

Bringing diagnosis closer to the patient

Some of the most important challenges for nanomedicine currently include:

- finding ways to translate advances in both technology and the understanding of the pathology of disease into preventive medicine;
- detecting disease at the earliest, most treatable stage;
- decreasing costs to healthcare services and increasing productivity at the same time;
- ensuring the cost of medical technologies is aligned with better patient prognosis;
- finding ways of improving on existing treatments and technologies.

This BRIEFING will examine how the application of knowledge of disease processes at the nanoscale and of nanotechnologies will impact the development of advanced point-of-care (POC) diagnostic devices and the impact that such products will be likely to have on healthcare systems.

Challenge

Much clinical diagnostic work is currently undertaken in centralised laboratories. This necessitates taking a sample from the patient, packaging, transfer to the laboratory facility where it is analysed, and sending the results back to the clinician, who then informs the patient. All of these steps involve time and cost. The challenge is to make this process more efficient, less expensive and more patient-friendly, whilst maintaining or even increasing diagnostic performance.

The key benefit of POC diagnostic devices is that they have the potential to accelerate the entire process from sample taking to informing the patient and move this process to clinicians' offices (including GPs), wards or to the patient's home under medical supervision. This implies a number of requirements in relation to design including:

- ease of use;
- portability;
- suitability for intended purpose and the ability to deliver results that are clinically relevant and meaningful for the intended users;
- accuracy, reliability and ease of maintenance;
- fast response times;
- elimination of false positives or negatives;
- for some applications, the ability to carry out multiple analyses simultaneously;
- robustness;
- the ability to integrate with IT and telecommunications systems;
- reduction in invasive sampling/sample volume;
- cost-effectiveness.

Background to nano developments

Advantages of using nanotechnologies in POC devices include miniaturising components, reducing sample quantities, very fast diffusion rates and a high degree of measurement specificity. Recent approaches in applying nanotechnologies to POC diagnostic devices include the following examples.

Nanosensors

A number of materials have been developed that can be effectively employed as the receptor component of a

biosensor. These include materials of biological origin, e.g. antibodies and enzymes, and manufactured synthetic materials, often incorporating features at the nanoscale.

Nanowires

The UK company QuantuMDx has deployed a nanowire-based sensor in its Q-POC device, currently undergoing field trials. The Q-POC is a handheld device, claimed to be capable of delivering a rapid and accurate medical diagnosis in less than 15 minutes with the same sensitivity and specificity as a traditional laboratory but at a fraction of the cost. The device uses disposable diagnostic cartridges that are being developed for the detection and diagnosis of a wide range of diseases and conditions.

Nanosensor arrays

The UK company Applied Nanodetectors Ltd has developed a nanosensor-based array platform that can be configured to detect multiple species. One particular exciting application of these sensor arrays is breath analysis, a non-invasive and patient-friendly process whereby small quantities of volatile organic compounds can be detected in human breath, forming a fingerprint that can be used for early disease detection and diagnosis, e.g. of lung cancer. These sensor arrays can also be integrated with mainstream semiconductor processes and manufactured at high volume.

Quantum dots

The Fraunhofer Institute for Applied Polymer Research in Germany, the University of Potsdam, CNRS Strasbourg and Lumiphor Inc, working as part of the EU FP7 project NANOGNOSTICS (quantum dot-based highly sensitive immunoassays for multiplexed diagnostics of Alzheimer's disease) have recently developed a novel and fast quantum dot-based FRET (Förster resonance energy transfer) technique that is suitable for multiplexed ultrasensitive detection and which produces an assay with a sensitivity 40 to 240 fold higher than one of the best-established single-analyte reference assays for five biomarkers.

Nano-cantilever arrays

The London Centre for Nanotechnology has recently been awarded a major UK Engineering and Physical

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Sciences Research Council grant to further develop a new nano-cantilever based device to help people living with HIV to monitor their health and the effectiveness of their treatments in collaboration with their physician. The nano-cantilever arrays measure HIV levels and other protein markers that can indicate a rise in the level of the virus and the body's response to it, and will enable patients to monitor the virus themselves under medical advice, reducing the frequency of doctor visits. It is also intended to act as an early warning system to tell patients to seek medical help if the virus is resisting anti-retroviral treatments. The device is also expected to have applications in developing countries that need rapid and affordable ways to diagnose and monitor patients.

Nanoelectronics

The BIOS Lab on a Chip Group, University of Twente, Netherlands has recently received a substantial early development stage grant from the European Research Council towards its eLab4Life Project. The key objective is to fabricate novel nanostructures that induce local electrical fields for the study of individual biomolecules and cells, and that can replace optical techniques which are difficult to integrate into portable devices. This research offers the opportunity for further miniaturisation of components to make commercially attractive POC diagnostic devices.

Magnetic resonance

Magnetic resonance is the phenomenon of absorption of certain frequencies of radio and microwave radiation by atoms placed in a magnetic field. T2 Biosystems Inc, a Massachusetts-based start-up, is in pre-market development of nanoscale magnetic resonance-based technology for use in bench-top instruments for small molecule diagnostics. The company claims that magnetic resonance technology will be faster, more reliable and potentially less expensive for both molecular and immunodiagnosics applications than current optically based tools, and expects to develop the technology for use in a range of POC diagnostic devices.

Nanoplasmonics

A plasmon is a quasiparticle resulting from the quantization of plasma oscillations. In recent years, surface plasmonics has become an increasingly attractive research field for developing label-free biosensors to be used as POC diagnostic tools for cancer and infectious viral diseases. A multi-disciplinary research team at Boston University has recently developed a novel label-free optofluidic-nanoplasmonic biosensor and has demonstrated the direct detection of live viruses from biological media at medically relevant concentrations with little to no sample preparation. This approach is expected to be readily adaptable for POC diagnostics to detect a broad range of viral pathogens in clinical settings, in defence and security applications, and in airports or other public facilities.

Impacts

Economic/Industry

According to a 2009 Espicom Report the POC diagnostic market grew by 11% in 2008 and was valued at US\$12.6

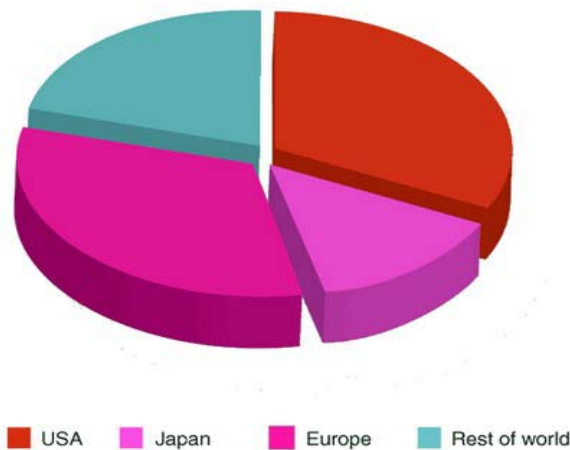


Figure 1a: In vitro diagnostic market shares in 2007 by region (Image: Expert Reviews Ltd, 2008)

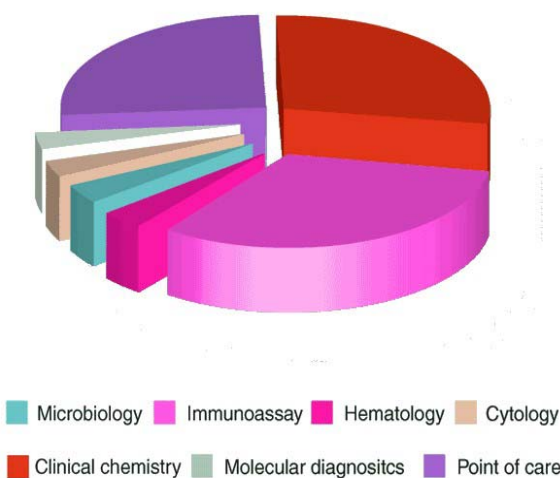


Figure 1b: In vitro diagnostic market shares in 2007 by product type (Image: Expert Reviews Ltd, 2008)

billion of which patient self-testing accounted for 71% (US\$8.9 billion) of the market. While a clear distinction must be made between true POC diagnostic procedures, as carried out by a medical professional, and patient self-testing (sometimes grouped together in market share figures), further growth of the overall market has certainly been driven by the increasing adoption of POC technologies. The huge and increasing incidence of Type II diabetes in both developed and emerging markets offer opportunities for development of POC Hb1ac diagnostic devices. Coagulation monitoring and pregnancy testing are also reported as showing positive market growth.

A December 2008 review of the POC diagnostics market predicts that further expansion of POC testing will develop, building on the higher-than-average growth for this area compared with the IVD market overall. It further reports that a synergistic market driver for the IVD sector is the focus on personalised medicine. Based on the patient's genetic profile and the characteristics of a particular condition, the aim is to avoid adverse reactions and to select drugs that will produce a positive response in that patient. Diagnostics are central to achieving this goal and economic arguments for volume testing within a central laboratory may be turned over in the future in favour of POC testing.

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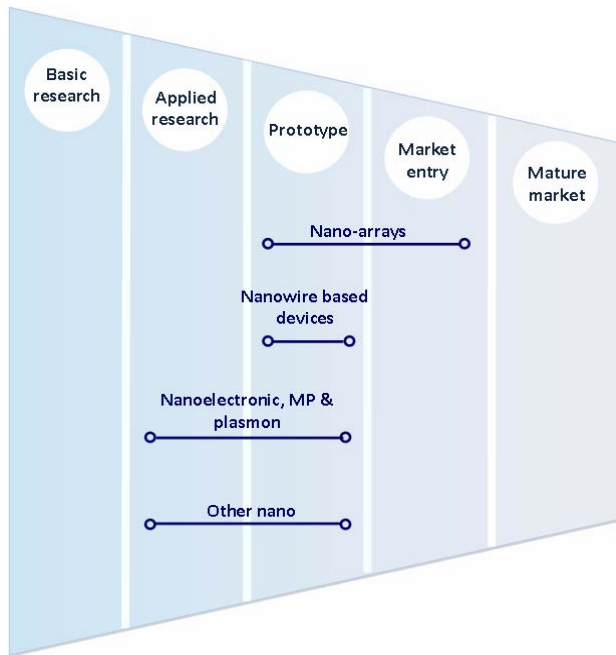


Figure 2: Indicative technology readiness levels (TRLs) for nanotechnology-based point-of-care diagnostic devices.

Impact on European citizens

Conventional methods of diagnosis are often time consuming, requiring well-equipped centralised laboratories and the intervention of skilled professionals other than the treating clinician. The use of rapid POC diagnostic devices could help reduce infrastructure costs, and improve patient outcomes by routine screening, monitoring or by facilitating early treatment, thereby reducing the chance of costly complications. In the case of infectious diseases, transmission rates could be reduced through early detection. The use of POC devices, however has implications for training of users and maintenance of the equipment.

The potential for economic benefit to healthcare systems, and therefore to society in general, is substantial as diagnosis could in many cases be performed in a short time, with a high level of accuracy and specificity, at the point of care thereby avoiding the costs and time associated with sample taking and packaging, transport and handling and processing using current technology at a centralised facility. The need for a patient to return to their clinician for the results of diagnostic tests would also be avoided thereby saving further costs to the healthcare system and freeing up resources.

Nanotechnologies have the potential to contribute strongly to this growth and, furthermore, the regulatory framework for in vitro diagnostic devices is generally favourable towards such innovation.

Challenges

Reducing costs

In common with other novel medical technologies, a key driver is budgetary pressure and cost-containment within healthcare systems, meaning that cost-effectiveness as well as performance must be demonstrable through processes such as healthcare technology assessment (HTA) that are being increasingly implemented in EU Member States. Nanotechnologies are

likely to play an important part in reducing costs in relation to;

- the further miniaturisation of products;
- improving accuracy;
- enabling faster, multiplexed diagnoses;
- increasing the range of diseases and conditions for which POC diagnostic devices can be used;
- reducing costs of manufacturing, e.g. through the incorporation of functional features into mass-produced chips and microfluidic systems.

Possible impacts on healthcare practice

While the trend towards transferring clinical diagnosis from central laboratories to the point-of-care has a major potential for reducing overall costs it may imply significant changes in healthcare practice and the way that medical professionals work. In his review of the POC market¹¹, David Huckle notes that "POC testing will change the established patient pathway with implications for the way professionals conduct their business. There is potential to greatly reduce consultation times if test results are available at the first meeting. This ensures earlier diagnosis and treatment (possibly even the correct therapy) for the patient and saves the clinician time.... the overall impact on improvement of patient outcomes and patient satisfaction will be the decisive factor."

Patent applications

A WIPO search using the general keyword "diagnostics" reveals a steady and continuing high level of patent activity over the last ten years in the diagnostics field (see figure 4). European and US companies such as Roche Diagnostics, Philips, Genentech, Medtronic, AstraZeneca, Novartis, Abbott and Isis Pharmaceuticals have prominent presence on the list, together with significant patent applications also in South Africa, Israel and Korea.

Refining the search to "POC diagnostics" reveals the emergence of other strong European and US players such as Human Genome Sciences Inc, Gilead Sciences Inc, Lion Bioscience AB, Array BioPharma Inc, Amgen Inc and Biocompatibles Ltd.

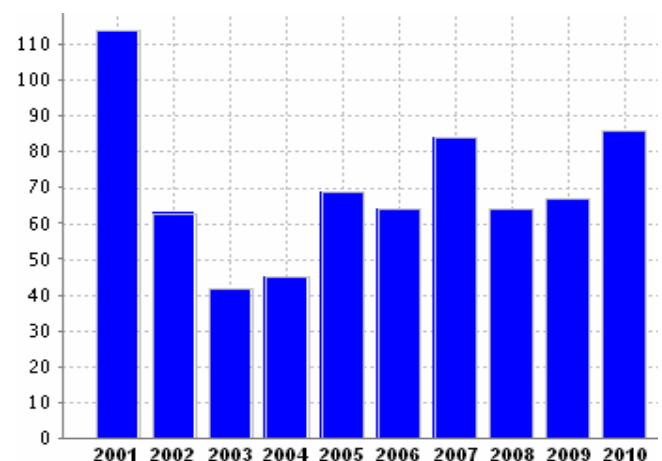


Figure 3: WIPO: POC diagnostics patents 2001-10

Ethical/societal concerns

There are a number of potential ethical issues that could arise from the shift from centralised laboratory-based clinical diagnostics to POC delivery of analyses:

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- Who will be delivering the new POC diagnosis? A specialist? The GP? A nurse?
- What implication will this have for the training of users? For design? For the instructions to the user or for warnings?
- How will the move to a POC delivery change the doctor-patient relationship?
- Will there be resource issues with the shift in site of delivery of clinical diagnoses?
- Could there be a transfer in the level of interpretation, decision-making or clinical responsibility?
- Indemnity issues concerning test results?
- Will the costs of POC diagnostic devices be affordable at the site of delivery, e.g. a doctor's office, with the current reimbursement system? Can these costs be balanced against potential savings in other parts of the healthcare system?
- Can the security of POC clinical data be assured?

EHS aspects

Relatively low quantities of reagents are consumed by modern clinical diagnostic technologies and, with the progression towards nanotechnology-enabled devices, tiny quantities of both biological samples and reagents are likely to be required in POC diagnostic devices. The quantities of waste products (like radioactive or toxic reagents) therefore are likely to be low. It is not yet clear whether nanomaterial-containing waste will be treated as hazardous or non-hazardous clinical waste.

The manufacture of POC diagnostic devices normally takes place in clean operating environments, thereby mitigating the risk of worker exposure to dangerous materials. There could, however, be potential environmental exposure from emissions from the manufacturing processes although these risks may be difficult to quantify. It should be noted that a relatively low mass of nanomaterial can represent a high number of nanoparticles.

The direct nano-based risks to users and patients are relatively low since the nanotechnology component remains outside the patient's body, thereby reducing many toxicological concerns. The risk of significant direct environmental exposure is also low as those nanomaterials that are utilised are embedded within the devices. At the disposal stage, potential environmental exposure and effects may occur through the air (incineration), soil (landfill) and water (sewage treatment).

Communication

Both patients and medical professionals are likely to welcome the availability of novel POC diagnostic devices and the prospect of fast, accurate diagnoses without the delay currently incurred through centralised laboratory based procedures. However, not all clinical diagnoses are likely to lend themselves to POC delivery at present and, even where POC diagnosis is used, there may be a necessity to carry out detailed follow-up tests in specialised laboratories. The increasing use of POC diagnostic devices will have important consequences for the way healthcare is delivered and for training needs of users. Communication should address current scientific developments and applications, and focus on the benefits to patients and potential cost-savings in the health-

care system, whilst acknowledging that there are potential impacts on the organizational aspects of healthcare delivery.

EU Competitive Position

The EU is competitive in the field of POC diagnostics with representation both of multinational players and the emergence of specialised small and medium-sized companies, both of which benefit from the robust, but comparatively innovation-friendly, regulatory environment for these devices. However, the future attitude of healthcare systems towards the adoption of POC diagnostic devices, together with reimbursement policies will determine the further development of this industry.

Summary

- The potential for the development of nanotechnology-enabled POC diagnostic devices is high.
- Their increasing availability and use could have significant patient benefits and cost-saving implications for health services.
- There are important issues to be addressed in the areas of designing for new user groups, training, clinical responsibility and security of data.
- The potential EHS impact of nanoscale components should be assessed in conjunction to the development of the devices: risks could occur during manufacture and following disposal.

Further Information

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