# The take-up of near-patient testing (lab-on-a-chip)

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In medicine, the confluence of nanotechnology and microfluidics has resulted in the "lab-on-a-chip" concept, whereby blood and other body fluid analysis to detect diseases may be conducted at home or at the point of care without the need for specialized laboratory equipment. Although the literature is full of research papers in this area, very few devices have successfully reached market. Some are available to specialists in the health services but even fewer available to the general public. Why is this and what is the future? The following is a review of where we are and the problems involved in realizing the dream of near-patient testing.

## 1. Introduction

The impetus to write this paper really started two years ago when my wife caught a respiratory infection and went to see her GP, who prescribed an antibiotic. Within about three days she had recovered but by then I had contracted the same infection. Not wanting a prolonged illness I went to see my own GP, who refused the same antibiotics on the grounds that they were overprescribed and probably wouldn't help. There followed a heated discussion about identifying the difference between viral and bacterial infections and the fact that, sitting in his office, he was quite unable to differentiate between the two. This initiated my reflexions on whether lab-on-a-chip devices could be deployed to address this problem.

## 2. Background

This section gives some background information as to where these devices are, the technologies involved, the problems of clinical approval and, finally, the problems of getting the devices into the market and returning a profit.

There could be real grounds to save money for the NHS (and, presumably, other state healthcare systems) if the problem of misdiagnosis of respiratory diseases is indeed widespread. Typically, laboratory analysis of a blood sample or sputum sample will take two or three days

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and probably cost of the order of £100. A good lab-on-a-chip device capable of yielding a more accurate diagnosis could benefit general practitioners. Other areas where such devices could be beneficial include: home testing, for which there is already a big market, dominated by home pregnancy testing and glucose testing for diabetics; and paramedic response, which is increasingly used for many casualties—lab-on-a-chip devices could extend their ability to diagnose more accurately.

At present healthcare costs the UK government nearly £142,000 million per annum or 18% of taxation and other income that the government raises.[1] Analysis of how much money is spent annually just on respiratory disease prescription reveals that it is about £142 million,[2] and the most common antibiotic, amoxicillin, costs about £18 million. In 2013, a study by Cardiff University found that antibiotic treatment failures had risen from just below 14% in 1991 to just over 15% in 2012.[3] In other words the saving of antibiotics through correct diagnosis is miniscule compared with the healthcare budget—not really a big market opportunity for the NHS. However, no doubt the patients would be happier and perhaps there are other as yet unquantifiable costs due to the impact on the symbiotic bacteria that live on our bodies, which are being destroyed by overprescription and may make us more susceptible to other infections.[4]

What is the lab-on-a-chip concept? It essentially comes from the technology of substrate structuring taken from the electronics industry and applied to making microfluidic channels on and in a chip, which is then inserted into some sort of relatively small controlling device, which then connects to a (laptop) computer for analysis and displaying results. Obviously such a device is portable and the only costs to the user are the control device and the chip as all GPs will have at least a laptop (Figure 1).

As yet there are very few sophisticated lab-on-a-chip devices on the market. However, there are numerous devices using nanotechnology for home testing. Typically they will use an antigen–antibody reaction, which is detectable either electrically or by some change in reflectance or absorptance upon laser illumination. Box 1 reveals a number of devices currently on the market, ranging in cost from £10 to £50 and requiring very little in terms of training to analyse results. Off-the-shelf commercial kits contain the necessary consumables enabling a number of tests to be carried out.

Who are the end users of these devices? The impression is that they are primarily targeted at general practitioners, but my own experience with my GP has been that he perceives he has received sufficient training for the identification of symptoms and that any further assistance might be useful but not beneficial if it takes his time. For instance, sending a blood or sputum sample to a laboratory is easy since most of the work will be done by a nurse. There is certainly a belief that individuals will be increasingly interested in their own health in a more "scientific"

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[1] *Public Spending Details for 2017*—HM Treasury Public Expenditure Statistical Analyses (PESA) [http://www.ukpublicspending.co.uk/numbers?units=p]

[2] *Prescription Cost Analysis England 2015*. Health and Social Care Information Centre (HSCIC) (2016) [http://content.digital.nhs.uk/catalogue/PUB20200/pres-cost-anal-eng-2015-rep.pdf]

[3] C. Currie et al., Antibiotic treatment failure in four common infections in UK primary care 1991–2012: longitudinal analysis. *BMJ* **349** (2014) g5493.

[4] Internal conflict: How we can make friends with harmful bacteria, [https://www.newscientist.com/article/mg23431200-400-internal-conflict-how-we-can-make-friends-with-harmful-bacteria/] over use of antibiotics may be destroying the symbiotic bacteria that live in and on humans.

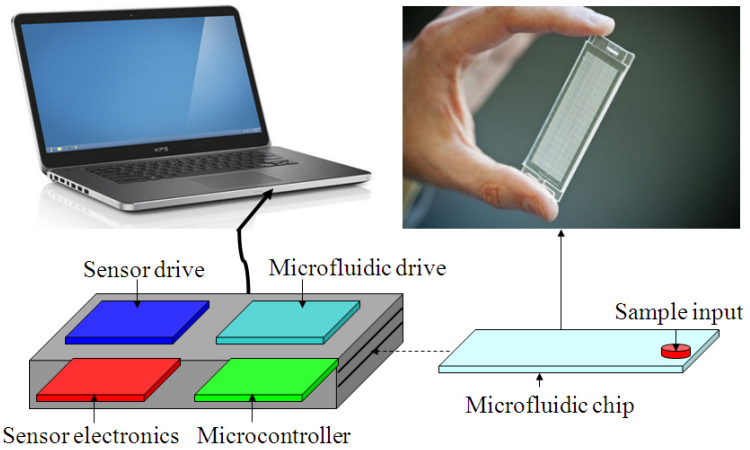


Figure 1. Lab-on-a-chip. The core device (lower left) will typically have the footprint of an iPhone, but be twice as thick. Into it is inserted the sample-bearing chip (upper and lower right). After analysis, data are output to an external processor (upper left) and the chip is ejected and discarded. Although the device contains its own microprocessor, this is used primarily to control the microfluidic and sensing functions, but more sophisticated data processing could be carried out on-chip. This begs the question of what is the precise definition of "chip". It would be technically feasible to integrate everything onto a monolithic chip and apply the sample (e.g., a blood droplet) directly to it, but since anything in contact with the sample must be discarded after use, this is presently seen as too costly.

Box 1. Market examples

| | |
|---|---|
| Cholesterol | BIOSAFE Cholesterol Panel (BIOSAFE Medical Technologies Inc) |
| | CardioChek HDL Cholesterol Test Strips (Polymer Technology Systems Inc) |
| | CARE Cholesterol (CARE Products Inc) |
| | CholesTrak (AccuTech LLC) |
| | EarlyDETECT Cholesterol Test (EarlyDETECT) |
| | First Check Home Cholesterol Test (First Check Diagnostics LLC) |
| | Home Access Full Cholesterol Panel (Home Access Health Corp) |
| Colorectal | EarlyDETECT Colorectal Home Screening Test Kit (EarlyDETECT) |
| | EZ DETECT (Biomerica Inc) |
| Diabetes | BIOSAFE Hemoglobin A1C Test (BIOSAFE Medical Technologies Inc) |
| | EarlyDETECT Glucose Home Screening Test Kit (EarlyDETECT) |
| Drug Abuse | First Check Home 12 Drug Test (First Check Diagnostics LLC) |
| Hepatitis C | Home Access Hepatitis C Test (Home Access Health Corp) |
| HIV | Home Access Express HIV-1 Test (Home Access Health Corp) |
| | Home Access HIV-1 Standard Test (Home Access Health Corp) |
| Menopause | Early DETECT Menopause Home Test Kit (EarlyDETECT) |
| Ovulation | Clearblue Easy Digital Ovulation Test (Inverness Medical Innovation Inc) |
| | First Response Daily Ovulation Test (Church & Dwight Co Inc) |
| Pregnancy | Clear Blue Easy Pregnancy Test (Inverness Medical Innovation Inc) e.p.t. (Pfizer) |
| | Fact Plus (Inverness Medical Innovation Inc) |
| | First Response Early Result Pregnancy Test (Church & Dwight Co Inc) |
| Prostate-Specific Antigen (PSA) | BIOSAFE PSA Screen (BIOSAFE Medical Technologies Inc) |
| Thyroid | BIOSAFE Thyroid Stimulating Hormone (BIOSAFE Medical Technologies Inc) |
| Urinary Tract Infection | AZO Test Strips (Amerifit Brands Inc) |
| | EarlyDETECT Urinary Tract Infection Home Test Kit (EarlyDETECT) |
| | Women's Wellbeing UTI (Consumer Choice Systems) |
| Yeast Infection | Vagisil Screening Kit (Combe Inc) |

way (i.e., measuring some parameters supposedly indicative of health) and simple pulse and oxygen level monitors are indeed finding their way into wristwatches and other wearable systems. For diabetics, glucose level detectors are essential; research laboratories will use lab-on-a-chip devices as they bypass the need for external laboratories and they require no clinical approval; but perhaps the most obvious market is health workers dealing with pandemics: the various 'flu and now Ebola and Zika viruses need fast and accurate diagnosis. This last-mentioned is at present where many lab-on-a-chip devices are aimed.

## 3. Technologies

The enabling technologies that make lab-on-a-chip devices possible fall into two categories: microfluidics and nanosensors. Let us first consider the microfluidic chip. Channels are cut in the substrate using semiconductor chip fabrication techniques that vary from hundreds of nanometres to hundreds of micrometres in the size of the features that can be created. The fluids in the channels are characterized by a low Reynolds number, which keeps flow laminar and requires only weak forces to move the fluid, typically by either pressure or electrokinetics. A typical arrangement might be a receptacle for receiving a sample of a few microlitres—a small drop, about one millimetre across, which may then be subdivided into several channels for the addition of a variety of chemicals and then feeding into a reaction chamber with a detection system. Typical blood cell size is 6–8 μm, and there are about a million such cells in a blood sample of that size.

Looking at disease diagnosis, typical targets for detection are either bacteria or viruses (Figures 2–4). The pneumonia bacterium is quite small, about 500 nm across, while the cold rhinovirus is even smaller, only 30 nm, and the 'flu virus capsid is slightly larger at 100 nm and characterized by the two antigens haemagglutinin (H) and neuraminidase (N). Unfortunately haemagglutinin is used as a blood agglomerator, hence the epithelial cells to which the virus attaches in the respiratory system are quite used to seeing these antigens, which are able to attach to the cells' receptors. Detection of these antigens using their reaction with antibodies is quite feasible but the problem with the 'flu virus is that the antigens change (an antigenic shift[5]) so that the blood antibodies fail to recognize the slight variation after a change in molecular structure of the protein. Consequently it is difficult to recognize individual strains of 'flu just from the antigens; for instance H3 N2 was characteristic of the Asian 'flu virus of 1968 while H1 N1 was the prevalent strain of the 2009 pandemic.

Typical analysis techniques rely on the antigen–antibody reaction, which can be detected by attaching a fluorescent molecule to the antibody and using an enzyme-linked immunosorbent assay (ELISA), or by using surface plasmon resonance after attaching a gold nanoparticle to the antibody, or by refractive index changes using optical waveguide lightmode spectroscopy (OWLS), or by a change in electrical resistance, for example of a carbon nanotube on which the antibodies adsorb. Figure 5 shows detection using a waveguide grating sensor with antibodies coating the diffraction grating and the sample placed on top. The resonant peak shifts as the reaction occurs.

[5] Antigenic shift results from recombination of the genomes of two different strains to form a new subtype having a mixture of the surface antigens.

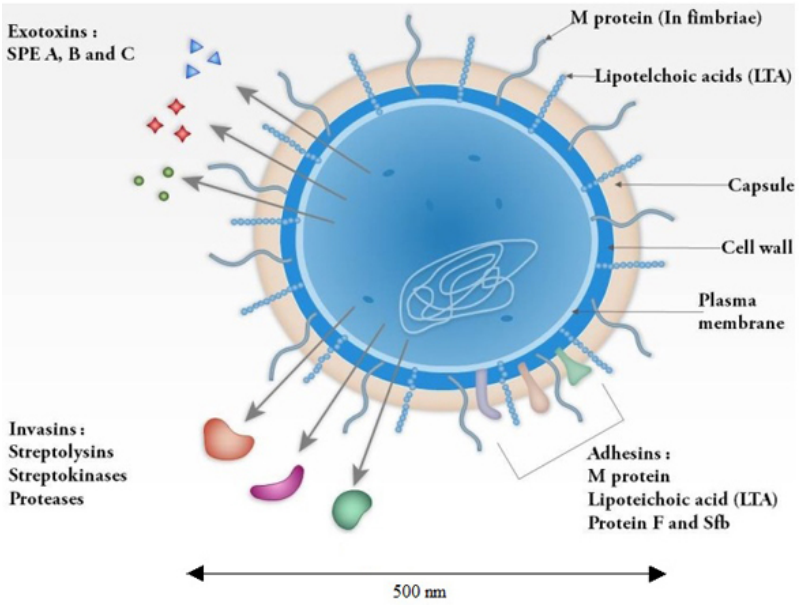


Figure 2. The pneumonia bacterium, (*Streptococcus pneumoniae*).

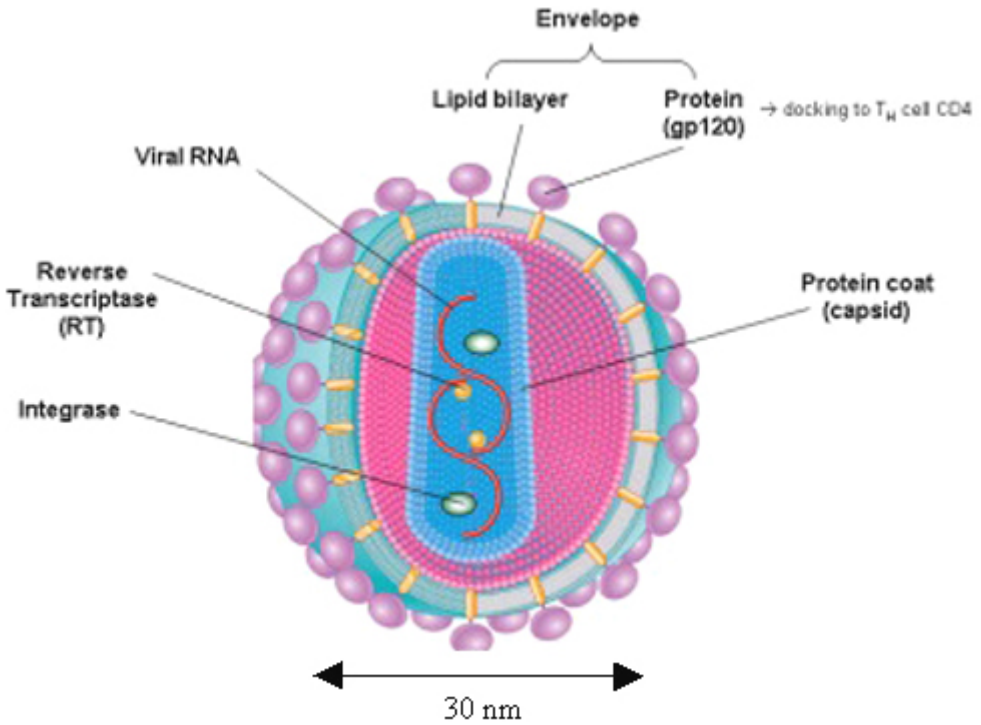


Figure 3. A cold virus (rhinovirus).

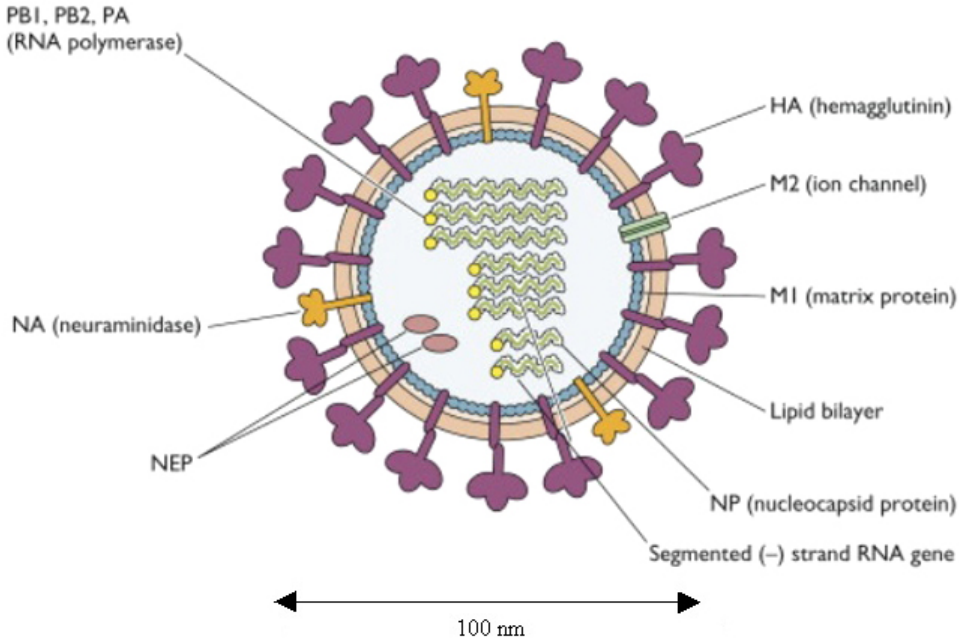


Figure 4. A 'flu virus (orthomyxovirus).

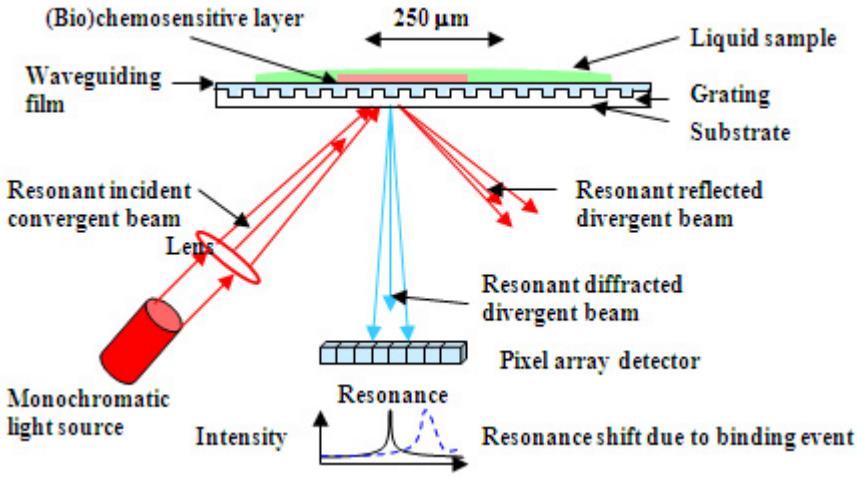


Figure 5. Waveguide grating biosensor.

More recently researchers have concentrated on identifying the virus by decoding the RNA. This involves a complex microchip: in a prior, off-chip step the sample is broken down, typically using benzyl chloride to destroy the cell wall and expose the RNA after centrifuging. The RNA solution is applied to the chip and PCR is then conducted with consecutive heating and cooling cycles taking about 15 min, and then the base pairs are identified using electrophoresis (Figure 6). The chip contains various chemicals and once used has to be treated as medical waste, hence it becomes a disposable item.

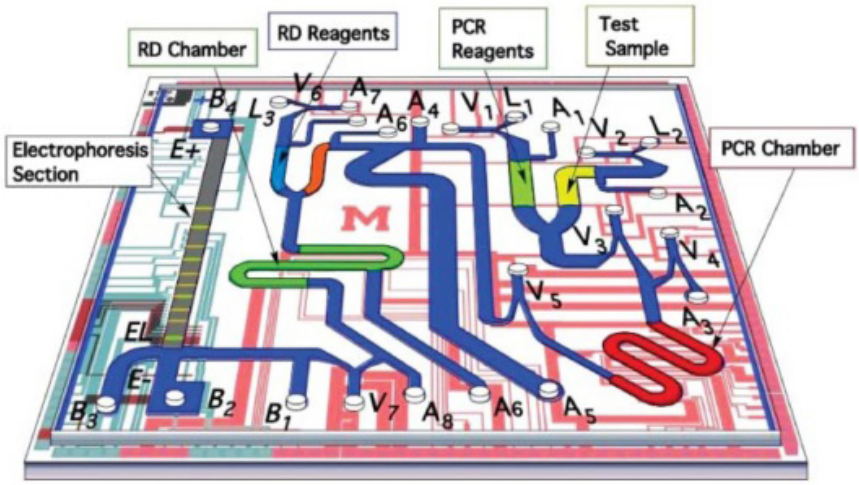


Figure 6. The polymerase chain reaction (PCR) and electrophoresis.

Perhaps most promising for DNA analysis is the nanopore sensor based on ion channels (Figure 7). By forcing the DNA (or RNA) through a nanopore with an applied voltage, the base pairs can be identified according to a characteristic change in electrical current through the pore. Typically the nanopore will be 2–3 nm in diameter—about the same as that of the DNA. An early problem was controlling this diameter to prevent the DNA passing too fast through the pore so that individual base pairs could not be identified.[6] It is interesting to note the typical human gene has about 100,000 base pairs, hence a full gene analysis would take tens of minutes. Fortunately, viral RNA is simpler and repeat patterns are identifiable. Reliability is achieved by using hundreds of pores in parallel and statistical analysis of the mass of data produced.

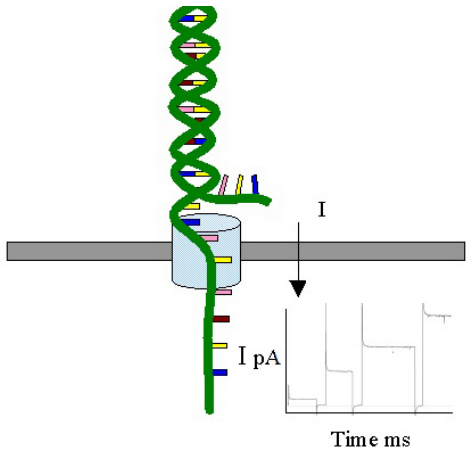


Figure 7. Nanopore sensor.

[6] P. Krishnakumar et al., Slowing DNA translocation through a nanopore using a functionalized electrode. *ACS Nano* **7** (2013) 10319–10326.

A further development is tunneling nanopore detection, in which the tunneling current across the pore changes with the individual bases (Figure 8). It is hoped that this technique may be able to identify each base in microseconds.[7]

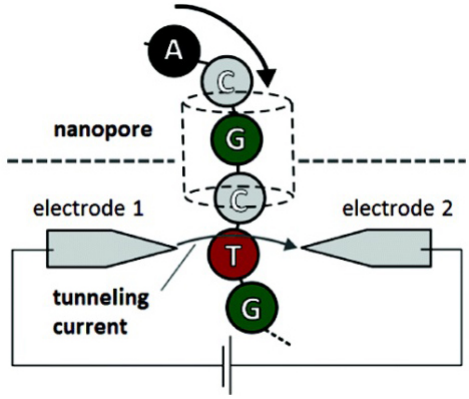


Figure 8. Tunneling nanopore detection.

## 4. Clinical approval

Having designed a suitable device, the next problem is clinical approval. For some medicines, this can take ten years of rigorous testing. However, there are waivers for single-use detection devices. In the USA, the Food and Drug Administration (FDA) has approved many diagnostic aids under the Clinical Laboratory Improvement Amendment.[8] This states that self-contained and fully automated test devices must use an unprocessed specimen and have no user intervention. There must be no specialized training and results must be easily interpretable while finally, and perhaps most difficult, results must be reliable (Box 2).

In the UK guidance is provided by the *In Vitro Diagnostic Medical Devices Directive*, which lists risks according to function, with higher risk requiring more testing.[9] The lowest risk is considered to apply to self-testing devices; intermediate risk to those using reagents, which would cover PCR devices; and the highest risk to those with the most dangerous infectious diseases as targets (Box 3).

## 5. Problems with the market

The final problem with these devices concerns the economics. Development costs are typically high for moving from the proof-of-principle stage that emerges from research: for ensuring that the analytical function fulfills all requirements for reproducibility and reliability; and for

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[7] A.P. Ivanov et al., DNA tunneling detector embedded in a nanopore. *Nano Lett.* **11** (2011) 279–285.

[8] *Recommendations: Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices* (OMB control number: 0910-0598). US FDA (2008) [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079632.htm]

[9] *Guidance on the In Vitro Diagnostic Medical Devices Directive 98/79/EC*. MHRA (August 2013) [http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007521.pdf]

Box 2. Waivers

- The Food and Drug Administration (FDA) has approved or waived approval for many devices capable of diagnosis of the diseases.
- The waiver or Clinical Laboratory Improvement Amendments (CLIA) requires the following of any approved device: Recommendations: Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices, OMB control number: 0910-0598.
- Self-contained and fully-automated test, and use of unprocessed specimens. In case of blood markers, this requirement bars the user from centrifuging blood to produce serum or plasma. Hence, the test must either use whole blood as sample or include an automated blood separation step without user intervention.
- No specialized training. Any user shall be able to operate the test without technical training, based on reading instructions written in English.
- Easily interpreted results. The readout should be directly usable for a clinical decision, without the need for additional calculation or calibration.

Box 3. UK and EU situation

Guidance on the In Vitro Diagnostic (IVD) Medical Devices Directive 98/79/EC (August 2013)

Device categories are, in order of increasing perceived risk: general IVDs, i.e. all IVDs other than those covered by Annex II and IVDs for self-testing such as blood gas analysers, therapeutic monitoring reagents and tissue processors;

- IVDs for self-testing (a device intended by the manufacturer to be able to be used by lay persons in a home environment) excluding self-test devices covered in Annex II;
- IVDs in Annex II, List B of the Directive: which, amongst others, includes reagent products for rubella, toxoplasmosis and phenylketonuria as well as devices for self-testing for blood sugar;
- IVDs in Annex II, List A of the Directive: which includes reagents and products for HIV I and II, Hepatitis B, C and D, and reagent products for determining ABO systems and anti-kell including those used to test donated blood plus tests for screening vCJD.

perfecting the display software; while the final microchip device must be disposable and therefore very low cost. An example of the dilemma that this engenders for business drivers is a large cigarette packet-sized blood analyser into which the microfluidic chip is placed (cf. Figure 1); it is WiFi- connected to a host computer. This device is reliable but expensive; about £500 for the main device, and tens of pounds for each disposable microfluidic chip.

PCR-based devices will soon be on the market with a disposable microfluidic chip and a cartridge containing the polymerases and reagents. It is hoped to sell the nanopore device for less than $1000 but at present it requires what will be expensive separate preparation of the sample to extract the DNA.[10]

[10] Finally there is the problem of reliability: false positives and false negatives. The US Centers for Disease Control and Prevention suggest that for 'flu diagnosis both false positives and false negatives will occur depending on the prevalence of 'flu in the community.[11] In all cases, if diagnosis is critical then full DNA analysis is recommended.

[11] *Rapid Diagnostic Testing for Influenza: Information for Clinical Laboratory Directors*. Centers for Disease Control and Prevention (2014) [http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm]

## 6. The future

It is difficult to know how much credence to attach to commercial predictions but the market is expected to almost treble by 2020 to nearly $18,000 million for microfluidic chips.[12]

The M chip designed for PCR analysis by Harvard University has been bought by Claros, now OPKO, who five years ago predicted a device cost of $500 and a chip for less than one dollar. This device is still not on the market.

So who will really use these chips?

Will the technology save the NHS? Probably not, only a radical culture change could do that.

Perhaps the real future is in pandemic response.

Certainly respiratory tract diagnosis would benefit from a cheap lab-on-a-chip device in a general practitioner's surgery and may help in reducing the overuse of antibiotics with all its attendant deleterious side-effects such as bacterial resistance.

Both the Ebola and Zika viruses focused attention on the problems of pandemic prevention by screening at airports, which could become a significant market.

In general, however, the market is uncertain. Early 'flu virus detection would be beneficial and could save health authorities money if those affected could be isolated. Returning to my GP, he has the attitude that he is pretty good at diagnosis and spending time to use a lab-on-a-chip device in a busy surgery is not cost-effective, he believes.

Wearables constitute a growing market as has been perceived by the electronics industry, but these are relatively simple devices monitoring skin temperature and heart rate. A tricorder from Star Trek is the Holy Grail and although hand-held terahertz scanners are a possibility, a portable MRI scanner is currently technically not feasible.

The cynical observer might look to the pharmaceutical industry to subsidize devices, in return for which they would be engineered so that the results they produce recommended or a least advertised remedies manufactured by the subsidizer! In fact, the commercial interests of "big pharma" are often self-contradictory. For example, Roche aims to find a drug that will eliminate diabetes, but after its takeover of Boehringer Mannheim it also possessed a flourishing business supplying devices to monitor blood glucose levels of diabetics.

Inevitably self-health monitoring devices will become a fact of life for those for whom it is either essential or because they are sufficiently interested, but will it make society healthier or merely encourage hypochondriacs?

[12] *Biochips Market by Type (DNA Chip (Genomics, Drug Discovery, Gene Expression), Lab-on-a-Chip (IVD & POC, Proteomics), Protein Chips), End User (Academic Institutes, Diagnostics Centres), Fabrication Technology (Microarrays, Microfluidics)*—Forecast to 2020. MarketsandMarkets (2016) [http://www.marketsandmarkets.com/Market-Reports/biochips-advanced-technologies-and-global-market-54.html]