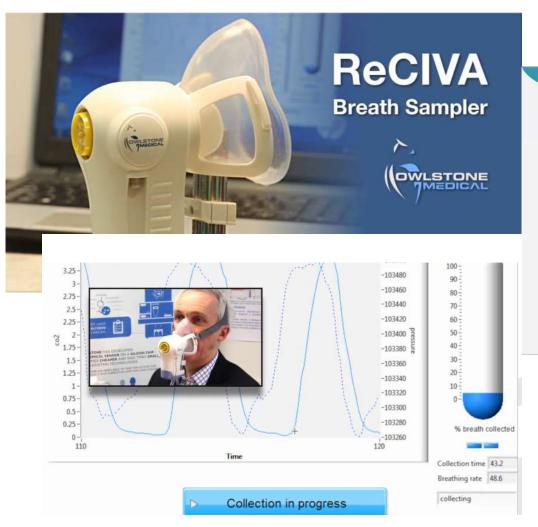


Courtesy of Owlstone Ltd



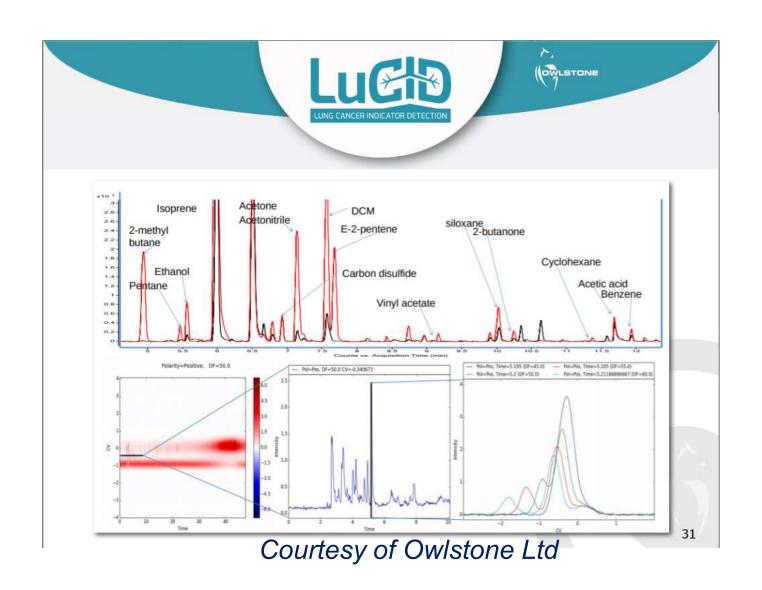
- £1.1M NHS contract
- Largest breath biomarker trial ever undertaken in the world
- Multi-centre across UK, Europe.
- Initial target recruitment 600; ~300 lung cancer patients and 300 controls. Extended to 2,500 to 3,000 for early stage detection.
- NIHR portfolio approved (UKCRN ID: 19914)
- Chief Investigator: Dr Robert Rintoul

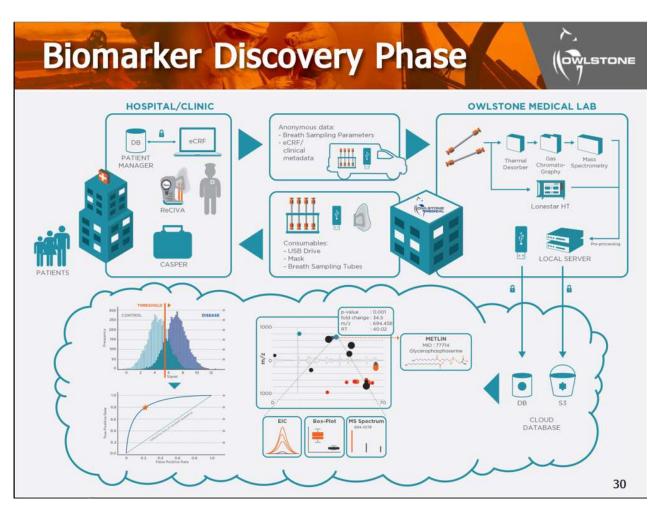






Courtesy of Owlstone Ltd





Courtesy of Owlstone Ltd



Patient breath sample is collected in doctor's surgery.



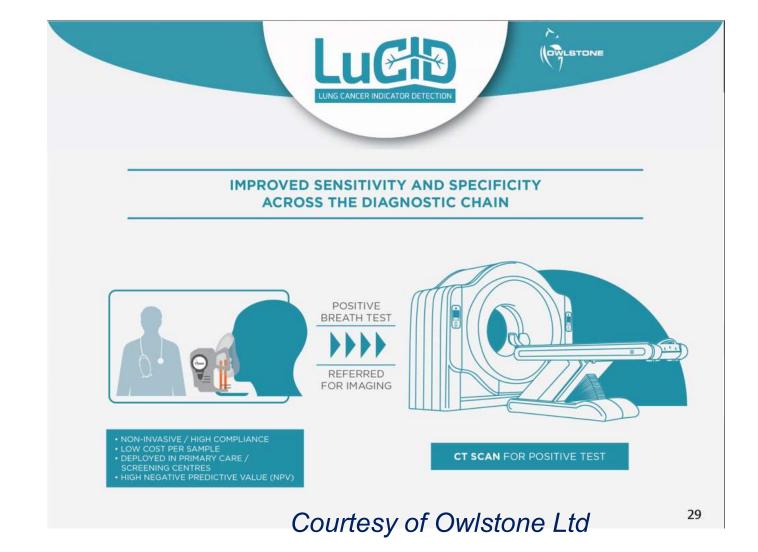
The breath samples are analyzed by Owlstone Medical's proprietary FAIMS technology.



2 Breath biomarkers are stored on a 'sorbent tube' and sent for analysis.



The results are sent back to the doctor. If biomarkers of disease are present the patient is referred for further testing.



Analytical science and Parkinson's diagnosis

The woman who can smell Parkinson's disease

By Elizabeth Quigley BBC Scotland news



Copyright @ 2018 BBC

Dr Tilo Kunath, a Parkinson's UK fellow at Edinburgh University, was one of the first scientists Joy spoke to.

Early study - tested Joy with six people with Parkinson's and six without.

Each wore a t-shirt for a day, then the t-shirts retrieved, bagged and coded.

"Her accuracy was 11 out of 12. We were quite impressed."

Joy identified six Parkinson's and was adamant one of the 'control' subjects had Parkinson's.

Eight months later the control individual informed the research team that he had been diagnosed with Parkinson's.

Joy wasn't correct for 11 out of 12, she was actually 12 out of 12.

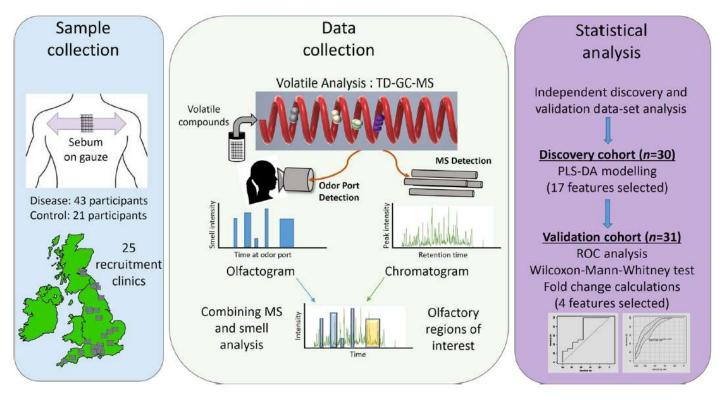
Inspired a much bigger study



Analytical science and Parkinson's diagnosis

- Professor Perdita Barran's research group at the University of Manchester are collaborating with Joy to characterise the specific chemical odours associated with Parkinson's
- Testing t-shirt samples from patients
- Applying Gas Chromatography-Mass Spectrometry to characterise the many components of the odours captured on the t-shirts
 - Laboratory based analytical science for fundamental understanding
- Overall goal is to create a clinical test for the early diagnosis of the disease
 - Simple test and/or device





Reference: Barran et al, ACS Cent. Sci. 2019, 5, 599-606

Copyright @ 2019 American Chemical Society

Comprehensive analysis of sebum from patients raises the possibility that individuals can be screened noninvasively based on targeted analysis of volatile biomarkers



The universal analytical scientist.....coming to a home near you soon?

Examples of the roving analytical scientist







References: http://www.drinkdriving.org, http://www.drinkdriving.org, https://www.drinkdriving.org, https://www.drinkdriving.org, https://www.drinkdriving.org<



Ceracor Ember

Non-invasive Hemoglobin monitoring sports training

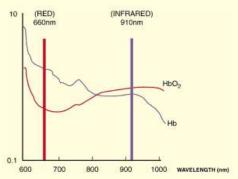




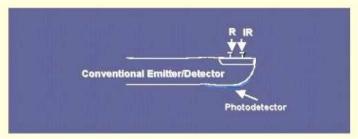
Reference: http://www.cercacor.com/#what-is-ember

The Science of Hemoglobin Measurement

The principle of pulse oximetry is based on the red and infrared light absorption characteristics of oxygenated and deoxygenated hemoglobin. Oxygenated hemoglobin absorbs more infrared light and allows more red light to pass through. Deoxygenated (or reduced) hemoglobin absorbs more red light and allows more infrared light to pass through. Red light is in the 600-750 nm wavelength light band. Infrared light is in the 850-1000 nm wavelength light band.



Pulse oximetry uses a light emitter with red and infrared LEDs that shines through a reasonably translucent site with good blood flow. Typical adult/pediatric sites are the finger, toe, pinna (top) or lobe of the ear. Infant sites are the foot or palm of the hand and the big toe or thumb. Opposite the emitter is a photodetector that receives the light that passes through the measuring site.

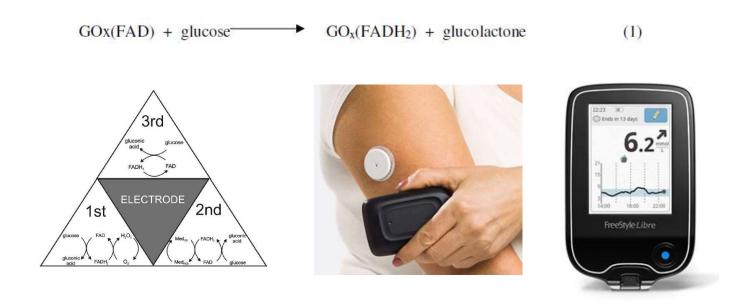


Pulse oximetry is a noninvasive method for monitoring a person's oxygen saturation (SO_2) .

A blood-oxygen monitor displays the percentage of blood that is loaded with oxygen.



Sensors – an evolving area providing new opportunities Real world example of advances in patient home monitoring Glucose and Diabetes



Courtesy of Abbott Diabetes Care



Abbott Freestyle Libre

THE FREESTYLE LIBRE SYSTEM

LIBERATING PATIENTS FROM THE HASSLES OF GLUCOSE MONITORING¹

How it works

1 APPLY a small sensor to the back of the upper arm





The FreeStyle Libre sensor



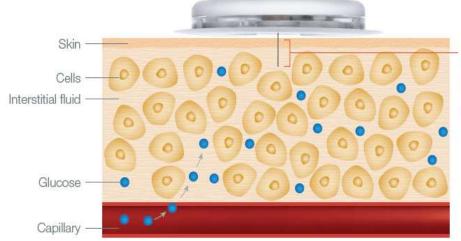
- Small and discreet, measuring 35 mm x 5 mm (similar to the size of a £2/€2 coin)
- You can wear it for up to 14 days
 Designed to be water-resistant and worn while bathing, showering, swimming¹, and exercising
- No finger prick required for calibration.



 Data on tile. Abbott Diabetes Care. The FreeStyle Libre system Iberates you from the h 95.7 % of parients surveyed (n=20) agreed that the FreeStyle Libra system reduces the h 'A flager prick test using a blood glucose maler is required during times of pably changing reflect blood clincose sewis or it thoughousement or immentities bronobysemia is seported.

Courtesy of Abbott Diabetes Care

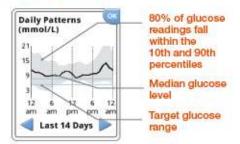




The sensor filament is less than 0.4 millimetres thick and is inserted 5 millimetres under the skin surface

Abbott Freestyle Libre

Dally Patterns



Shows the variability of glucose levels over multiple days to give a quick snapshot of glycaemic control.

Time in Target



Shows the percentage of time glucose readings were above, below and within the target glucose range, helping motivate patients to get more of their readings within the target range.

Low Glucose Events





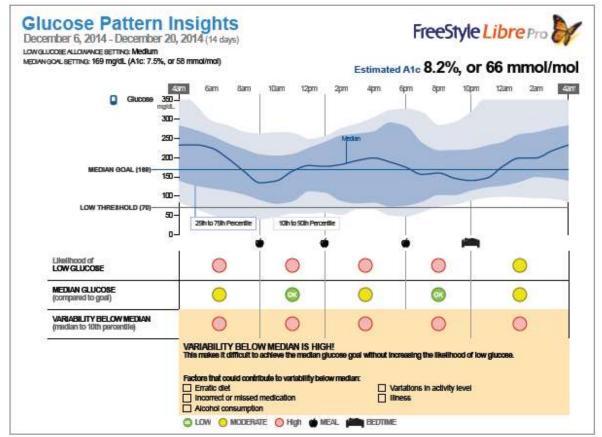
Shows the total number of low glucose events at 4 different times of day, Low glucose events are recorded when glucose readings are lower than 3.9mmol/L for longer than 15 minutes.







Abbott Freestyle Libre





60 million real-world glucose tests reviewed

DIABETES RESEARCH AND CLINICAL PRACTICE 137 (2018) 37-46



Contents available at ScienceDirect

Diabetes Research and Clinical Practice





Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: A European analysis of over 60 million glucose tests



Timothy C. Dunn a, Yongjin Xua, Gary Hayter, Ramzi A. Ajjan b

" Abbott Diabetes Care, 1360 South Loop Road, Alameda, CA, USA

^bThe LIGHT Laboratories, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds LS2 9JT, UK

ARTICLEINFO

Article history Received 12 July 2017 Received in revised form 8 November 2017 Accepted 18 December 2017 Available online 24 December 2017

Keymords: Flash glucose monitoring Blood glucose monitoring frequency Real-world data Glycaemic measures

ARSTRACT

Aims: Randomised controlled trials demonstrate that using flash glucose monitoring improves glycaemic control but it is unclear whether this applies outside trial conditions. We investigated glucose testing patterns in users worldwide under real life settings to establish testing frequency and association with glycaemic parameters

Methods: Glucose results were de-identified and uploaded onto a dedicated database once readers were connected to an internet-ready computer. Data between September 2014 and May 2016, comprising 50,831 readers and 279,446 sensors worldwide, were analysed. Scan rate per reader was determined and each reader was sorted into twenty equally-sized rankordered groups, categorised by scan frequency. Glucose parameters were calculated for each group, including estimated HbA_{1c}, time above, below and within range identified as 3.9-10.0 mmol/L.

Results: Users performed a mean of 16.3 scans/day [median (IQR): 14 (10-20)] with 86.4 million hours of readings and 63.8 million scans. Estimated HbA1c gradually reduced from 8.0% to 6.7% (64 to 50 mmol/mol) as scan rate increased from lowest to highest scan groups (4.4 and 48.1 scans/day, respectively; p < .001). Simultaneously, time below 3.9, 3.1 and 2.5 mmol/L decreased by 15%, 40% and 49%, respectively (all p < .001). Time above 10.0 mmol/L decreased from 10.4 to 5.7 h/day (44%, p < .001) while time in range increased from 12.0 to 16.8 h/day (40%, p < .001). These patterns were consistent across different countries.

Conclusions: In real-world conditions, flash glucose monitoring allows frequent glucose checks with higher rates of scanning linked to improved glycaemic markers, including increased time in range and reduced time in hyper and hypoglycaemia.

© 2017 Abbott Diabetes Care. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). Copyright @ 2017 Abbott Diabetes Care. Published by Elsevier Ireland Ltd





Innovations and a vision of the future



Science fiction becoming science fact

Portable analytical instruments for detection of drugs and explosives – **Have you been tested?**



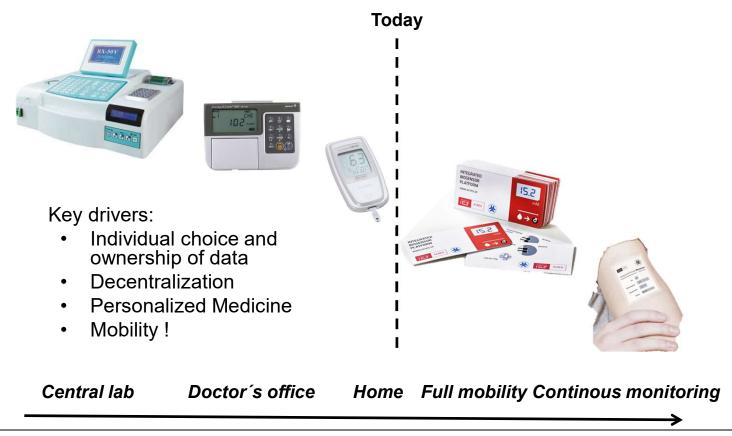








From lab based analysis to remote continuous monitoring





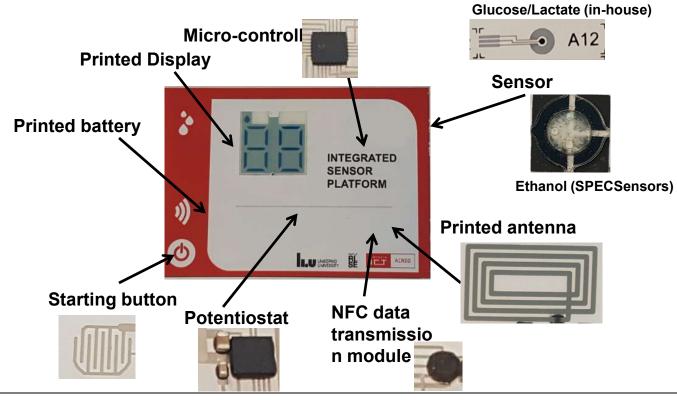


RI. SE





The miniaturised integrated platform

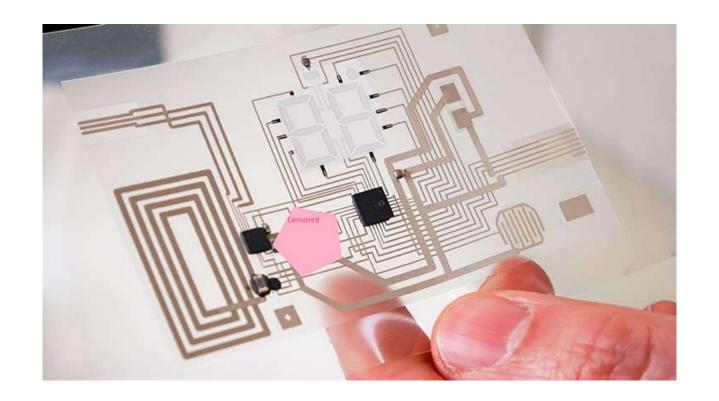




















Targets for detection, our know-how portfolio

Parameter	Invasive	Where to measure	Important for
Oxygen	yes	Body fluids(blood or Interstitial fluids)	General assessment of hospitalised patient conditions
рН	both	Sweat or body fluids (blood or interstitial fluids)	Patient hydration and maybe wound healing
Na	both	Sweat or body fluids (blood or interstitial fluids)	Patient hydration and other diseases
CI	yes	Body fluids (blood or interstitial fluids)	Patient hydration and other diseases
Lactate	both	Sweat or body fluids (blood or interstitial fluids)	Diabetes or physical activity or poor oxigenation
glucose	yes	Body fluids	Diabetes
Creatinine	yes	Body fluids (blood or interstitial fluids	Renal function
Conductivity**	both	Body fluids (blood or interstitial fluids) or skin (non-invasive)	Evaluation of stress or patient hydration.
Ammonium	yes	Body fluids (blood or interstitial fluids	Renal and liver function
Phenylalanine	yes	blood	Phenylketonuria in newborn
β- hydroxybutyrate	yes	blood	diabetes
Amylase	no	saliva	Stress
Affinity based sensors	yes	Blood, interstitial fluids, saliva	

Acreo have a proprietary technology for microneedle sampling

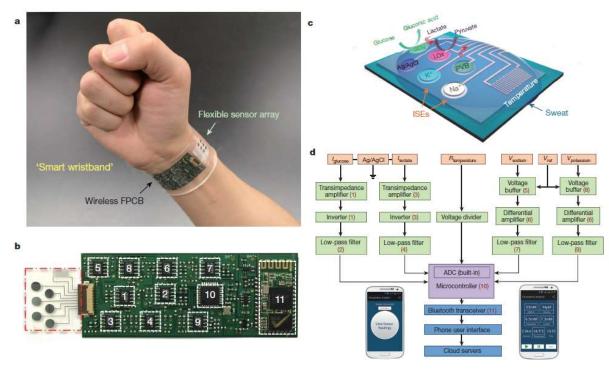
Minimally invasive sampling







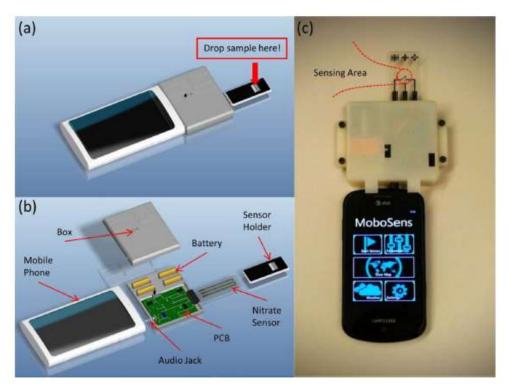
More analytical chemistry laboratories you wear Getting a sweat on.....



Reference: Nature, Volume 529, January 2016. Gao et al, University Of California, Berkeley



The analytical chemistry laboratory in your mobile phone Environmental analysis





Reference: Sensors and Actuators B 209 (2015) 677-685. X. Wang et al, University Of Illinois-

There is big challenge for the technology development

- Specificity
- Validation of measurement
- Cost for end user
- Cost for health service
- Cost/health benefits
- Time to develop
- Ease of use
- Ease of understanding and interpretation
- Very few examples available commercially when you consider the thousands of publications in the area





Al is also transforming healthcare....



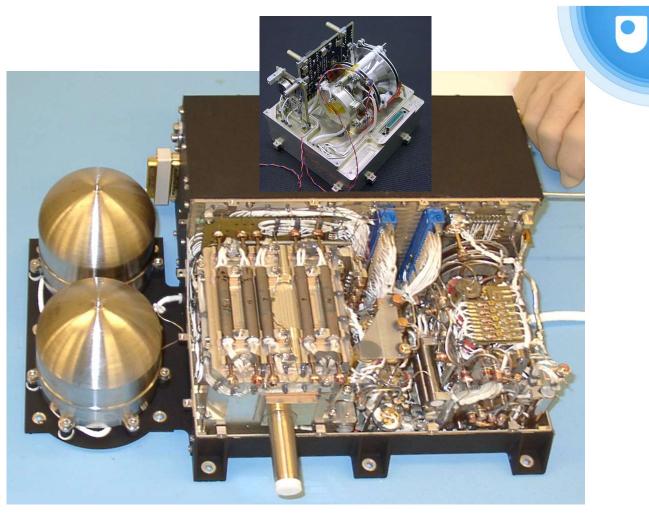
...diagnosis and prediction of disease progression... and now R&D





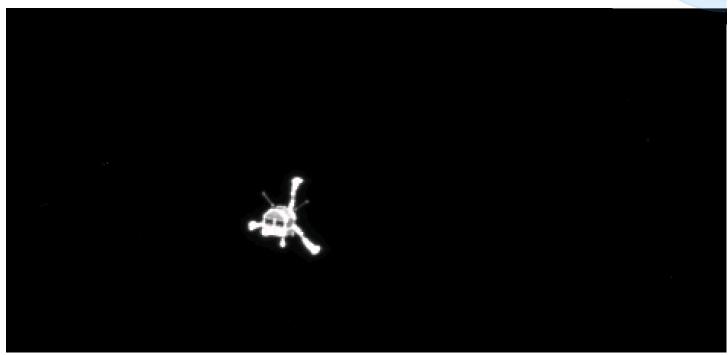
If you can record the mass spectrum of a comet anything is possible......

A bit more fun with analytical science in space

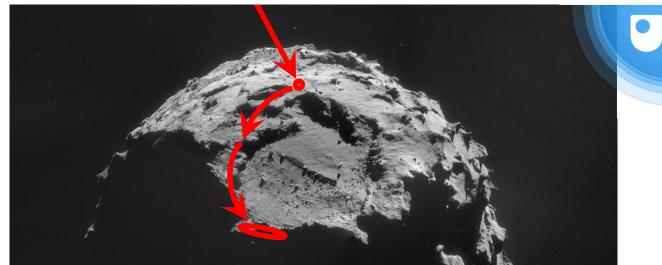


Courtesy of Professor Ian Wright



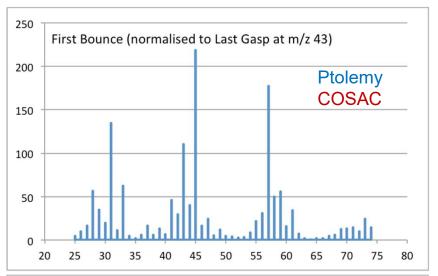


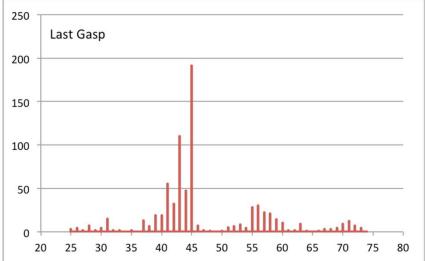
Courtesy of Professor Ian Wright





Date and Time (UTC)	Ptolemy measurement	Results	Comments
12 - Nov 15:43:46	MS sniff (13 minutes)	6 Mass spectra	9 minutes after landing. Water and rich in organics
13 - Nov 06:35:15	MS sniff (10 minutes)	6 Mass spectra	comet day. Mainly water, very low organics
13 - Nov 08:37:18	MS sniff (10 minutes)	6 Mass spectra	comet dusk. Philae in shadow
13 - Nov 10:39:20	MS sniff (10 minutes)	6 Mass spectra	comet night
13 - Nov 12:41:21	MS sniff (10 minutes)	6 Mass spectra	comet night.
14 - Nov 02:54:36	MS sniff (2 minutes)	6 Mass spectra	comet late night
14 - Nov 12:36:52	MS sniff (2 minutes)	6 Mass spectra	comet early night. Mainly water, very low organics
14 – Nov 22:38:19	HTO/CASE (40 minutes)	275 Mass spectra	Attempt to analyse material collected in CASE oven during landing and any concentrated coma.



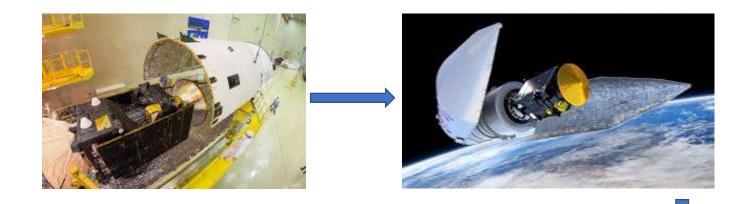




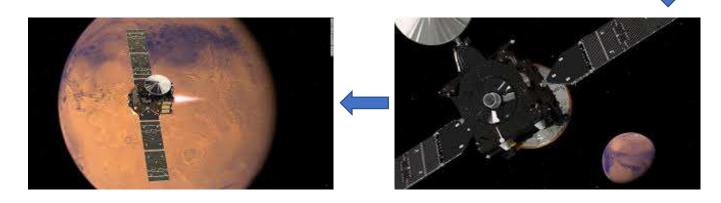




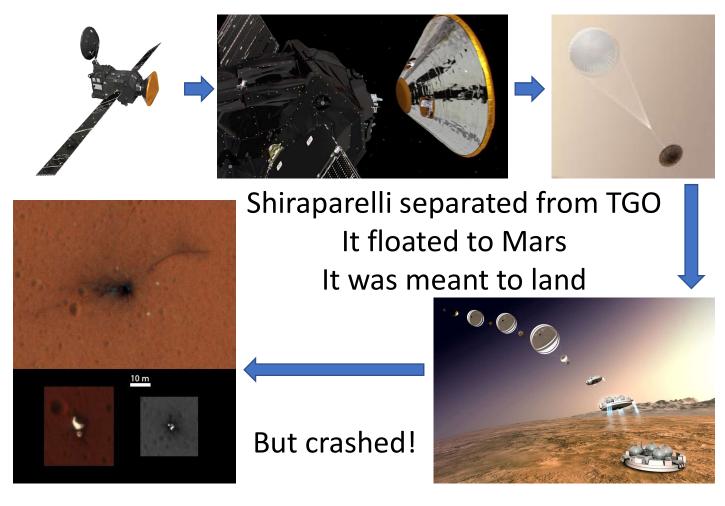




ExomarsHow long did it take to get there? 7 months



What did it do when it arrived?



The home analytical scientist and implications for the future

- Earlier disease diagnosis
- Better disease control and medicine compliance
 - Less interventions and doctor/hospital visits
 - Prediction and understanding of disease exacerbations
- Longer term disease understanding (after a medicine is on the market)
 - Future design of new medicines
- Demonstration of the long term effectiveness of a medicine
- Real world data
- Potential to save money and resources for the NHS and other health care providers around the world
 - effectiveness of a medicine demonstrated
 - pay on performance
- Data transferred to doctor/hospital/pharmaceutical companies
 - Remote intervention and advice



The big BUT.....

- Big Data evaluation and interpretation
- Misuse or misunderstanding of the data
 - may encourages episodic treatment
 - only taking medicine when the device says there is a problem
 - guaranteeing the data is simply presented, easily interpreted and correctly understood



Acknowledgements

- Professor Zoltan Takats Imperial College, UK
- Professor Paul Monks and colleagues University of Leicester, UK
- Professor Guido Verbeck University of North Texas, US
- Professor Perdita Barran University of Manchester, UK
- Juan Muntaner Abbott Diabetes Care, Germany
- Dr Billy Boyle Owlstone Medical Limited, UK
- Professor Ian Wright Open University, UK
- Peter Newham AstraZeneca, UK
- Matt Bonam AstraZeneca, UK
- Dr Diane Turner Anthias Consulting, UK

All images in this presentation are included unambiguously for educational purposes only



Acknowledgements



Paul Monks Michael Wilde Rebecca Cordell Luke Bryant



C. L. Paul Thomas Dahlia Salman Dorota Ruszkiewicz University Hospitals of Leicester



Salman Siddiqui Hitesh Pandya Chris Brightling

Amisha Singapuri Neil J. Greening Caroline Beardsmore Timothy Coats Erol Gaillard Toru Suzuki Leong L. Ng Jane Blower Jacqui Shaw John Le Quesne

Robert C. Free
Bo Zhao
Aarti Parmar
Misty Makinde
Matthew Richardson

Acknowledgements



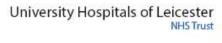




Leicester Biomedical Research Centre





















So finally.....

What are your thoughts on this vision of the future?

Confidentiality Notice

This file is private and may contain confidential and proprietary information. If you have received this file in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this file is not permitted and may be unlawful. AstraZeneca PLC, 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, CB2 0AA, UK, T: +44(0)203 749 5000, www.astrazeneca.com

