

D2.3: User Challenge 3

Taking technology for identification and characterisation of infectious diseases to individuals by designing smart swabs, hand-held or portable devices that analyse fluids

Grand Challenge: The development of a robust, cost-effective, mobile, individual/near target device that can rapidly either directly, or through interface with a system, identify and characterise appropriate infectious diseases

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1 Introduction

The devices described by UC3 fall into two major categories - which have very different socio-economic and ethical implications.

- 1 UC3 alone – e.g. a simple dip-stick test or lateral flow device, such as those used in pregnancy testing kits (UC3A)
- 2 A device where the output is integrated into the global network and informatics systems described by UC1 (UC3B)

There is a third category where linking the test result into a network becomes optional. An example of this would be running a lateral flow test, or similar, and photographing the result etc. Whilst there is the potential for misuse (e.g. an operator could photograph a different test result) this kind of device would help with record keeping and analysing trends etc. The basic UC3A device (when utilised by non-professionals) needs careful positioning in order to minimise the impact of loss of data – for example, the ability of the Health Protection Agency and similar bodies to provide national surveillance data. This potential ‘vulnerability’ is fully addressed by the development of UC3B devices, where results will automatically be recorded and analysed.

The Foresight programme has not aimed to define all the technical features and product specifications of the UC3 diagnostic devices, but to consider a series of emerging capabilities. This being said, it is accepted that any developer will need to consider sample type and preparation, TTF (time to first result), device throughput, the need for auxiliary equipment (including fridges for reagent storage) and bio-safety, including waste disposal of bio-hazardous materials.

Clearly the environment in which a device is to be deployed has a major impact on product specification and design, and poses unique challenges in developing countries, where there may be no clean water or electricity. Careful consideration must be given to providing high-quality tests linked to quality control and quality assurance systems. As far as possible the use of UC3 devices should be integrated into professional systems of healthcare and animal welfare etc.

The test characteristics (i.e. disease specificity and sensitivity, and analytical sensitivity) will impact on false positives and negatives – ideally minimum product specifications should be agreed between different users before developing and positioning the devices. It is clear that the minimum specifications will vary from one disease to another, but they may also vary between countries and will depend on whether the test is being carried out by a professional or non-professional.

An ideal device/system would offer inexpensive, minimally invasive, rapid and robust tests near the point of decision or action. The rapid development and transfer of new and improved assays to the device, in response to new

pathogens or more virulent drug-resistant strains of known organisms, would be highly desirable.

The ability of the devices to measure multiple classes of pathogens and molecules simultaneously should be considered throughout the text (microarrays are reviewed in S6) – this may be of particular significance in Africa where the journey to a health post may take several days and a general rapid screen would be attractive.

It is recognised that the detection, identification and monitoring (DIM) of infectious diseases can be achieved by detecting the presence of a pathogen and/or by evaluating a host's response to an infective agent - both of which can be considered at the nucleic acid and protein level. The technologies should consider utilising biological fluids and volatiles from plants, animals and humans alongside dust particles and vectors that may carry infective agents.

The impact of a diagnostic test on the management of an infectious disease is influenced not only by the test's characteristics but also by the economic and social environment, and general infrastructure in which the test is deployed. The future control of infectious diseases (D3) along with issues related to culture and governance (D4) and public perception of risk (D7) should be considered in any product design and specification.

Ultimately UC3 devices could take us into the realms of appealing, yet very real, technologies such as smart hiking boots, capable of detecting disease in soil etc., and smart toothbrushes able to respond to the presence of pathogens and the signatures of disease in saliva.

2 Key future capabilities for User Challenge systems

It is the focus of this section to comment on how existing technologies may evolve, and the impact that developments are likely to have on realising the UC3 capabilities. A considerable number of point of care (POC) devices are in routine use today. They range from bench-top and hand-held-meters to simple non-instrument based dipsticks and lateral flow systems. For reference, a selection of today's state-of-the art devices is described in Appendix 1.

Any diagnostic device/system is limited, in part, by the biomarkers it employs to detect disease. There are many areas where fundamental research into new or improved biomarkers is required. The list is particularly extensive for animals, as classically these diseases are diagnosed by clinical symptoms without the aid of *in vitro* diagnostic tests. In animals, the development of new biomarkers to aid in DIM of the following would make a significant difference to animal welfare and the spread of disease:

- The ability to distinguish between vaccinated and infected animals
- The identification of drug-resistant pathogens

- Bovine Spongiform Encephalopathy (BSE)
- Identification of the persistently infected carrier animal, as with Foot-and-Mouth Disease (FMD)
- The diagnosis of mycobacterial infections in animals

In order to prepare ourselves more adequately against future zoonotic threats, biomarkers of wildlife diseases should be identified – of particular importance will be the determination of pathogens in non-clinical reservoir species (e.g. the avian influenza virus in birds and West Nile virus in mosquitoes).

The identification of drug-resistant pathogens is a cross-cutting issue and is arguably of even more significance in human diseases than in animals. Drug resistant TB and HIV are serious threats. As with animal diseases, identification of the persistently infected carrier is critical: in sub-Saharan Africa the diagnosis of malaria in adults and children over five presents problems. Many older children and adults are carriers so that the patient presenting with parasitosis and fever is not a straightforward diagnosis.

In line with other discovery programmes, the true bottleneck is likely to be the validation rather than identification of candidate biomarkers. Advances in proteomics coupled with informatics have fundamentally changed the paradigm of discovery of novel biomarkers. Multiple approaches to marker discovery at the genomic and post-genomic levels are becoming standard. Research in a variety of clinical and scientific disciplines will move towards a better understanding of the disease process (in plants, animals and humans) from which new markers will emerge. A comprehensive programme to identify biomarkers capable of detecting pre-symptomatic disease would have clear benefits. It may not be practical, cost-effective or even desirable to screen all animals, for example, however, one could imagine screening populations at risk.

One way of achieving this goal (i.e. detecting pre-symptomatic disease) is to study the immune signatures of the disease process (S12). Infection of an animal host with a pathogen results in rapid changes in gene expression and protein synthesis by cells of the host's immune response. It is accepted that considerably more fundamental research is required in order to fully elucidate and interpret disease signatures, and to distinguish between a host's response to infection and other conditions or diseases. For example, inflammatory cytokines are raised in auto-immune disease, cancer and cardiovascular disease, as well as in response to infectious agents. Differentiating between background fluctuation, individual variability and meaningful changes will pose complex challenges – this may be especially difficult in subjects with other disorders; the baseline immune signature of a patient with systemic lupus erythematosus, for example, is likely to be significantly different from a normal healthy profile. Research should address at what point an individual or animal has succumbed to an infection rather than simply encountered it. Within the time frame set by the Foresight programme (i.e. up to 30 years) it is unlikely that we will see the measurement of immune signatures on hand-held devices (personal communication from Dr

Anne O'Garra); however, the research is a powerful tool for UC2 and will ultimately inform UC3.

The detection of VOCs (volatile organic compounds) is described in UC4 and reviewed in S2 and could also aid in the detection of pre-symptomatic disease – research in this area is most advanced in plants.

In addition to detecting pre-symptomatic infections it may also be possible to ascertain an individual's/animal's/populations' susceptibility to disease and aid in the selection of the most appropriate therapy (theranostics). As technologies advance, UC3 devices will have the ability to sequence the host genome and identify single nucleotide polymorphisms (SNPs); further fundamental research is required to map SNPs to susceptibility etc.

Sample type and sample preparation are important parameters to consider in the design of UC3 devices. It is clear that individuals will favour minimally invasive (ideally non-invasive) sample collection procedures. Dr David Brown, from the Health Protection Agency, reports on the salivary diagnosis of infectious diseases. It has been known for several decades that IgG and IgM antibodies are found in oral fluid and reflect those found in plasma – although at a much lower concentration. Research assays for the diagnosis of a wide variety of viral diseases, by measuring antibodies to viral antigens in saliva, have been reported. Tests for measles, mumps, rubella and HIV have been commercialised.

Sample preparation, where necessary, needs to be rapid, efficient and robust, and integrated into the device. Advances in genomics and bioinformatics (S6), coupled with improvements in the technologies used to measure and sequence nucleic acids (including sample preparation) will play a significant role in the design of a UC3 device. For nucleic acid tests, significant improvements in sample processing will need to be achieved; today's routine technologies tend to use modular systems where the processing is carried out before placing the samples on sequencing or microarray instruments.

A key message from this part of the Foresight programme is the need to develop robust portable molecular diagnostic devices capable of functioning in extreme conditions (e.g. in the absence of clean water and electricity). This is a difficult and complex challenge as both sequencing and microarray technologies are highly sensitive to fluctuations in temperature. A number of isothermal amplification technologies have been developed including loop-mediated isothermal amplification (*Notami et al., 2000*), helicase-dependant amplification (*Vincent et al., 2004*) and rolling-circle (*Detter et al., 2002*). Developments from these technologies may allow the rapid and specific DNA isothermal amplification required for the development of small-scale integrated devices. Alternatively, microfluidic systems incorporating a series of exothermic and endothermic reactions may provide a solution to providing an amplification technology in a challenging environment.



Fig. 1

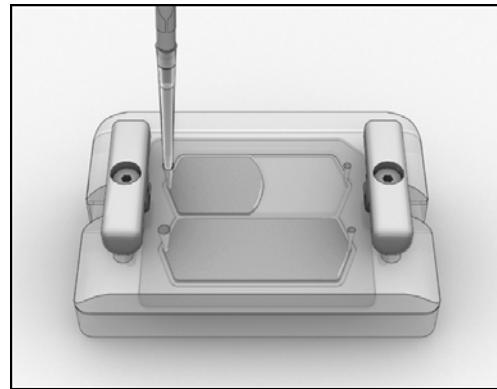


Fig. 2

Current state of the art technology for both sequencing and microarray is bench-top and exemplified by the ABI 454 sequencing instrument (Fig. 1). Liquid handling and signal detection components tend to dictate the size. The 454 sequencing chip is ~ 7cm square and ~ 6mm thick (Fig. 2) and could be made considerably smaller for fewer samples – i.e. is not a limiting step in the development of a hand-held device. The current commercial focus of companies such as ABI and Solexa is reported to be improving the technology, promoting high throughput instruments, and achieving the US \$1000 human genome sequence.

Early stage companies, however, are developing unique platforms and technologies that may be of direct relevance to the development of POC devices. Indeed some of these companies, which are mainly in the United States, already market POC devices for infectious diseases (see Appendix 1).

No discussion on emerging technologies for hand-held devices would be complete without reference to advances in biosensor technologies (S7). As technology progresses it is envisaged that sensors will become the heart of a device rather than a separate element. As with other areas of diagnostics, users will look for solutions and systems that are less expensive, whilst being faster, more sensitive, efficient and robust. Sensors will be smaller and more compatible with microfluidic systems; allowing integration with sampling technologies etc. It is anticipated that on-board sample processing and sensor calibration will become standard. Nanotechnology will open new sensing formats and materials for improved performance. In addition nanostructured materials may enable better coupling to bio-recognition components (classically antibodies and nucleic acid probes but new binding agents continue to evolve). Local intelligent processing (*in senso*) of the sensor outputs will reduce the bandwidth for onward transmission of results. In the context of personalised healthcare the combination of minimally invasive sampling, microfluidics, local processing and wireless connectivity has led to the concept of 'digital plasters'.

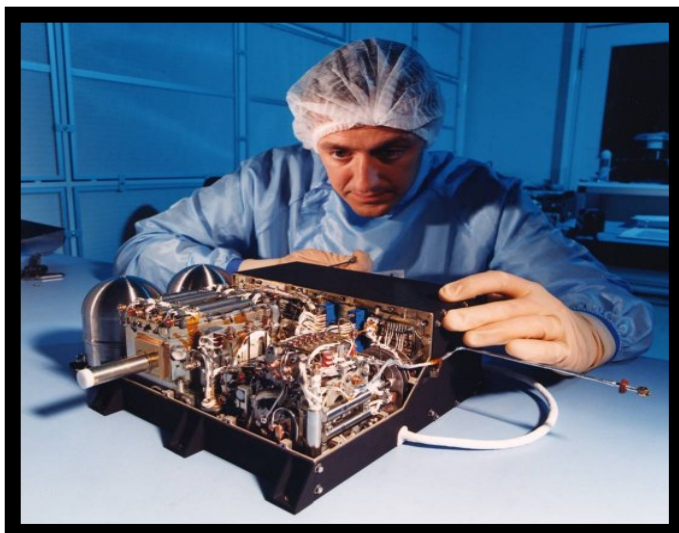


Fig. 3

Mass Spectrometer (MS) systems, especially when coupled to Gas Chromatographs, are at the heart of most 'gold standard' analytical procedures. MS techniques allow the unequivocal identification and quantification of specific analytes in complex mixtures. MS further allows the analysis of samples of unknown composition, where all the components need to be determined.

However, until recently their large size, complexity and cost has prevented their general use, except at specialist laboratories.

Field portability, transportability and miniaturisation are areas of increasing interest, driven mainly by planetary exploration, environmental and homeland

security issues (especially those related to bioterrorism). Figure 3 is an image of the flight model of Ptolemy (kindly supplied by Dr Geraint Morgan who acknowledges The Open University and Rutherford Appleton Laboratory, and the financial support of the PPARC). The instrument has a mass of 4.1 kg and is the size of a shoe-box. Further information regarding Ptolemy and the Rosetta space mission can be found at <http://ptolemy.open.ac.uk>. The Open University, funded by the Wellcome Trust, is currently investigating the translation of this technology to a number of healthcare applications. *In situ* mass spectrometry is rapidly becoming a reality and developments in manufacturing techniques, in particular MEMS, has meant that some hand-held mass analysers, for specific applications, already exist (*Workshop, Lido Beach, 2005*).

An important aspect of the design of all mass spectrometers is their requirement for very low operating pressures ($1E^{-3}$ to $1E^{-6}$ mbar depending on the type and design of analyser). The significant effects of pressure on performance of the analyser (sensitivity and resolution) highlight the importance of the need for suitable miniaturised vacuum pumps for use with miniature analysers. It is the availability of these pumping systems that will drive the availability of any future hand-held MS systems and in turn their cost, power, mass, size and analytical capabilities.

The potential global market for deployable MS devices has recently been recognised by some of the major vacuum pump manufacturers and by technical design companies. A prototype miniature drag pump is currently being evaluated by the Open University and NASA, for use on future Mars missions. The pump has a mass of 130g and is similar in size to a D-type battery. The cost of such an item is currently prohibitive for terrestrial applications; however

market forces would inevitably reduce this cost if the design proved viable and there was sufficient demand.

The detection of biomarkers and microorganisms has been highlighted by many researchers in the field of Microsystems and Nanotechnology (MNT). Publications reporting single molecule or organism detection limits are appearing with increasing frequency. Although eye catching, such demonstrations don't necessarily equate to 'real world' detection limits for two reasons:

- In complex matrices analytical sensitivity is often limited by the non-specific background rather than the detection capability
- MNT allows measurements to be made on very small volumes, nL to pL, and it is therefore misleading to express detection limits in terms of molecules rather than concentration. Thus the ability to detect, say, a single virus particle in 1 nL corresponds to 10^6 viral particles /mL – a much more modest detection limit.

Thus whilst MNT provides the capability of sampling and measuring 1nl; at a required detection limit of 10^3 cfu /mL a false negative result will be obtained the vast majority of the time.

Therefore:

- MNT based sampling is likely to be unsuitable for detection of the low numbers of organisms necessary for DIM applications.
- If MNT based detection systems are to be used, selective amplification or concentration will be necessary.

However, MNT does offer:

- New materials and structures (e.g. quantum dots, nanoparticles, carbon nanotubes and surface enhanced Raman scattering substrates) for detection.
- Systems integration for portable devices.
- New measurement methods (cantilevers, micro- and nanoelectrodes).

There are three areas where MNT could make an impact on the design of UC3 devices by providing:

- Microsystems for conventional detection methods following bulk sampling and concentration/amplification. Examples could include PCR on chip, microfluidic enhanced immunoassays and microarrays for immune signatures.
- Novel reagents for biomarker/organism detection based on new materials and structures, in either conventional or microsystem formats.

- Personalised, wirelessly connected, user ‘transparent’ devices.

As described in the Introduction, the output from UC3 can be integrated into the global networks described by UC1 – the preferred output of the UC3 device for efficient integration into the systems should be considered. In principle any output can be converted into an appropriate format and signal. However, issues such as efficiency, security and potential for misuse should be considered in designing the UC3B device.

Mobile phone companies recognise that a technical system consisting of intelligent sensor networks connected to a mobile phone network could provide a wide range of opportunities of relevance to health and healthcare. It is estimated that significant advances will be made over the next ten to 15 years. Three working areas can be identified:

- Fitness and Lifestyle
- Preventative Healthcare
- Professional Diagnosis and Therapy

Mobile phones able to measure pulse and blood pressure are on the horizon; systems that will be able to detect, identify and monitor infectious diseases form part of a longer-term vision. What is clear is that companies such as Vodafone are moving in this direction.

From the hardware perspective, it is necessary to take into account both the ‘User Plane’ (e.g. the sensors and user interfaces) and ‘Network Plane’ (backhaul and core improvements). From the software perspective the need for new applications may also present themselves – companies will need to work closely with healthcare providers and authorities to provide the best possible solutions.

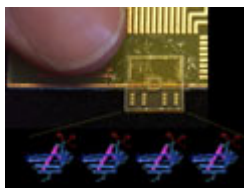


Fig. 4

In 2005, researchers from the University of Cambridge and the Medical Research Council (MRC) were awarded a grant of £1m to develop a device for the rapid and cost-effective detection of human diseases. In a press release (<http://www.admin.cam.ac.uk/news/dp/2005111703>) it is reported that the device will be small and portable, similar to a mobile phone, and will be able to detect cancer, as well as infectious viruses such as avian flu. The device will utilise tiny electronic transistors, ten times smaller than a grain of salt, called Thin Film Transistors (TFTs). Human samples can be placed on a small disposable card containing the TFTs (see Fig 4).

The trend towards the use of mobile-phone-type devices in healthcare is accelerating. At Medica 2005 a Korean company presented a mobile phone

linked into a glucose test. It is entirely feasible that more devices will emerge out of Korea or other developing countries (especially China or Taiwan) where there is a strong emphasis on advances in biotechnology and IT in a less structured regulatory environment etc. Although, in principle, devices placed on the European market will still need to comply with the European Directives, regardless of the country of origin, it may be faster to develop devices in an environment where regulation is less stringent and overheads are less costly. Devices developed outside Europe, even if they have not been adequately validated, will impact on peoples' expectations and drive forward the development of high quality devices. Realistically, it may be very difficult to stop people purchasing devices over the internet or while travelling. For example, although the advertising and sale of HIV testing kits direct to the public has been banned in the UK since 1992 (HIV Testing Kits and Services Regulations 1992 (SI 1992 No 460)), an FDA cleared HIV testing kit is available for sale on the internet which would not be difficult to acquire while travelling.

Finally, it is worth noting that informatics is a potential rate limiting step in the development of more sophisticated forms of UC3 (see review by Logan and Wood in Appendix 2, S3, S4 and S6). It is expected that almost all analyses carried out on scientific instruments, which are presently located in off-line laboratory facilities and used by highly skilled laboratory staff, will eventually be developed into POC techniques. The challenge is to ensure all data systems and knowledge management engines are similarly developed.

The quantity of data that will be produced by network integrated hand-held/portable devices will be vast. Maximising its utility in an efficient and secure manner will be a challenge for the future and needs to be addressed as part of a product concept and design.

3 The role of the systems in managing future risks

The development and positioning of UC3 devices should aim to minimise future threats (T1) and ultimately provide a better quality of life for all individuals. The potential of UC3 devices to make a significant impact on managing future risks is impressive and scores three out of three stars for all disease categories of particular concern, except for the detection of new pathogens or novel variants of existing pathogens (see T1 section 3). Even in this category the devices could be of value simply by identifying that an individual or animal has a bacterial infection, for example, which is not recognised by any of the known disease panels. Similarly a visibly ailing plant that fails to give a positive test may have an as yet unidentified virus etc. As discussed in the synthesis of the User Challenges, it is envisaged that UC3 will eventually be able to identify new pathogens and novel variants but this capability is likely to be realised outside the timeframe being considered here.

The hand-held devices described by UC3 fall into a number of categories, not only in terms of the capability of the technology as described above (i.e. a

simple versus UC1 integrated system) but also in terms of where the devices are to be used and by whom. The fact that Foresight is charged with looking at the potential utility in developing and developed countries, across plants, animals and humans, results in a diverse range of locations for deploying the devices and an equally diverse range of potential users/operators. The locations include: hospitals, clinics, doctors' offices, pharmacies, the home (self-testing), farms, cattle markets, fields, borders, airports and ports, abattoirs, food processing plants, kitchens and supermarkets. The users include: the general public, doctors, nurses and healthcare workers, farmers, veterinary surgeons, inspectors, and immigration and other government officials. Thus UC3 encompasses a diverse family of potential devices, of varying complexity and cost. Some devices may be suitable for self-testing and for use by non-skilled personnel; others will be more suited to use in healthcare centres, intensive care units or cattle markets etc. While the technology itself (e.g. requirement for electricity, size, weight and cost of device etc.) will go some way to defining where a device is deployed, other factors such as the need for counselling and professional intervention will also play a role in positioning the devices (see section on barriers and enablers).

The list of potential users and possible locations for the deployment of hand-held/portable devices begins to scope out the impact that the effective use of these diagnostic tools may have on trade, animal welfare, healthcare and the food industry. Within this document it is not possible to discuss all the potential applications but to give a number of examples where hand-held devices may play a role in the future.

With respect to human health, UC3 devices will help doctors make better-informed medical decisions during patient consultations. The simple ability to distinguish between a bacterial and viral infection in a doctor's office would help General Practitioners when prescribing antibiotics. Taking this a step further the device could be used to identify drug-resistant infections (e.g. MRSA) allowing selection of the most appropriate therapeutic interventions. In these situations the POC device would be operated by a doctor, nurse or other healthcare worker, in a doctor's office, clinic or hospital ward etc. There are a number of advantages here – not least the maintenance of a professional-patient relationship and the opportunity for counselling, which is particularly desirable for HIV and other STIs (see barriers and enablers section).

It is well documented that the early diagnosis of *chlamydia trachomatis* has a significant impact on the management and repercussions of this disease. In its early stages, where treatment is simple, effective, and inexpensive, there are no clinical symptoms in either men or women. If left untreated *C. trachomatis* can lead to pelvic infection, infertility and tubal pregnancies in woman – babies born to women with *C. trachomatis* can develop serious eye infections and pneumonia. Non-diagnosed infection leads to unnecessary patient suffering and costs the NHS in excess of £50 million annually. However, the potential knock-on costs of leaving chlamydia infection untreated include:

- Treating the spread of disease to other individuals.

- Infertility counselling and costs associated with IVF treatment.
- The cost of managing and treating babies born either blind and/or with pneumonia as a consequence having an infected mother.
- Chlamydial infection also increases the risk of HIV, where the costs of management and treatment are significantly greater.

According to studies reviewed by the third USPSTF (U.S. Preventive Services Task Force), such is the problem of chlamydia that the cost of screening women who are not pregnant and who are at risk may be less than the cost of treating chlamydia and its complications at a later stage. The Department of Health, with the support of Boots Group plc (the UK's leading health and beauty retailer) and the Health Protection Agency, has initiated a chlamydia screening programme.

FDA cleared rapid self-test kits for gonorrhoea, hepatitis, HIV-1&2 (in combination), syphilis and chlamydia can already be purchased off the internet from, for example, AT First Diagnostic. The challenge, therefore, falls away from the technology (although improvements could undoubtedly be made) to education, public engagement and an understanding of the infrastructure etc. in which the devices are to be deployed (see barriers and enablers). If populations at risk of chlamydial infection, who would not choose to visit a clinic or seek professional advice, could be encouraged to self-test this would be a forward step. A positive result may encourage an individual to visit a clinic and seek treatment.

A review of paediatric HIV disease under different intervention scenarios has been prepared for Foresight by Professor Marie-Louise Newell (T8.6). Currently, an estimated 2000 new paediatric HIV infections occur each day, nearly all through mother-to-child transmission (MTCT), occurring before, during and after delivery through breast feeding. Close to 90% of paediatric infections occur in sub-Saharan Africa where the prevalence of HIV infection among women of childbearing ages reaches 40% or more in some parts of the southern end of the continent. A number of interventions are available to either prevent the acquisition of infection in young adults, to block mother-child transmission, and to delay disease progression in infected children. Furthermore it is estimated that, in certain African countries, MTCT will increase by up to 50% by 2015 and 100% by 2030. Therefore, the idea of screening pregnant women for HIV infection in sub-Saharan Africa is attractive. Whilst certain interventions, such as elective Caesarean section may not be possible, largely because of limited resources, other interventions can be employed – with varying degrees of success (T8.6). The use of a robust hand-held device for the diagnosis of HIV in pregnant women could be expected to have a significant impact on MTCT and on HIV in the wider community – through increasing general disease awareness, education and testing partners and families. Eventually pregnant women may self-test but in rural African area where there are competing priorities it is envisaged that a healthcare worker, possibly a volunteer, would go out into the local communities – this is likely to be more effective than asking women to visit a

health post or clinic. The device should be robust and simple to operate and capable of being used with no or little formal training.

The most obvious application of UC3 devices in Africa is likely to be in diagnostic and surveillance systems which support coordinated disease control programmes e.g. HIV-TB-malaria or FMD. Not surprisingly, introduction of the devices may not be effective in controlling disease unless there are marked improvements in healthcare and levels of wellbeing more generally. In Africa UC3 devices could also fulfil a useful role in the study of disease transmission between wild animals, domesticated animals and humans. The evolving problem of bovine tuberculosis in Southern Africa is a prime example. The use of UC3 devices to establish specific diagnosis in wild animals at the time of capture and sampling could also be a useful decision support tool in wildlife animal disease management. Furthermore, the UC3 devices could be invaluable in animal and plant quarantine services in Africa.

An annex to the modelling review paper entitled ‘The future risks of FMD in the UK’ (T8.6) is given in Appendix 3. In the main report the authors assume a seven-day infectious period throughout, but in the annex shorter periods of five and six days are considered. The infectious period is defined as the time from the onset of infectiousness to the culling of all animals on the farm. The average basic reproductive ratio (R) across Great Britain is calculated using the modellers’ estimated 2015 figures for farm density and animal numbers. The proportion of farms with average R values >1 along with the proportion of 10 x 10 km areas with average R values > 1 is tabulated below. (If R <1 each primary case doesn’t produce enough cases to replace itself so that the disease dies out).

	Average infectious period (days)		
	7	6	5
Farms with R>1	21%	18%	15%
10 x 10km areas with R>1	15%	12%	9%

The figures stress the importance of early detection and control at the farm level. It is reasonable to expect that the availability of hand-held devices could play a critical role in reducing the average infectious period.

Two emerging infectious diseases of amphibians are rapidly becoming a serious biodiversity concern. Namely, Chytridiomycosis (caused by the fungus *Batrachochytrium dendrobatidis*) and Ranaviral disease (caused by iridoviruses of the genus *Ranavirus*). These diseases appear to be spread by the anthropogenic introduction of non-native organisms to new areas and exemplify trans-boundary animal diseases. With respect to *B. dendrobatidis*,

initial DNA sequence data show little variation in the sequence of the pathogen from continent to continent – indicating a recent spread. The bullfrog, *Rana catesbeiana*, is globally traded as food and may be an efficient carrier host. Similarly, iridoviral diseases that cause heavy mortality in wild and farmed fish are emerging in several parts of the world. These viruses could spread throughout the EU with a potentially devastating impact on aquatic ecosystems and aquaculture. Imports of ornamental fish and amphibians into the EU may be a route for the introduction of some of these viruses, since the regulatory controls for imports from developing countries within this sector are not as stringent as they are for the aquaculture sector. Whilst trade restrictions and regulations may help to prevent the further spread of disease, the ability to detect *B. dendrobatidis* and iridoviruses with a hand-held device would undoubtedly help in the effective control and eradication of these diseases. The movement of fish within a country, as well as internationally, should be monitored. Detection of pre-symptomatic disease, for example in ports, would be particularly advantageous.

In the DIM of plant diseases, opportunities exist to extend testing from labs to the point of decision making. In this respect UC3 devices could be used to accept or reject consignments and, where appropriate, order the destruction or quarantine of plant material. In the case of international trade, testing may move from point of entry/inspection to point of production or packing. Hand-held devices could be

used to certify and select material for planting (seed stock or mother planting schemes) and verify plant diseases in the field – along with selection of the most appropriate pesticides. A number of hand-held devices for the detection of plant pathogens are described in Appendix 1.

The role that UC3 devices will play in the future will in part be dictated by the public's enthusiasm to self-test, which in turn will be influenced by education, the media and the nature of the device (non-invasive tests that slot into mobile phones are likely to be seen as more appealing than simple lateral flow devices). The market for self-diagnosis is growing and many individuals are taking a more active interest in their own healthcare. This is exemplified by the emergence and utility of web-sites such as NHSdirect.nhs.uk, MayoClinic.com, Diagnose-me.com, Yourdiagnosis.com and Medicdirect.co.uk. It is now common in the UK for a proportion of patients to take self-researched information on their symptoms, or chronic disease management, to consultations and an increasing proportion of UK GPs have real-time access to the internet

POC-type devices are likely to have the greatest impact and more extensive applications in areas where there is no or limited laboratory back up (e.g. sub-Saharan Africa) – see equity section.

UC3 devices linked into the global networks described by UC1 offer additional benefits afforded by the opportunity to maximise the data through bioinformatics and modelling etc (Appendix 2).

4 The costs and benefits of selected future capabilities and their robustness to uncertainty

As the devices have not been defined we can only highlight the fact that cost is a significant issue. The basic development and manufacturing costs should be considered alongside the costs of implementation (from both a financial and socio-economic perspective) training, maintenance and waste disposal etc.

In the world of biosensors, it has been estimated that the costs of data collection for validation of a device/system can be in the order of £1-2 million. This figure assumes a working laboratory prototype and excludes Research and Development costs. The initial evaluation of the device normally requires around 200 to 500 measurements taken over a 12-month period. The cost of validation can present a problem to SMEs (small to medium enterprises) wishing to attract investors. In general, diagnostic companies take an active interest only when a system has been validated. This leads to a 'funding gap', as in the absence of commercial interest it can be difficult to raise venture funding. If the evaluation is satisfactory and the device is launched onto the market it may take a further two to three years, at a cost of around three to five million pounds, to generate the data required for full submission to regulatory authorities, such as the FDA, and approval of the devices as commercial medical diagnostic tools. As an interim step, products can be launched as 'research only' devices, which generates revenue while data are collected for regulatory submission – profits can be used to offset costs.

A report examining the cost benefit outcomes in relation to introduction of hand-held devices for the detection and identification of three infections: human TB, bovine TB and HIV, has been prepared by Chris Desmond and Tony Barnett from the London School of Economics (the full manuscript can be obtained directly from Tony Barnett). The analysis concludes that:

- The availability of hand-held device for the diagnosis of human TB could result in gains if deployed in a health system such as the NHS.
- The same gains could only be realised in sub-Saharan Africa if the devices are introduced alongside marked improvements in healthcare and levels of wellbeing more generally.
- There could be important cost savings in the UK with regard to bovine TB
- In Africa, there is little to suggest that UC3 devices would offer any benefits or be widely adopted by most cattle keepers. There is a small possibility that they might be attractive for niche producers in high demand urban markets
- In the UK, hand held test devices for HIV testing would very likely save NHS laboratory and staff costs. The scale of saving would depend on whether retail or clinical provision was decided on. Availability of free ARVs would be an important factor in encouraging people to take the

risk of self-testing *after* particular sexual encounters (most likely) or at regular intervals if adopted as part of a sexual lifestyle.

- Given the existing gender relations and economic constraints on sexual decision making for many people in Africa, it is unlikely that technical innovations will make any substantial contribution to HIV prevention. If introduced to antenatal clinics it would certainly reduce the cost of surveillance and may have a role to play in improved and expanded surveillance but in relation to prevention programmes, the conclusion must be 'marginal'.

As indicated, the benefits of any future technology is greatly influenced by the economic environment and infrastructure etc. into which it is deployed. In times of war, when priorities change along with public acceptance and perception of risk (see D7), devices may be developed and deployed in different and possibly unforeseen ways. Other uncertainties include the nature of 'unknowns' and step-changes in technology.

5 The factors influencing the development of the future capabilities

The reviews on Future Control, Culture and Governance and the Public Perception of Risk (D3, D4 and D7 respectively) are pertinent to the factors influencing the development of future capabilities. Some key issues include:

- The economic environment – while this may seem an obvious point, the global nature of infectious diseases makes this a complex issue.
- The proposed mechanisms for effective integration into current systems of healthcare and trade etc. With respect to healthcare, some of the issues are discussed in more detail under barriers and enablers.
- Who pays and who benefits – this will effect the enthusiasm of organisations to develop and promote the technologies
- The regulations surrounding the development, validation, manufacture and sale of medical devices will undoubtedly effect the development of UC3 devices. Today, the regulatory requirements of in vitro diagnostic medical devices are covered by the IVD Directive (98/79/EC) and Medical Devices regulations 2002 (S.I. 2002 No. 618). Regulations will come into play at both a national and international level. They will be concerned not only with the performance of the devices (i.e. do they produce high quality, reproducible data of relevance), but also with issues such as health and safety, which will be important when considering waste disposal. The reader may wish to refer to the Medicines and Healthcare Products Regulatory Authority's (MRHA) guidance note 19 which gives information on the current regulations for self-testing kits.

- Economic growth in developing countries with high-tech capabilities – it is entirely feasible that some of these technologies will emerge out of China, for example, where there is a keen interest and core capability in both IT and biotechnology.
- Antimicrobial and vaccine development programmes are likely to influence future requirements. For example, if a vaccine is developed UC3 technology may need to distinguish between vaccinated animals and those that have been infected. Alternatively the availability of a vaccine may make testing and trending a disease appear more justifiable. The availability of novel antimicrobials for pathogen resistant organisms will influence the development of UC3 devices to select the most appropriate treatment regime.

6 The barriers and enablers to implementing the key capabilities

In the case of barriers and enablers, UC3 devices not linked into global networks probably offer the greatest concern (i.e. UC3A). The major barriers to implementing the more sophisticated device (UC3B) include cost, the need for international cooperation etc., and the time required for developing the integrated technologies and systems. However, devices linked to global networks could overcome or help to minimise a number of concerns – for exemplifying linking the results to networks and databases would ensure an accurate record of the test and help maintain high quality results – by checking that the device had been used and maintained appropriately etc. Despite this individuals may wish to remain anonymous, especially if they suspect they have an STI.

Limiting who runs the tests may enable UC3 devices to be more readily accepted by professional organisations; this would allow control over the interpretation of results and subsequent actions, data management and the maintenance of records etc. It is likely that as tests become more readily available there will be a trend from the doctor to the patient, from veterinarians to farmers and from plant inspectors to growers etc.

A wide variety of barriers and enablers have the potential to impact on the development and implementation of UC3 devices. The major factors are given below:

- In humans, the area of most concern, and hence a potential major barrier, is that testing may become detached from the healthcare and regulatory systems. A parallel exists with plants and animals – the relationship between veterinarians and farmers, and plant inspectors and growers etc could suffer. This concern is greatest for non-professionals using UC3A type devices (e.g. self-testing). Using the human case as an example, care should be taken to ensure that:

- The professional-patient relationship is maintained and patients receive the appropriate treatment and referrals to counsellors and specialists. There is a fear that professional interpretation of results, in the context of clinical symptoms, could be lost.
 - Education programmes are in place to ensure that individuals are aware of the importance of alerting contacts, where appropriate, of the potential risk so that they can receive the necessary screening etc. This is of particular relevance to STIs. It should be made clear that professional support is available to help trace and inform contacts.
 - The 'new' system encourages individuals to run approved tests and report positive results to their GP or other healthcare worker. Tests of variable reliability and stability etc. are likely to become available. Poor quality tests have the potential to cause havoc. Approved tests should be robust, reproducible and of high quality; backed by quality control and quality assurance schemes.
 - Clear instruction on how to operate the device and run the test (in picture format if possible) is given.
 - Education programmes inform users how to use and interpret the tests – in the case of UC3B this could be achieved with the aid of the device itself. This is a complex issue as tests will not be 100% sensitive and specific. Furthermore, bioinformatics, which may be required for the interpretation of microarrays, can introduce further uncertainty.
 - It is clear what actions should be taken if a result is positive.
 - Even with a negative result individuals are encouraged to seek professional advice if they have concerns.
- As a consequence of the above points professionals may feel their livelihoods are threatened which could act as a barrier to the implementation of the devices.
 - Introduction of hand-held devices might be accelerated in areas where there is a practical need - e.g. in rural areas where support to rural practitioners is driving the development of telemedicine infrastructure. Hand-held devices could offer 'lab reports' to the telemedicine consultation.
 - Non-cooperation and unwillingness to report positive results (with a UC3B device this would be harder to hide) could be an issue.
 - Social stigma – this may be an enabler rather than a barrier as individuals may prefer to self-test than attend an STI clinic.

- Establishing close partnerships between the device developers, users and professional bodies (e.g. the NHS, FAO and OIE) could aid in the acceptance and effective deployment of the technologies and alleviate concerns.
- International co-operation (especially important for linking into UC1 but also in respect to Trade and Immigration agreements).
- Public perception of risk (D7) and ethical issues will also influence the development of UC3 devices. Many of the factors highlighted above, such as the need to maintain a professional-patient relationship, require careful ethical consideration. In addition, aspects such as privacy, data security and who has access to the information are all areas for key discussion. Ethical issues are also discussed in the 'equity' section of this report. Other related factors include:
 - Misuse of test on third parties – especially for STIs.
 - Deception of insurers, employers etc. as to health status.
 - Linkage to direct-to-consumer products – this could be a barrier or enabler.
 - Developers may fear litigation for false positive and/or negative results.
 - Training and support may be problematic in developing countries, which may increase the North:South divide.
 - The availability of a test may skew healthcare and surveillance towards a disease when it is not the greatest risk or threat.
- People's perception of disease and risk clearly affects their willingness to be tested – this is especially significant in Africa. It should be noted that the concept of infection is absent in most pre-biomedical African thinking and in certain areas, blood is considered to have special values. Lay testing for diseases with stigma (e.g. STIs) is likely to be met with fear and mistrust in certain communities.
- Intellectual property may act as a barrier or enabler in taking technology forward (see Appendix 4 for a formal statement from the Patent Office).
- Cost is clearly an issue in the development of any technology and has been addressed in other sections of this report. It may be possible to "piggyback". Nanogen and CombiMatrix, for example, have used technology that emerged from the microelectronic industry; this trend is likely to continue.

7 Issues of equity

Issues of equity will be affected by who pays for the devices. If farmers, growers and individuals pay – without reimbursement or other incentives down the line, then the technologies will be adopted, at least initially, by the more wealthy sectors of society. Where the device is placed should also be considered – a POC instrument in an intensive care unit may be something that not every hospital can afford and may increase the so called ‘postcode lottery’. As indicated above, rural areas may adopt hand-held devices more readily out of a need. It can be seen that issues of equity vary for the different categories of POC-type devices. As UC3 embraces a family of devices to be employed in diverse range of settings this is to be expected.

The UK’s private health systems, where economics and incentives are balanced towards technology, would be likely to pick up the technologies first – where they could be used, for example, to monitor MRSA in hospitals.

In developing countries, the provision of hand-held devices, linked to telemedicine facilities will enable more efficient diagnostic assessment of patients and minimise costs associated with precautionary referral for assessment to central specialist services. Satellite phones and satellite radio services, often funded by non-government organisations, have enabled communications linkages with health services in remote settings to bypass poor land-based infrastructures.

The Africa synthesis report (A1) points to an increasing reliance in Africa on syndrome-based diagnosis, without recourse to specific diagnosis (i.e. detection and identification). This is coupled with an acutely low capacity for laboratory-based diagnosis at sub-national level, plus a weak institutional and financial resource base.

The market force approach inevitably means that UC3 devices will trickle down opportunistically from the UK to Africa and from human healthcare to animal healthcare. When one considers that ~ 75% of emerging human infectious diseases have an animal origin, and that Africa has a high burden of known infectious diseases and a high wild animal population; Africa is far more likely to be a source of future severe infectious diseases than the UK. This highlights the need for African involvement in UC3-related programmes at all stages of development and for the early establishment of SMART UK/Africa partnerships. These partnerships could be imperative if future infectious disease risks, in plants, animals and humans, are to be managed effectively. UC3 devices could be designed to aid disease surveillance at the risk source, i.e. in Africa, but with a realisation that such a need could not be met mainly by market forces and that there would need to be some public intervention. International development and/or non-governmental research funding could play in facilitating targeted research both in the UK and in Africa through some form of object-oriented, smart partnerships. Clearly it would be advantageous if African institutions, such as the African Union, NEPAD and the African Development Bank, were to invest in DIM systems as a policy priority.

The issues of equity, social, ethical and cultural factors are perhaps most significant for UC3. The following are some of the key questions that are likely to be encountered in Africa with regard to promoting the new technologies. They evolve around community engagement and equity for Africa.

- How do local perceptions of the state and of trans-national agencies influence their potential assessment of risk and of externally introduced risk control?
- Who promotes and distributes the device, and what are people's previous experiences and current attitudes to this agent, e.g. the government or an overseas aid agency?
- What are the likely consequences of diagnosis? Can a positive case find treatment? Are there control measures by government institutions that make diagnosis and reporting worthwhile?
- What are local understandings of the common good, to which disease DIM could contribute?
- What is the risk that society will perceive ulterior motives by governments or specialists?
- What is the risk that Africans and African commodities could be excluded simply because of prior exposure to some infection in the past rather than because of actually carrying infection?
- Are African laboratories sufficiently resourced in human capacity, financial and laboratory facilities (construction and equipment) to readily assimilate the new DIM technologies?
- What is the risk that African scientists will turn out to be predominantly 'diagnostic kit technicians' (kit-users) rather than evolve into world class specialists of infectious diseases?
- Could technology inventions or modifications made in Africa to suit African diseases or socio-economic conditions be excluded from integration into new diagnostic technologies by restrictive patent rights and over-protected intellectual property rights?
- Could industry leaders and international development agencies be persuaded to promote an 'open-source' approach to diagnostic technologies, so as to encourage African scientist and institutional participation?
- How can Africa, which has the highest burden of infectious diseases, avoid being left in the slow lane?

The above and other considerations make it imperative that some novel mechanisms are needed, on one hand, to communicate the benefits of the new technologies to African policy makers and the society at large and, on the

other, to assimilate African institutions and scientists as partners in the rapidly evolving technologies. The smart partnership proposed in the African Vision for Infectious Diseases (A1) would go a long way towards such an objective. Another facilitator would be an 'open-source' approach to infectious disease diagnostic technology development. This might accelerate the uptake of the new technologies in the countries of need, i.e. Africa, and the active participation of African scientists in the technology revolution for the DIM of infectious diseases. As Africa has the highest burden of infectious diseases it is also most advisable that institutions based in Africa be part of the global alliance for the new approaches to the DIM of infectious diseases.

8 Suggested actions to realise greatest public good

Throughout the report various actions have been highlighted. They have been brought together here, along with more general comments, for consideration:

- Coordinate efforts more effectively in the UK and internationally. The international perspective is especially important for the UC1/UC3 interface but also for Trade etc.
- Encourage fundamental research and collaboration – engage RCs, OGDs and industry (see UC2 for an overview of the research areas of most significance to the development of future diagnostic tests).
- The requirement for new and improved biomarkers is set out in the key future capabilities section. If we are successful in finding markers for the following, developing devices to measure the markers, and deploying the devices in an effective infrastructure we could expect to see a significant impact on animal and human health and the spread of disease in the future.
 - The ability to distinguish between vaccinated and infected animals and humans.
 - The identification of drug-resistant pathogens in animals and humans (drug resistant HIV and TB would be a priority).
 - BSE
 - The identification of the persistently infected carrier.
 - The diagnosis of mycobacterial infections in animals.
 - Biomarkers of wildlife diseases could be especially important in preparing ourselves more adequately against future zoonotic threats.
 - Markers able to identify diseases in plants animals and humans before any signs of disease or symptoms (in relation to UC3, this is very long term).

- A key message for UC3 is the need to develop robust portable molecular diagnostic devices capable of functioning in extreme conditions (e.g. in the absence of clean water and electricity). Realisation of this capability would have a significant impact on the DIM of infectious diseases, especially in sub-Saharan Africa.
- Develop a device to distinguish between bacterial, viral infections and no infection – helping to avoid the overuse of antibiotics and build-up of antibiotic resistance.
- Consider devising a rapid scanning device for MRSA.
- Ensure that a FMD test is available on the devices in case there is an outbreak.
- Establish an HIV screening programme for pregnant women in sub-Saharan Africa in order to reduce MTCT.
- Encourage the public to embrace new technology in an appropriate manner (i.e. to be selective and use devices approved by professionals).
- Inappropriate poor quality handheld tests will inevitably become available for sale, especially over the internet. It is imperative that the public should be engaged, at an early stage, to avoid, as far as possible, the misuse of devices and misinterpretation of results.
- Forge strong links with companies not normally associated with DIM, who may have an interest in this area in the future (e.g. mobile phone companies).
- Support the generation of UK, internationally integrated, bioinformatics systems.
- Provide a forum for professions and experts concerned with plant, animal and human diseases, their diagnosis and control, to interact.
- Move towards a UK/ European CDC equivalent.
- Establish SMART partnerships, especially between the UK and Africa. Throughout the Risk, User Challenge and Africa reports, the need to establish SMART UK/Africa partnerships has been highlighted. Africa is far more likely than the UK to be a source of severe infectious diseases: 75% of emerging human infectious diseases have an animal origin and Africa has a high burden of known infectious diseases and a high wildlife animal population. In addition, the programme would undoubtedly benefit if African institutions, such as the African Union, NEPAD and the African Development Bank, could be encouraged to invest in DIM systems as a policy priority.

- Actively seek partnerships in China and other countries where these technologies may emerge.

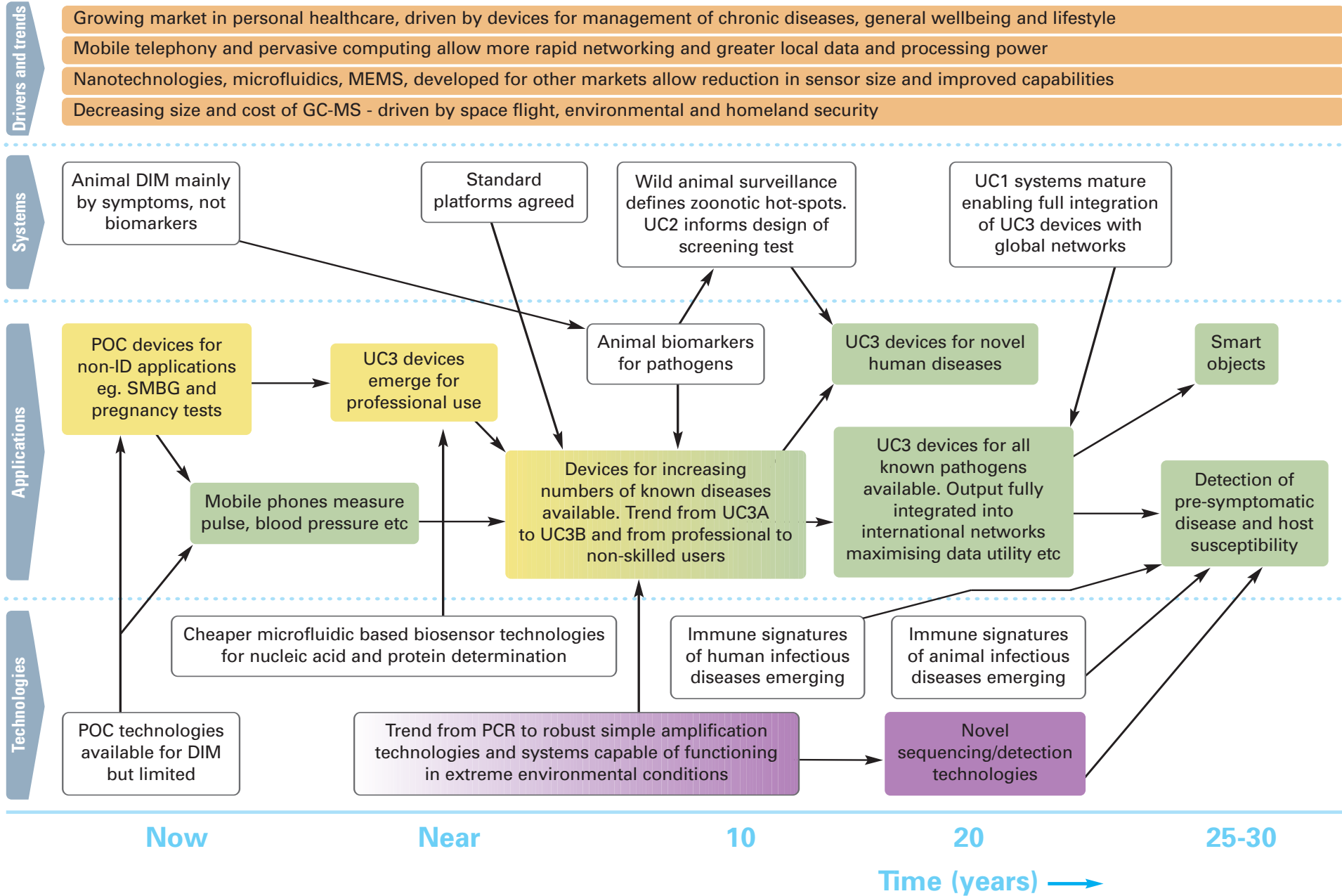
It is accepted for all of the above, that the technologies will only make a difference if they are introduced within a working infrastructure alongside access to appropriate interventions. The global nature of infectious diseases means that their DIM and subsequent control can only be achieved through international agreements and networks.

9 Roadmap

A roadmap has been constructed that draws upon the above analysis, and which sets out in graphical form: important future DIM applications and systems, key technological steps, and important drivers and trends affecting the development and implementations of the systems. This is provided below, together with a glossary of terms.

UC3 Roadmap

Stand-alone devices – UC3A
 Devices linked to networks – UC3B



UC3 roadmap glossary

(Terms that are not defined are deemed to be self-explanatory)

Animal biomarkers for pathogens

The availability of biomarkers for pathogens in animals will undoubtedly aid in the speed and accuracy of diagnosis.

Animal DIM mainly by symptoms, not biomarkers

In general, animal diseases are diagnosed by clinical signs without the use of biochemical markers.

Cheaper microfluidic-based biosensor technologies for nucleic acid and protein determination

This is a self-explanatory capability.

Decreasing size and cost of GC-MS – driven by space flight, environmental and homeland security

GC-MS is the effective combination of gas chromatography and mass spectroscopy for the identification and quantification of molecules in complex mixtures. GC-MS is considered the gold standard for the determination of a wide range of analytes. However, the size, complexity and cost of mass spectrometers have prevented their routine use, except in specialist laboratories.

Field portability, transportability and miniaturisation are areas of increasing interest, driven mainly by planetary exploration, environmental and homeland security.

In situ mass spectrometry is rapidly becoming a reality and developments in manufacturing techniques, in particular micro-electro-mechanical systems (MEMS), have meant that some hand-held mass analysers, for specific applications, already exist.

Detection of pre-symptomatic disease and host susceptibility

These capabilities will only be realised after a significant amount of fundamental research (see UC2). The detection of pre-symptomatic disease may emerge from a comprehensive understanding of the immune signatures of disease. Within the timeframe set by the Foresight programme (i.e. up to around 30 years), it is unlikely that we will see the measurement of immune signatures on hand-held devices. However, they may begin to appear at the end of the roadmap timeframe.

The detection of volatile organic compounds (VOCs) is described in UC4 and reviewed in S2 and could also aid in the detection of pre-symptomatic disease – research in this area is most advanced in plants.

In addition to detecting pre-symptomatic infections, it may be possible to ascertain an individual's/animal's/population's susceptibility to disease. As technologies advance, UC3 devices will have the ability to sequence the host genome and identify single nucleotide polymorphisms (SNPs); further fundamental research is required to map SNPs to susceptibility etc.

Devices for increasing numbers of known diseases available. Trend from UC3A to UC3B and from professional to non-skilled users

This will be a natural progression in around 10 years. After this time, improvements in speed, cost and sensitivity will continue.

Growing market in personal healthcare, driven by devices for management of chronic diseases, general well-being and lifestyle

Point-of-care devices for self-monitoring of blood glucose and pregnancy testing are routine today. The trend towards devices for other conditions and general well-being will proceed independently of infectious disease diagnostics and will drive DIM forward.

Immune signatures of animal infectious diseases emerging

Immune signatures of human infectious diseases emerging

Infection of an animal or human host with a pathogen results in rapid changes in gene expression and protein synthesis by cells of the host's immune response. An appreciation of the immune signatures of disease will aid the detection of pre-symptomatic infection and our understanding of pathogens and the disease process in general.

Mobile phones measure pulse, blood pressure etc.

Mobile phone companies recognise that a technical system consisting of intelligent sensor networks connected to a mobile phone network could provide a wide range of opportunities of relevance to health and healthcare. Mobile phones able to measure pulse and blood pressure are on the horizon; systems that will be able to detect, identify and monitor infectious diseases (UC3B devices) form part of a longer-term vision for companies such as Vodafone.

Mobile telephony and pervasive computing allow more rapid networking and greater local data and processing power

It is envisaged that pervasive computing devices, which range from personal digital assistants to the microchips in cars, appliances and telephones, will give rise to an explosion of interconnected smart devices marketed to make our lives easier and more productive. Mobile telephony and communication technology will continue to advance as part of this network. The development of UC3B devices will undoubtedly benefit from these networks and systems.

Nanotechnologies, microfluidics, MEMS, developed for other markets allow reduction in sensor size and improved capabilities

Micro-electro-mechanical systems (MEMS) is the integration of mechanical elements, sensors, actuators and electronics on a common silicon substrate through microfabrication technology. MEMS promises to revolutionise nearly every product category by bringing together silicon-based microelectronics with micromachining technology, making possible the realisation of complete systems on a chip. Clearly, this kind of system has direct relevance to the development of UC3 devices.

Microfluidic systems and capabilities are also a key component of UC3 devices – these systems vary considerably in their complexity and suitability for UC3.

The impact of nanotechnology on the design and development is discussed under UC3 key future capabilities. Essentially, nanotechnology will offer new sensing formats and materials for improved performance.

Novel sequencing/detection technologies

Continuous improvement in sequencing power will eventually result in a portfolio of rapid novel technologies. Similarly rapid, highly sensitive detection technologies will continue to evolve.

POC devices for non-ID applications e.g. SMBG and pregnancy tests

A number of high-quality devices for self-testing exist today. The market for self-monitoring of blood glucose and pregnancy testing is well established. POC devices for cardiac markers are also in routine use.

POC technologies available for DIM but limited

Hand-held devices of varying quality are available for the detection of infectious diseases (see UC3, Appendix A). The integration of hand-held devices into the effective management of DIM starts from this point. Initial barriers for the implementation of UC3A devices are more related to infrastructure than to technology – this is especially true in developing countries.

Smart objects

These could include blue-sky devices such as smart hiking boots that would automatically sample soil samples, and smart toothbrushes that would alert the user to the presence of an infectious disease.

Standard platforms agreed

Ideally, standard platforms would be open systems and different manufacturers could produce cassettes etc. to slot into the devices. In the commercial world such an open system may not be financially attractive. However, the possibility of encouraging manufacturers to work together should be discussed.

In both the immediate and long-term future, intellectual property will inevitably play a key role in the design and manufacture of UC3 devices – companies should be encouraged to license technologies to ensure that inventions are fully exploited and that progress is not blocked.

Efforts should be made to ensure that developing countries will have access to appropriate technologies – care should be taken not to increase the north-south divide.

Trend from PCR to robust simple amplification technologies and systems capable of functioning in extreme environmental conditions

Polymerase chain reaction (PCR) and other nucleic acid amplification technologies are routine today. A key message from the Foresight project is the need to develop robust and portable molecular diagnostic devices capable of functioning in extreme conditions (e.g. in the absence of clean water and electricity). This is a difficult and complex challenge as both sequencing and microarray technologies are highly sensitive to fluctuations in temperature.

UC1 systems mature, enabling full integration of UC3 devices with global networks

This box represents the maturation of the capabilities described by UC1. These capabilities include the collection, storage, manipulation, modeling and management of data from multiple sources (i.e. effective bioinformatics). At this point, UC1 will be bringing together and making sense of data from satellite remote sensing, web crawling, UC3B devices, UC4 systems and UC2 screening procedures etc.

UC3 devices emerge for professional use

While a number of UC3 devices are already in professional use (e.g. used by clinicians and plant growers), this box represents a greater acceptance and integration of hand-held devices into our healthcare and equivalent management systems for plants and animals. At this early stage, the devices will be UC3A

(i.e. not linked into comprehensive networks). In many cases, the barriers to implementing these technologies relate to infrastructure, habit and a fear that professionalism and quality will be lost. Ensuring that devices are deployed in a regulated environment will be paramount to their acceptance by professionals.

UC3 devices for all known pathogens available. Output fully integrated into international networks maximising data utility etc.

This box represents a major milestone in the evolution of UC3 devices.

UC3 devices for novel human diseases

These devices will emerge in conjunction with UC1 and UC2 as described under the “Wild animal surveillance” box. Ultimately this capability will evolve to identify novel pathogens without the direct intervention of UC2. For example, one can envisage a UC3 device recognising that a pathogen was present but that it wasn’t in any current databases. An interactive UC3B device could instruct the user to insert a separate cassette which could sequence the pathogen etc.

Wild animal surveillance defines zoonotic hotspots. UC2 informs design of screening test

Wildlife surveillance and data modelling from UC1 will inform UC2 of potential hotspots where pathogens are most likely, because of opportunity and environmental change etc., to make the species jump from animal to human. In the first instance, UC2 may upgrade its screening regimes in hotspots. Through its databases and knowledge, UC2 experts will advise on the development of a diagnostic for the pathogen in humans, and on effective rapid transfer of the test to a UC3 device.

Appendix 1

State of the art UC3 devices of today

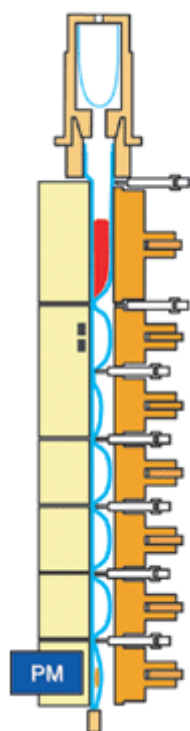
(Penny Wilson)

A considerable number of point-of-care (POC) devices are in routine use today. They range from bench-top and hand-held-meters to simple non-instrument based dipsticks and lateral flow systems. Blood glucose and pregnancy testing devices currently dominate the market, but a wide variety of other tests are available including cardiac, tumour and allergy markers, haematological and microbiological tests.

Further information on the POC market today can be obtained from the DTI's Global Watch Mission Report entitled 'Point of care diagnostics: the way forward – a mission to California' which was published in 2004.

Early stage companies are developing unique platforms and technologies that may be of direct relevance to the development of POC/hand-held devices.

Indeed some of these companies, which are mainly in the United States, already market POC devices for infectious diseases. These include HandyLab's microfluidic system (<http://www.handylab.com>) and IQuum's novel lab-in-a-tube (Liat™) platform (<http://www.iquum.com>) – Fig. 1.



The Liat™ Tube uses a flexible tube as a sample vessel and contains all assay reagents pre-packed in tube segments separated by peelable seals. Multiple sample processing actuators in the Liat™ Analyzer compress the Liat™ Tube to selectively release reagents from tube segments, move the sample from one segment to another, and control reaction conditions.

The Liat system automates all testing processes from sample preparation to amplification to real-time detection. By reducing complex nucleic acid testing to three simple steps, the lab-in-a-tube technology enables non-specialised personnel to conduct sophisticated testing.

Ionian Technologies Inc (<http://www.ionian-tech.com>), a spinout from the Keck Graduate Institute, is a biotechnology firm focusing on molecular diagnostics for emerging and infectious diseases. The company has developed a novel, isothermal, rapid nucleic acid amplification technology based on the detection of DNA or RNA fragments (usually eight to

Fig.1

24 bases) generated directly from the target nucleic acid. The company has been awarded a significant grant to develop a hand-held device for biothreat detection.

CLONDIAG chip technologies GmbH (<http://www.clondiag.com>) is a German company that has developed an integrated platform for genomic diagnosis at the POC. The company's Assay Processor (AP) combines sample preparation, target amplification and labelling, analysis of the target for specific markers and interpretation of raw data within a single system.

Emerging technologies such as smartDNA (<http://www.investigen.com/smartdna.html>) are set to revolutionise nucleic acid testing. Investigen is developing unique smartDNA test strips that react to the presence of target nucleic acid sequences, without the need for amplification. A change in colour indicates that the target is present.

In the plant world Port Check (<http://portcheck.eu.com>) is looking to develop and evaluate real-time PCR (TaqMan) assays for a number of key harmful organisms, including *phytophthora ramorum* (sudden oak death) and pinewood nematode; and transfer these assays to field portable real-time PCR platforms. CSL's Pocket™ Diagnostic tests provide on-site lateral flow devices for a range of horticultural tests (<http://www.pocketdiagnostic.com/splash2.html>). The organisation already has a presence in Africa where it sells kits for Potato virus Y, Tomato yellow leaf curl virus, *ralstonia solanacearum* and *xanthomonas hortorum* pv. *Pelargonii*.

Dr Helen Lee, Reader in Medical Biotechnology at the Department of Haematology of the University of Cambridge, has dedicated her career to diagnostics development and over the last ten years has focused her efforts on developing diagnostic kits that serve the needs of developing countries. Technologies under development involve sample preparation and rapid detection of infectious disease targets (DNA, RNA, antigen or antibodies). Dr Lee's team has developed a rapid and inexpensive dipstick test (Firstburst 1) for the detection of *chlamydia trachomatis*.

- Simplicity – a non-specialist can be trained in ten minutes.
- Rapidity – results are obtained in less than 25 minutes.
- Cost – less than 50 pence in developing countries.
- Stability – remains stable in high temperatures and humidity.
- Non-invasive samples.

Dr Lee also has an extensive HIV programme in place.

Appendix 2

Bioinformatic capabilities will be critical to the development and implementation of all the User Challenges. Labformatics Ltd was commissioned to prepare a document for UC3, but many of the issues discussed relate to informatics in general. The authors make the point that bioinformatic capabilities may be the rate limiting step of novel diagnostic systems, including point-of-care devices of the future.

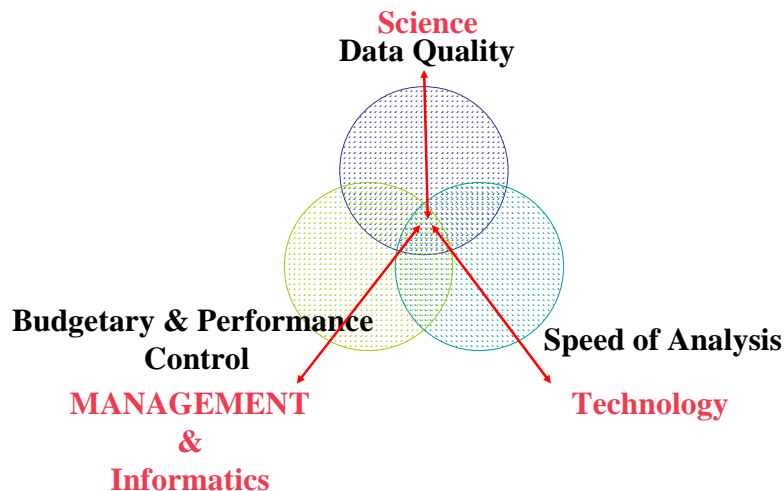
Informatics View – Present day practice and awareness of potential future challenges

Gordon Logan and Simon Wood Labformatics Ltd

Comments on the Technology Approaches to User Challenge 3

One of the major issues is the delivery of such systems in a manner that meets the individual need of the patient; linked to the equally important delivery of Health Informatics and population analytics. This needs to be carried out in a manner that consistently evolves with both the diagnostics and informatics technology development and consequent deployment.

Scientific Management Performance – Balancing Expertise



Analytical Instrumentation Sciences

It is assumed that the existing scientific instruments business is maturing to the delivery of highly-automated and highly-specialised instrumentation. This differs from the traditional diagnostics products in advancing the technologies adopted in genomics and systems, and places much more emphasis on informatics and non-linear statistics to provide diagnostic information. In parallel, although these instruments and systems are evolving to be more technologically advanced, the actual user interface needs to be simplified and intuitive to a number of customer experience groups with differing levels of user need, from plug and play operator users through to 'high end' analytical scientists. In this environment 'ease of use' requires a great deal of expensive development support.

The most analogous work today is carried out by screening instruments working at the proteome level, with the goal of using this screening science as a vehicle for the delivery of pharmaceutical treatments which are tailored to a particular patient's 'drug profile map'. Clearly this will permit an understanding of why certain individuals are more prone to infection than others. These data processing vehicles are currently under investigation and should be looked at further in the context of infectious disease diagnosis.

To date, one of the major longer-term concerns of many suppliers of today's analytical technology, for potential automated screen developments such as biomarkers, is processing the data sets with a high degree of sensitivity and specificity.

An example of a more recent technology development, and used in the laboratory today, is that of Tandem Mass Spectrometry; which could replace traditional wet biochemistry screening techniques, due to potential ease of use, price point for sample preparation and data information production.

Data Standards and Curation

Current and parallel thinking in the area of laboratory informatics gives some guidance as to future needs. At present the pharmaceutical industry is very focussed on the delivery of IT systems which permit easy and secure access to IP information which may not be relevant today but must be accessible for future utility. Most historical data of a scientific nature remains in paper notebooks. Clearly we have hundreds of years of experience of looking after paper and less than a generation of looking after electronic data. Current horizon thinking in this specialty has concerns that include ensuring all electronic file formats delivered today can be used in the future. We are now in a period of data collection that is unrivalled, but our ability to offer equally unrivalled processing analytics is not yet at parity. There are a number of reasons for this, but one of the major issues is a poor understanding of the maturation model for informatics within the scientific community in general.

Suppliers of diagnostic instruments have a generally poor record of data standardisation, making inter and intra data analysis difficult for users. Most analytical instrument systems produce data that requires qualitative analysis,

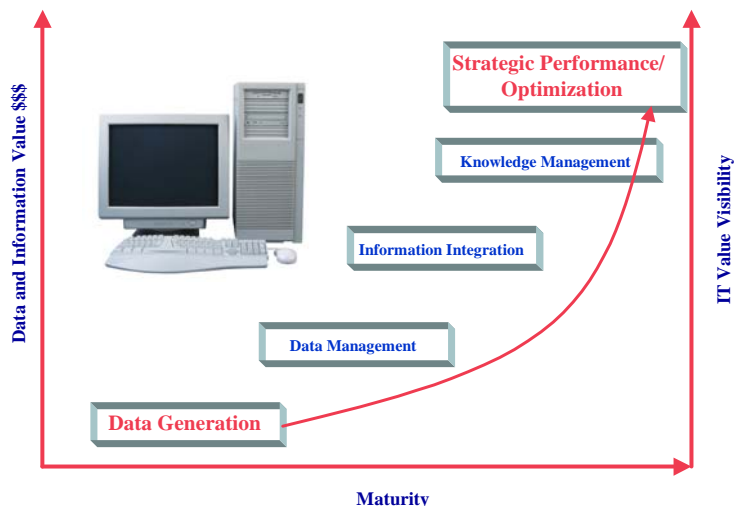
and specificity is often difficult. For example, with biomarker work to date, particularly with microarrays and mass spectrometry, a significant rate limiting step is seen, which is the ability of these systems to deliver a data--information--knowledge work flow and transfer engine that is as robust as the analytical technique itself.

We have collated enormous amounts of peptide sequence data over the past decade, but the development of informatics engines to utilise this data and turn it into knowledge remains a largely academic and/or (expensive and commercially sensitive) industrial pursuit. The informaticians required to work in this area are not being trained in anything like the numbers that will be required to cover even the expectations of 'Infectious Disease Identification'. The discipline is multi-faceted, requiring a solid background in biology and computing science, and to date remains a postgraduate activity, requiring many years of continuous training. Essentially, a major practical aspect of any informatics deliverable deals with the management of constant technological and scientific progress serviced by IT strategies, which are also subject to constant and complex technological change. The need for parallel thinking about how data is to be collated, processed and reported is paramount.

Informatics; a potential rate limiting step

It is expected that almost all analyses carried out on scientific instruments, which are presently located in off-line laboratory facilities and used by highly skilled laboratory staff, will eventually be developed into POC techniques. The challenge is to ensure all data systems and knowledge management engines are similarly developed. Therefore the requirement of suppliers is to ensure the user experience is simple, with no loss in deductive capacity (this will be inherent in the delivery system). One of the major IT challenges in moving to this vehicle is the loss in control of data delivery technology. It is unlikely that end users will permit or tolerate the standardisation (imposition) of a particular technology format. Similarly the data processing and reporting formats will also be subject to this challenge. For instance in some countries particular testing informatics might be more relevant than in others and personal information might be subject to different regulation at many levels of statute. This mix of technology need and informatics expectation must be seen as a vital part of any future endeavour. The maturity of such systems is summarised in what Labformatics calls the Laboratory Informatics Maturity Model and is deliberately analogous to the Capability Maturity Model-Index (CMM-I).

Laboratory Informatics Maturity Model™

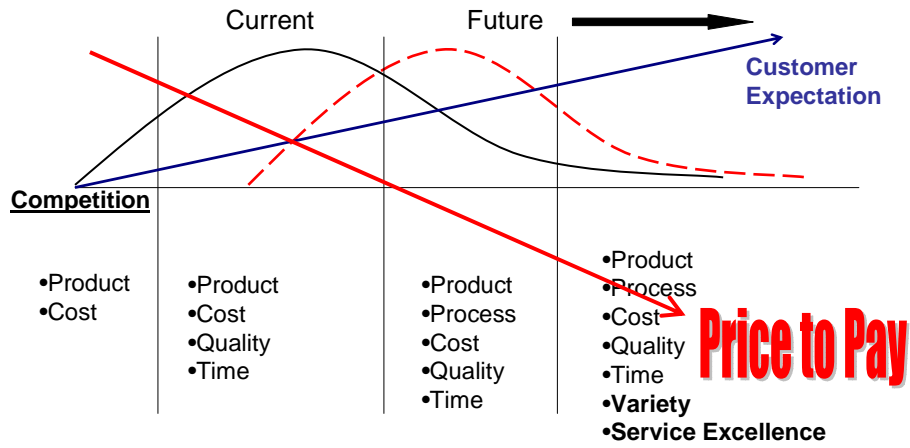


It might be possible to start with a view that ensures the allocation of part of any instrumentation or diagnostics development programme, at the basic scientific level, also allocates some effort to the delivery of the expected outcome from the data acquisition, data processing, data curation, security, information reporting and knowledge management activity. Also it should be stressed that support from non-academic and government informatics groups must be sought. Unlike the diagnostics business, IT for scientists in this specialty is generally built upon applications, such as databases, operating systems and software development tools, which are predominantly used widely in other sectors; this includes open source products. The development of systems using IT tools that are used universally, and not just in our industry sector, is vital in any future consideration; we don't wish to be looking after technologically advancing instrumentation with software that is inherently redundant. By definition this requires significant awareness of the technological expectations of the commercial IT industry and their previous performance in this sector. To date performance has been mixed, and is due in no small part to the continued poor interface between IT and science, and the lack of energy shown in bringing IT needs into the scientific development cycle at an early enough stage.

Competitive Collaboration

Significantly, like all systems of this type, the competitive 'cost' to the end user will continue to fall but the customer expectation will continue to rise. If secure commercially centric technological decisions are not made at the appropriate time i.e. as early as possible in the development cycle, the overall system deliverable will be uneconomic long term and hence short-lived.

Competitive Advantage – from Product to Service (adapted from Cokins 1996)



Appendix 3

ANNEX TO FUTURE RISKS OF FMD SPREAD IN THE UK

M.J. Keeling, Warwick University

The figures below show the effect of earlier detection (and control) of infected farms on the average basic reproductive ratio across Great Britain, using the estimated 2015 farm density and animal numbers. The methodology is as described in the main report. The three predictions assume an average of seven, six and five days being infectious, where this measures the time from the onset of infectiousness to the culling of all animals on the farm. In the previous figures seven days infectious period has been assumed throughout. To provide a more quantitative understanding of the effects of more rapid detection, we can calculate the proportion of farms with basic reproductive ratios above one (for 7 days = 21%, for 6 days = 18% and for 5 days = 15%), or the proportion of 10km x 10km squares where the average basic reproductive ratios above one (for 7 days = 15%, for 6 days = 12% and for 5 days = 9%). Both these figures and the maps stress the importance of early detection and control at the farm level.

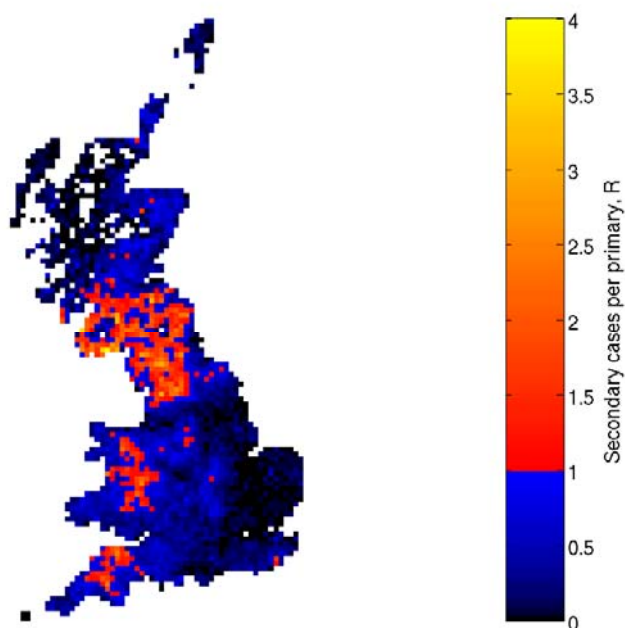


Figure A.1. Risk map for 7-day infectious period.

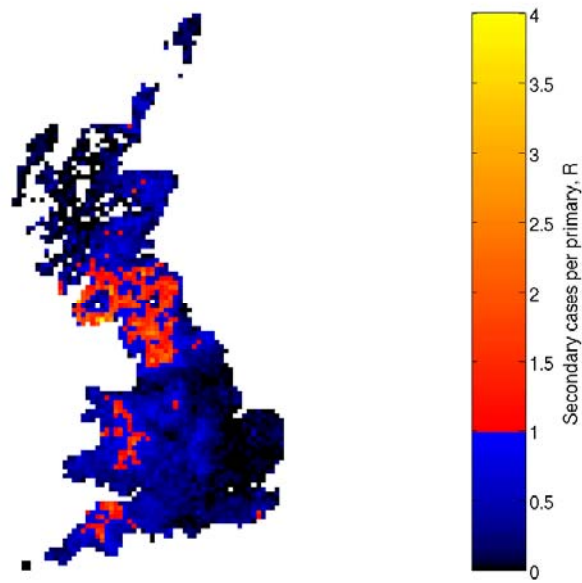


Figure A.2. Risk map for 6-day infectious period.

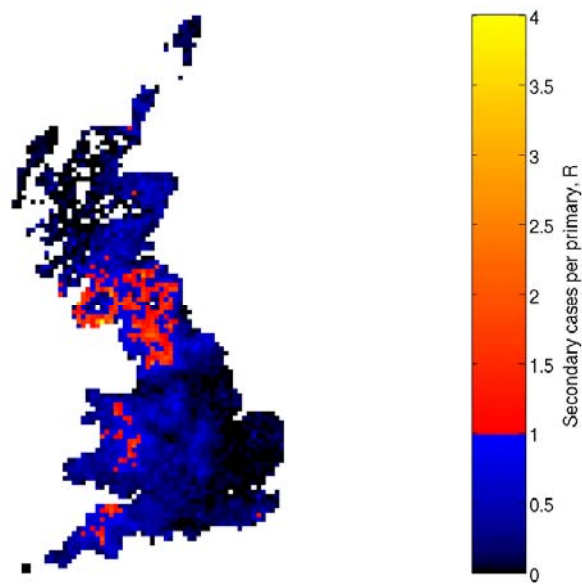


Figure A.3. Risk map for 5-day infectious period.

Appendix 4

Intellectual Property Issues Associated with the Development of UC3 Devices

In both the immediate and long-term future, intellectual property (IP) will inevitably play a key role in the design and manufacture of UC3 devices. Understandably, diagnostic companies often develop closed systems, protected by their own IP, as a way of securing market share and recovering research and development costs. The possibility of encouraging manufactures to work together should be addressed – could companies be encouraged to license technologies more widely? In particular efforts should be made to ensure that developing countries will have access to appropriate technologies and care should be taken not to increase the North: South divide.

Tony Howard, Deputy Director of the UK Patent Office, was asked to comment on future trends in IP. He provided the following statement.

"The patent and indeed the IP system as a whole, tends to evolve over time in response to the changing technological, business, political environment and how to meet the challenge of the information age. Recent years have seen considerable discussion on how the IP system can serve the needs of developing countries and the appropriate level of protection for inventions involving living material (including genes) and information technology. It is reasonable to assume that these areas will continue to be the focus for discussions in the future and that the scope and availability of patent and other forms of IP protection may change as a result. The aim will always be to ensure that IP is an enabler of innovation, rather than an end in itself, to provide secure conditions for research and development, but without tying up increasing flows of information."

One area of relevance to the project, especially, UC1, is the possibility of inventions being assigned to computers and intelligent networks – under present patent law only a human can make an invention. Whilst this is not a topic of debate today, it may need to be addressed over the next ten to 20 years – complex issues of ownership may arise.

The reader may also be interested Patenting Lives (www.patentinglives.org), a project led by Dr Johanna Gibson, at Queen Mary Intellectual Property Research Institute. The project gathers together interdisciplinary experts to consider intellectual property protections and restrictions on life forms, and particularly the impact on developing and least developed countries. The patenting of life forms raises many critical questions, not only with respect to ethical and moral also cultural, social, and economic development.

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All the reports and papers produced within the Foresight project 'Infectious Diseases: preparing for the future,' may be downloaded from the Foresight website (www.foresight.gov.uk). Requests for hard copies may also be made through this website.

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