



The Royal Academy  
of Engineering

UK Focus for Biomedical Engineering

# Personalised Medicine: the challenge for biomedical engineering

Policy Paper

June 2008

## **Executive summary**

Medicine in the 21<sup>st</sup> century should reduce the unit-cost of healthcare. Central to this aim is the delivery of early and effective care targeted to the particular needs and characteristic biomedical and demographic profile of the individual patient. The implied changes in models of care will be underpinned by significant scientific and engineering developments.

This report outlines key engineering challenges and recommends the following priority research areas for support:

- Translational research combining informatics, mathematics and engineering with clinical and biomedical sciences to map disease progression and response to therapy.
- Advances in multi-modal data fusion towards real-time integration of morphological, functional and molecular imaging, together with metabolic phenotyping as a precursor to public health interventions.
- Convergent platforms harnessing wireless technologies linked to intelligent software in the clinical environments and in the home.
- Decision support to ensure consistency of care and extending to novel approaches to patient information and self-care.

This report recognises the need for novel practices supported by new investment in biomedical engineering, and parallels the report 'Systems Biology: a vision for engineering and medicine' by the Academy of Medical Sciences and Royal Academy of Engineering, 2007<sup>1</sup>

## 1. Introduction

Advances in medical science, biomedical engineering and molecular biology, reinforced by social attitudes centred on consumer choice, point towards tailoring medical care to the specific needs of individual patients. The agenda of personalised medicine is further driven by growing economic, social and technological pressures, including:

- Cost of healthcare provision, for the ageing population and to better manage chronic diseases and cancer. This has generated a growing demand for ambulatory care, autonomous monitoring and control, and intelligent decision support for clinicians and patients alike.
- Litigation, which diminishes margins for human error thus spurring greater reliance on technological assistance.
- The accelerating pace of science and technology, which is opening up new and compelling possibilities for healthcare development with a concomitant growth in public expectations.

Personalised medicine is at the cusp of a very considerable worldwide market, where the UK is well placed to assume a position of leadership. Success in exploiting this industrial base will impact on the balance of trade with our main economic competitors. However, this success relies on more than advances in biomedical engineering alone, and also requires step changes in a broader context to remove current bottlenecks. The changes needed include:

- A more informed dialogue with the public on ethical issues, expanding on existing good practice<sup>2</sup> to obtain clear guidance on the balance between individual privacy and public good on such matters as post-market surveillance, access to data and tissue, informed consent and patient sovereignty regarding choice of treatment. This should extend to the regulatory and legal framework around specialist matters such as the development of so-called 'orphan medicines' whose effect is very significant but only for relatively small patient populations.
- Combating inherent conservatism in the medical and allied professions. This requires specific training to promote a better understanding of the technology already involved in advanced medical equipment together with an appreciation of its enabling potential to effect radical change in models of care.
- Better integrated health economics to support forward planning with an emphasis on preventive rather than curative practice, delivered through integrated care provision. Evaluation methods need to properly account for the cost-effectiveness of novel interventions ranging from pharmacogenetic studies to the benefits of ICT, as has been recognised elsewhere<sup>2 3</sup>. It has been noted that lack of evidence from rigorous evaluation of technology "has been used to hold back the provision of emerging technologies by those whose objective it is to contain costs"<sup>4</sup>.

- Better integration of healthcare technologies with each other and with clinical practice; this impacts on open standards for medical equipment and more standardised clinical protocols.
- More effective procurement practices to promote training and investment in the medical industry base from start-up companies upwards.

This briefing report reviews some of the engineering challenges that are expected to shape personalised medicine. These cut across disciplinary boundaries along three main themes:

- *Translational research in pharmacogenomics and systems biology*  
- necessary to harness fundamental models from pharmacogenomics and systems biology to derive clinical tools that are affordable and robust.
- *Convergent technologies in disease management*  
- the convergence of complementary modalities in medical instrumentation, around the management of specific pathologies.
- *Moving the point of care to the ambulatory patient*  
- the impact of rapid developments in ICT have the potential to move the point of care away from the hospital and increasingly towards the ambulatory patient.

## **2. Translational research in pharmacogenomics and systems biology**

Consider the case of a cancer patient possibly requiring aggressive adjuvant therapy. Current prognostic guidance based on clinical signs and immunohistochemistry leaves concerns about both over- and under-treatment, especially in patients with early stage disease. This places a focus on defining disease biology to complement, if not to replace, traditional histological measurements of cell differentiation. This has raised significant technical challenges in bioinformatics to achieve robustness in the identification of complex metabolic pathways from noisy measurements, which often exceed in number the maximum available sample size.

The interface between molecular biology, wet biology, clinical progression, informatics, mathematical sciences and machine learning is now a focal point of highly interdisciplinary research with high expectations for delivery of radical insights into disease progression. An example is the possibility that particular biological pathways cause tumours to metastasise very early in their development, simultaneously signalling to prevent metastatic growth. If even small tumours with this pathology are excised, this will activate the dormant micro-metastases leading to a generalised cancer within months of surgery. Detailed non-linear statistical analyses of prospectively acquired longitudinal data over long periods of follow-up has identified the presence of early, unexpected peaks, from which this hypothesis was generated and then tested in animal models<sup>5</sup>.

Current research aims to characterise these patients from large integrated data sets of clinical and bioinformatics data so as to identify the characteristic profile for a group of patients who may, in principle, be saved by carefully timed adjuvant

therapy. This example shows how the interface between advanced methods in different disciplines can challenge widely accepted models of care; in this case the possibility that tumour surgery may itself have deleterious effects. A further extension of this approach is to combine information from molecular biology, morphological and clinical measurements into an integrated, time-evolving, bio-profile to support screening for early onset of specific pathologies, perhaps while still pre-symptomatic. This framework is closely integrated with systems biology<sup>1</sup>. It has the potential for significant savings at a time when, for example, Alzheimer's disease may have initially developed more than five years before a clinical diagnosis is made in over than 50% of cases<sup>6</sup>.

More generally, recognition of the inadequacy of the genome sequence to fully explain the fundamental nature of many disease processes has intensified research on pathway networks to link gene expression with phenotypic outcomes. This requires exploration of both genetic predisposition and a wide range of environmental factors. Interactions between genes and age, ethnicity, diet, smoking and/or other life style effects impact significantly on general health and well being. This has been studied using metabonomics, which combines analytical tools such as NMR spectroscopy and mass spectrometry with multivariate statistical analysis to generate complex metabolic profiles of biofluids and tissues, with the aim of profiling the metabolic responses of key intermediary biochemical pathways<sup>7,8,9</sup>. Such analysis has been shown to be of considerable value in providing detailed information regarding the metabolic status of an organism, in characterising the metabolic phenotype of genetically modified organisms and in discerning and predicting a wide range of pathological conditions<sup>10</sup>. Moreover, this approach has proven value in assessing the efficacy of therapeutic interventions in animals and humans. In some cases, it is even possible to predict drug metabolism prognostically from a baseline metabolic profile<sup>11</sup>. Ultimately, this will enable targeted therapies to improve response rates, minimise adverse effects and reduce over-treatment.

In order to achieve a deeper understanding of the links between gene expression and metabolic perturbations, integrative studies linking gene expression and metabolite profiles at timed intervals are required, with a view to achieving a more holistic vision of biological processes at a whole systems level. Since MS and NMR spectroscopic analyses are relatively high throughput and low cost on a per-sample basis, they can be used to generate metabolic signatures to direct appropriate sampling points for genomic/proteomic analyses which are considerably more expensive in comparison. Examples of this integrative approach can be drawn from a number of fields including dysmetabolic syndrome and insulin resistance, pharmacology and toxicology, functional genomics, epidemiology and nutritional intervention.

A lot of information is already available on the variability of drug response (up to 30-fold), as well as side effects, yet the impact of this knowledge on day-to-day clinical practice has been almost negligible<sup>2</sup>. There is huge potential for savings in both research and routine clinical care arising from pre-selection of trial populations, more targeted therapy, systematic post-approval monitoring and even a more detailed modelling of patient compliance.

Furthermore, recent advances in analytical and bioinformatic technologies have enabled the adaptation of metabonomics to large-scale population screening, for example detecting prevalence of intake of analgesics and alcohol in the population at large. This raises the possibility of using metabolic phenotyping to inform public health interventions.

### **3. Convergent technologies in disease management**

The huge amount of data that is becoming available covering multiple facets of disease presentation, aetiology and progression, will place a key role on informatics for patient management and therapy choice, through equipment such as prognosis workstations integrating data from a variety of sources. For example, it will be necessary to combine biomedical imaging systems so that both morphological and functional information can be acquired. This would enable, for instance, the application of metabolic imaging for tumour delineation, which is of importance for identifying infiltrating strands which may not be apparent even during surgical excision.

Real-time imaging systems will be necessary to follow, guide and monitor therapeutic procedures such as radiotherapy, thermal therapy or targeted locally activated drug delivery. Molecular imaging will have a key role in targeted therapies by tracking biomarkers, e.g. by visualising mechanisms for perfusion to identify viability in cardiac disease and mechanisms of proliferation in cancer.

Wireless and nano technologies will be key drivers for patient monitoring both within and away from the hospital environment. Intelligent alarms at the bedside, for instance, could impact directly on quality and cost of intensive care, while care in the home is already a recognised priority area for healthcare.

The practical implications of these developments reach beyond technology and into clinical practice. For example, standardisation of data recording and treatment protocols is essential to reduce transcription errors and to minimise the occurrence of missing data. This is usually not missing at random since routinely collected data are typically conditioned on promoting audit compliance at an affordable cost, rather than designed to support knowledge discovery and decision support for clinicians. Despite this, no single healthcare centre, however large, can sustain idiosyncratic data. There are substantial opportunity costs arising from diverse clinical practices where multi-centre, prospective data acquisition may be feasible.

Decision support will have to resolve the mathematical challenges around fusion of multimodal data; together these make-up the individual's bioprofile. The health-related data it comprises should be distributed over time, points of care and pathological domains, comprising genetic markers through physiological measurements and clinical signs.

A further implication of this expansion and convergence of technological instruments of care is that the physician will need to understand more fully the various disciplines involved with reference to impact on patient care, and also to engage with an increasingly technical, automated and instrumented environment where powerful hardware merges with intelligent software. This will require

changes to current education methods and ways of working in multi-disciplinary teams.

#### **4. Moving the point of care to the ambulatory patient**

Continuing improvements in the effectiveness of medical care have introduced a shift in clinical need from acute to chronic disease. Patient-centric rather than disease-centric care will mean moving healthcare delivery away from the hospital or surgery and towards the patient, at their home or place of work.

Remote care, possibly enabled through telemedicine (whether for management of chronic diseases or to support early discharge from hospital), and self-care (including independent home-care for the aged), will be underpinned by further innovation in ICT, medical informatics and methods of artificial intelligence. An example would be models of total telecare and ambulatory care with automated dialogue between the instrumentation and the patient. Such autonomous processes can potentially reduce the level of direct intervention by the clinician, promoting adherence to therapy and protecting the patient by automatically sending alerts in the event of adverse incidents.

Greater involvement by the patient in making treatment choices is also an inevitable consequence of the emergence of the world-wide web. There are ethical issues about the nature of informed consent, relating to quality of publicly available information, level of detail, appropriateness of messages and relevance to the patient's individual condition and clinical need. Knowledge is recognised as a driver for 21<sup>st</sup> century medicine and is integral to the 'choice and voice' agenda<sup>12</sup>.

This report recognises information as a form of intervention together with a need for quality assurance, in a manner analogous to data cleaning by identifying sources of error, as well as increasing personalisation of information delivery. In essence, this amounts to a methodology for a voluntary regulation of sectors of the internet, to sit alongside quality marks and accreditation schemes already required for other types of electronic transactions with the public<sup>13</sup>.

More creative approaches are available for accessing more remote constituencies. Examples include; automatically generated medication reminders to reduce repeat admissions from involuntary lack of compliance with therapy regimens, the use of computer games to promote messages about sexual health and the use of mobile phones to engage diabetics in social networks where advantage is gained by better control of glucose levels<sup>14</sup>.

The substantial potential savings linked to these novel approaches extend to lifestyle interventions which can have surprisingly positive impact on long-term clinical outcomes. Consider a randomised controlled trial, examining percutaneous coronary intervention with stenting vs. a 12-month exercise prescription following routine coronary angiography. At the end of the 12 month period the minimal lumen diameter was significantly higher in patients who underwent the clinical procedure. However for patients with stable coronary artery disease, there was a markedly superior event-free survival rate for the exercise cohort. This is associated with lower costs owing to reduced re-hospitalisations and repeat re-

vascularisations<sup>15</sup>. The suggested explanation for this unexpected outcome is that coronary disease is symptomatic of systemic disease resulting in blockages elsewhere in the circulatory system, which are not addressed by stenting but are affected by exercise.

## 5. Conclusions

Medicine today is largely post-symptomatic and centrally delivered while, to remain sustainable, it will need to become more preventive, personalised and patient-centred. In the future, this is expected to change towards a pre-symptomatic and targeted treatment model. Addressing the engineering challenges of personalised medicine has implications for wholesale reviews of models of care and the balance between involvement of traditional care providers and self-care, just as it moves the treatment plan closer to the specific needs of the individual patient. It will require further innovation in interdisciplinary science drilling down to the level of genetic expression and phenotypes, integration of signals from different modalities in real-time, and a more creative exploitation of ICT.

The use of genomics and proteomics will increase so that the optimum therapy choice will take explicit account of the genetic make-up of the individual. This will require a greater degree of scientific development coupled with technological automation and integration to achieve total disease management through prediction, screening, diagnosis, guided surgery, treatment choice and monitoring. Demand for this level of personalisation is already pressing across the spectrum of health management, including lifestyle interventions, chronic diseases, critical illness, drug resistance and hospital acquired infections<sup>16</sup>.

It is important to recognise that the route from advances in biomedical science and engineering into clinical practice operates on different timescales across different service needs. The following gives an indication of the relevant timeframes:

- *Chronic and acute conditions*  
Examples in this report show innovative approaches to dosage control in different groups of chronic sufferers, for instance among young diabetics. It is possible in the short to medium term to develop more extensive, detailed and automated monitoring for a range of chronic conditions. Regenerative medicine (including stem cells and tissue engineering) also holds significant promise for using organ regeneration as a practical clinical intervention. This is relevant to diabetes, Alzheimer's disease, stroke, heart failure and spinal injuries. Skin and corneal implants, for example, have already developed into commercial products. Provided the blockages identified earlier in this report are addressed, large-scale direct healthcare benefits in these areas can accrue within as little as 5-10 years from now.
- *Ageing population*  
This is a priority because of both social needs and healthcare costs. Home-monitoring and biomechanical aids already exist but a new generation of devices with a greater degree of autonomous intelligence needs to be developed. These would play a proactive role in detecting early or sporadic

onset of functional impairment. With appropriate investment, gains in quality of life and reduction in secondary care interventions arising from preventive care could be made widely available within 10-15 years.

- *Cancer*  
Once again there are already some examples of highly effective targeted treatment, notably the impact of Herceptin in disease free survival among breast cancer sufferers who express the *cerbb2* mutation. However, the impact of pharmacogenetics has still a long way to go and the 'Personalised medicines: hopes and realities report' from the Royal Society<sup>2</sup> makes it clear that a realistic timescale for realising in full the potential of genetics<sup>17</sup> is likely to be in the range of 20-25 years.
- *Rare conditions and mutant diseases*  
These pose considerable challenges to clinical practice. Antibiotic development is needed to combat non-response to currently available drugs. New viruses threaten widespread infections which exact a high financial cost even when contained. There is considerable value in decision support for detection and treatment of rare conditions, there are equally strong barriers arising from low benefit-cost ratios for inherently small patient cohorts, and from pragmatic considerations (such as large-scale training) were this service available in primary care. Advice on adverse effects from interactions between medical compounds can be implemented in the short-term. However, comprehensive alerts for complex and rare medical conditions, and the pharmaceutical research needed to track new mutations and to eradicate sporadic infections on a large scale, will probably exceed a 25 year timescale.

## 6. Recommendations

Leadership in radically new models of healthcare delivery will become increasingly dependent on rapid advances in science, engineering and technology. While there already are significant interdisciplinary funding initiatives with a healthcare focus, this review has identified four priority areas:

- *Translational research*  
Metabolic phenotyping can form the basis for targeted large-scale lifestyle interventions as well as mapping disease progression and response to therapy. Moreover, identification of disease sub-types and elucidation of phenotypic pathways open the way to personalised therapy (including drug discovery), thus maximising treatment response and minimising adverse effects. There is a considerable way still to go in developing mathematical science and informatics for accurate and reliable modelling of these very large and complex biological networks.
- *Multi-modal data fusion*  
Integration of multiscale measurement has vast potential for delivery of decision support. This includes molecular biology, histology, electrophysiological measurement, morphological and functional imaging, clinical signs and indeed population based hospital episode statistics. It involves tailoring patient specific physiological models to clinical data and

extends to integration of electronic health records in large federated databases that are distributed yet reliable and secure. Further exploration of electromagnetic spectrum is also needed to devise novel, minimally invasive, analytical imaging modalities capable of operating a low cost.

- *Convergent platforms*

Ideally there would be inter-operability of clinical measurement platforms of different commercial sources, operating in different modalities and integration into workable data management systems with multimedia patient records. This requires wide-ranging research covering harmonised standards, reliable, efficient and effective wireless technologies, data fusion and information management with formal semantic ontologies, among others.

- *Decision support*

Objective measurement is needed in key areas of clinical management, including cytology. It is also recognised that best practice should be more consistent across healthcare providers. Failure reporting must become more systematic with systemic filters put in place using better decision support. Patient information should embrace the electronic age to cater for widely different levels of intended involvement in informed consent to treatment. This requires novel approaches to patient information. Considerable potential exists also for interactive models for self-care, in particular for younger age groups where chronic diseases can take a heavy toll. Furthermore, autonomous, privacy protecting activity monitoring can enable independent living to a later age, especially in the face of episodic need for health or social care support.

Finally, public engagement is crucial in enabling the development of pre-emptive medicine, which mitigates the need for high cost care. This is not just to ensure acceptance of novel forms of healthcare delivery, but also to expedite efficiency and effectiveness in design and deployment, especially as models of care evolve from curative to preventive and so from passive to participatory.

## **7. Acknowledgements**

Contributors to this report include Dr. E. Holme, Imperial College London, Dr. L. Fass, GE Healthcare and consortium members from the FP6 Network of Excellence Biopattern.

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May 2008

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