

**Personalised medicine for cancer: from molecular
signature to therapeutic choice**

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Summary

In the field of cancer medicine, great strides have been made in understanding the fundamental biology of cancers and impressive treatments have emerged resulting in markedly prolonged survival for many patients. These advances mean that cancer could well become a chronic disease within the next 20 years, but that promise depends on sustained investment in innovation in both diagnostics and therapies as well as society's willingness to pay for both.

The two great challenges facing cancer medicine in the future will be an understanding the biology of the very wide range of cancers affecting different organs and the increased prevalence of the disease that can be expected in an aging population. How will biomedical science and healthcare systems rise to these challenges? An understanding of the way in which advances have been applied in personalising treatments in the past points a way ahead to address future challenges.

Our cancer future will emerge from the interaction of four factors: the success of new technology, society's willingness to pay, future healthcare delivery systems and the financial mechanisms that underpin them. The only way to reduce the costs of cancer care is to ensure that the right patient gets the right treatment. Investing in sophisticated diagnostics is a clear imperative in making personalised medicine for cancer a reality.

Introduction

The age of the world's population is rising dramatically. This will increase the total burden of cancer with many patients living with considerable co-morbidity. At the same time new technology in many areas of medicine is bringing improvements to the quality and length of life. Major innovations in the following six areas are likely to have the greatest impact on cancer.

- molecularly targeted drugs with associated sophisticated diagnostic systems to personalise care
- biosensors to detect, monitor and correct abnormal physiology and to provide surrogate measurements of cancer risk
- our ability to modify the human genome through systemically administered novel targeted vectors
- the continued miniaturisation of surgical intervention through robotics, nanotechnology and precise imaging
- computer driven interactive devices to help with everyday living
- the use of virtual reality systems which together with novel mood control drugs will create an illusion of wellness

Over the last twenty years a huge amount of fine detail of the basic biological processes that become disturbed in cancer has been amassed. We now know the key elements of growth factor binding, signal transduction, gene transcription control, cell cycle checkpoints, apoptosis and angiogenesis (1). These have become fertile areas to hunt for rationally based anti-cancer drugs. This approach has already led to a record number novel compounds currently in trials. Indeed targeted drugs such as rituximab, trastuzumab, imatinib, erlotinib, lapatinib, bevacizumab and cetuximab are now all in widespread clinical use. Over the next decade there will clearly be a marked shift in the types of agents used in the systemic treatment of cancer.

Because we know the precise targets of these new agents, there will be a revolution in how we prescribe cancer therapy. Instead of defining drugs for use empirically and relatively ineffectively for different types of cancer, we will

identify a series of molecular lesions in tumour biopsies. Future patients will receive drugs that target these lesions directly. The human genome project provides a vast repository of comparative information about normal and malignant cells. The new therapies will be more selective, less toxic and be given for prolonged periods of time, in some cases for the rest of the patients' life. This will lead to a radical overhaul of how we provide cancer care (2).

A considerably increased investment in more sophisticated diagnostics is now urgently required. Holistic systems such as genomics, proteomics, metabolomics and methylomics provide fascinating clues as to where needles can be found in the haystack of disturbed growth. By developing simple, reproducible and cheap assays for specific biomarkers a battery of companion diagnostics will emerge (3). It is likely that for the next decade these will be firmly rooted in tissue pathology making today's histopathologist essential to move this exciting field forward. Ultimately the fusion of tissue analysis with imaging technologies may make virtual biopsies of any part of the body — normal and diseased a real possibility (4).

Individual cancer risk assessment will lead to tailored prevention messages and a specific screening programme to pick up early cancer and have far reaching public health consequences. Cancer preventive drugs will be developed to reduce the risk of further genetic deterioration. The use of gene arrays to monitor serum for fragments of DNA containing defined mutations could ultimately develop into an implanted gene chip. When a significant mutation is detected, the chip would signal the holder's home computer and set in train a series of investigations based on the most likely type and site of the primary tumour.

There will be an increase in the total prevalence of cancer as a result of improved survival as well as change in cancer types to those such as prostate cancer with longer survival. This will create new challenges in terms of assessing risks of recurrence, designing care pathways, use of IT and improving access to services. There will be new opportunities for further targeting and development of existing therapies as experience grows with risk factors over the longer term. Careful monitoring of patient experiences could help in improving results. Cancer could soon be a long term management

issue for many patients where they enjoy a high quality of life even with a degree of chronic illness (5).

The funding of cancer care will become a significant problem (6). Already we are seeing inequity in access to the taxanes for breast and ovarian cancer and gemcitabine for lung and pancreatic cancer. These drugs are only palliative, adding just a few months to life. The emerging compounds are likely to be far more successful and their long term administration considerably more expensive. Increased consumerism in medicine will lead to increasingly informed and assertive patients seeking out novel therapies and bypassing traditional referral pathways through global information networks. It is likely that integrated molecular solutions for cancer will develop, but unless issues related to access are addressed, this will lead to far greater inequity than at present. Cost effectiveness analyses will be used to scrutinize novel diagnostic technology as well as therapies.

The past

The personalisation of cancer therapy is not new. The first recorded reference to cancer was in the Edwin Smith Papyrus of 3,000 BC where eight women with breast cancer are described. The writings of Hippocrates in 400 BC contain several descriptions of cancer in different sites. But our understanding of the disease really began in the 19th century with the advent of cellular pathology and the beginnings of modern surgery.

Successful treatment by radical surgery became possible in the later part of that century thanks to advances in anaesthetics and antiseptics. Radical surgery involved the removal of the tumour containing organ and its draining lymph nodes in one block. Halstead in Johns Hopkins was the main protagonist of the radical mastectomy, Wertheim the hysterectomy, Trotter the pharyngectomy and Miles the abdomino-perineal resection of the rectum. These diverse surgical procedures all followed the same principles. The 20th century ended with the conservation of organs by minimising the destruction caused by surgery and replacing it with radiotherapy and for some sites effective adjuvant therapy with drugs. The surgical staging of cancer was one of the first personalised approaches. It led to tailoring the aggression of surgery to the likely sites of spread of the disease. The development of

conservative breast surgery was based on logical stepwise clinical trials and has led to a revolution in the individualisation of surgery and adjuvant treatment based on tumour size, stage, grade and lymph node involvement. The advent of sentinel node biopsy as a surrogate for axillary involvement and the use of PCR technology to detect micrometastases in nodal biopsies represents a modern extension of this work. Gene expression studies are now being used to select patients for more aggressive adjuvant post surgical chemotherapy regimens based on the likely predicted natural history of their tumour for both breast and lung cancer.

Radiotherapy has come a long way since the first patient with a nasal tumour was treated in 1899, only a year after the discovery of radium by Marie Curie. Although radiobiology developed as a research discipline it has really contributed little to clinical practice. The rationale behind modern fractionated radiotherapy comes as much from empirical trial and error as from experimental results. Radiotherapy is remarkably successful for certain areas of the body. Increasing sophistication in equipment, coupled with dramatic strides in imaging have led to great precision in planning and execution of treatment so sparing critical normal tissues and increasing the dose to the tumour. Again the high dose volumes treated with radiotherapy are highly individualised based on structural anatomy of tumour and critically sensitive normal tissues. Less success has been achieved in tailoring the total radiation dose and fractionation. Molecular radiobiology has really had minimal impact on clinical practice so far but this could change dramatically over the next decade. It is unlikely that molecular signatures will have significant impact on the practice of radiotherapy – which will eventually be used for fewer and fewer patients as systemic therapies become more successful.

The sinking of the US battleship John B Harvey in Bari harbour by the Germans in 1942 led to the development of effective chemotherapy. The warship was carrying canisters of mustard gas for use in chemical warfare. Survivors developed leucopenia and this led Goodman and others back in the US to experiment with halogenated alkylamines in patients with high white cell counts — lymphomas, leukaemias and Hodgkin's disease. From the first publication in 1946 the field has blossomed with over 200 drugs now available

in our global pharmacopoeia. But as with radiotherapy our clinical practice is based mainly on empiricism (7). Most currently used drugs were found serendipitously from plants or fungi — taxol, vincristine, doxorubicin — and not by rational drug design. Although very successfully used in combination for lymphoma, leukaemia, choriocarcinoma, testicular cancer and several childhood cancers, results in metastatic common solid tumours have been disappointing with little more than palliative benefit (Figure 1). The advent of molecularly targeted drugs promises to change this dramatically.

The future

Within 20 years cancer will be considered a chronic disease, joining conditions such as diabetes, heart disease and asthma. These conditions impact on the way people live but will not inexorably lead to death. The model of prostate cancer, where many men die with it rather than from it, will be more usual. Progress will be made in preventing cancers. Even greater progress will be made in understanding the myriad causes of cancer. Our concepts will be different to today's, and the new ways in which cancer will be detected, diagnosed and treated will be crucial to understanding the future.

When a cancer does develop, refinements of current technologies and techniques — in imaging, radiotherapy and surgery — together with the availability of targeted drugs will make it controllable. Cure will still be sought, but will not be the only satisfactory outcome. Patients will be closely monitored after treatment, but fear that cancer will definitely kill, still prevalent in the early years of the twenty-first century, will be replaced by an acceptance that many forms of cancer are a consequence of old age.

Looking into the future is fraught with difficulties. Who could have imagined in the 1980s the impact of mobile phones, the internet and low-cost airlines on global communication? Medicine will be overtaken by similarly unexpected step changes in innovation. For this reason, economic analysis of the impact of developments in cancer care is difficult. The greatest benefit will be achieved simply by assuring that the best care possible is on offer to the most patients. This would be irrespective of their socio-economic circumstances and of any scientific developments. But this is unrealistic. Technologies are developing fast, particularly in imaging and the exploitation of the human

genome. Well-informed patients, with adequate funds, will ensure that they have rapid access to the newest and the best — wherever it is in the world. More patients will benefit from better diagnosis and newer treatments, with greater emphasis on quality of life (8). Innovation will bring more inequality to health if the parties do not work together to ensure they address the challenges of access. The outcome of the same quality of care differs today between socio-economic groups and will continue to do so.

Clinicians in Europe will continue to be dependent on technologies primarily designed for the major health market in the world — the United States which currently consumes nearly 55% of cancer medication but contains less than 5% of the population. European legislation covering clinical trials could bring research in the UK to a grinding halt, while ethicists — zealously interpreting privacy legislation — could impose restrictions on the use of tissue. Targeted niche drugs will be less appealing to industry as the costs of bringing each new generation of drugs to market will not be matched by the returns from current blockbusters. The delivery of innovation will be underpinned by patient expectation. The well-informed will be equal partners in deciding the health care they will receive. Much of it will take place close to their homes using mechanisms devised by innovative service providers (9).

This has huge implications for the training of health professionals and the demarcations between specialties. Emerging technologies will drive the change. Intra-professional boundaries will blur — doctors from traditionally quite distinct specialties may find themselves doing the same job. And clinical responsibilities will be taken up by health professionals who will not be medically qualified. All professionals are likely to find challenges to their territory hard to accept. Table 1 shows the challenges that need to be addressed in order to deliver most health benefit.

Table 1: The challenges of cancer care

Increasing the focus on prevention.
Improving screening and diagnosis and the impact of this on treatment.
New targeted treatments — how effective and affordable will they be?
How patients and their carers' expectations will translate into care delivery
Reconfiguration of health services to deliver optimal care
The impact of reconfiguration on professional territories
Will society accept the financial burden of these opportunities?

Prevention and screening

At the beginning of the 21st century 10 million people in the world develop cancer each year (10). The cause of these cancers is known in roughly 75 per cent of cases: 3 million are tobacco-related; 3 million are a result of diet; and 1.5 million are caused by infection. In the UK, 120,000 people die from cancer each year, even though many are preventable — with a third related to smoking. But cancer prevention absorbs only 2 per cent of the total funding of cancer care and research. Anti-smoking initiatives are considered to be successful — although it has taken 50 years from the time the association between smoking and cancer was first identified. In the 1960s, 80 per cent of the population smoked; by 2005 the average was under 30 per cent. This masks real health inequality — the percentage of smokers in the higher socio-economic classes are in low single figures, while the percentage in the deprived is still about 50 per cent in parts of the country. Despite the known risks, if friends and family smoked and there was no social pressure to stop, there was no incentive. Banning smoking in public places will lead to a further drop of about 4 per cent. Increases in tax had been a powerful disincentive to smoke but the price of a packet of cigarettes is so high that smokers turn to the black market: as many as one in five cigarettes smoked is smuggled into the country. Lung cancer, for example, is a rare disease in higher socio-economic groups — it is a disease of poverty.

Lessons from anti-smoking initiatives will be instructive for prevention in the future. Although the link between poor diet, obesity and lack of exercise and cancer has not been confirmed, there is sufficient circumstantial evidence to suggest that strong associations will be found. There will be bans on advertising for crisps, sweets and soft drinks on television, the introduction of a health tax on these products and a ban on sponsorship of any public event by manufacturers of these products. By 2010, obesity among the middle classes will be socially unacceptable, but it will remain common among the economically disadvantaged. Creating meaningful, imaginative incentives for people to adopt healthy lifestyles will be a major challenge.

The future prevention picture will be coloured by post-genomic research. It is now accepted that about 100 genes are associated with the development of a whole range of cancers. The detection of polymorphisms in low penetrance cancer related genes — or a combination of changed genes — will identify people of increased risk. Within 20 years most people will be genetically mapped. The information —gained from a simple blood test — will be easily stored on a smart-card. Legislation will be required to prevent this information being used to determine an individual's future health status for mortgage, insurance and employment purposes. However, the process of mapping will reveal that every person who has been screened will carry a predisposition to certain diseases. People will learn to live with risk.

Today the average age of diagnosis of cancer in the UK is 68. Improvements in screening, detection and diagnosis will reduce this. A predisposition for some cancers, that manifests itself in a patient's 70s or 80s, will be found in young adult life and detected and corrected successfully in the patient's 30s. Increasing age will remain the strongest risk predictor. Little of what has been described is not happening already in some form but the computing power of the future will bring accurate calculation of risk and predictions will take place on an unimaginable scale. Screening programmes will be developed on a national basis if they are simple, robust and cheap. Patients will expect the screening to take place at a convenient venue for them — in shopping malls and not be painful or overly time-consuming. Health professionals will demand that any programme is accurate and does not give misleading

results, and governments will demand that its costs will lead to more effective use of other resources. Novel providers of risk assessment services are likely to emerge.

Table 2: Balancing cancer risk

Great health inequity exists in smoking related diseases
Novel prevention strategies are likely to lead to similar inequity
Creating meaningful incentives to reduce risk will be essential
Individually tailored messages will have greater power to change lifestyles
Biomarkers of risk will enhance the validation of cancer preventive drugs
Novel providers of risk assessment and correction will emerge

Detecting cancer

Cancers are fundamentally somatic genetic diseases that result from several causes: physical, viral, radiation and chemical damage. There are other processes implicated for example, chronic inflammatory change, immunosurveillance and failure of apoptosis. In the future, cancer will no longer be understood as a single entity — it will be considered to be a cellular process that changes over time. Many diseases labelled as cancer today will be renamed, as their development will not reflect the new paradigm. Patients will accept that cancer is not a single disease and increasingly understand it as a cellular process. Many more old people will have increased risk or a precancer. This has huge implications for cancer services. Today, most diagnoses of cancer depended on human interpretation of changes in cell structures seen down a microscope. Microscopes will be superseded by a new generation of scanners to detect molecular changes. These scanners will build up a picture of change over time, imaging cellular activity rather than just a single snapshot. We will have the ability to probe molecular events that are markers for early malignant change. This dynamic imaging will lead to more sensitive screening and treatments; imaging agents which accumulate in cells exhibiting tell-tale signs of precancer activity and will be used to introduce treatment agents directly (11).

Imaging and diagnosis will be minimally invasive and enable the selection of the best and most effective targeted treatment (Table 4). Even better imaging will be able to pick up pre-disease phases and deal with them at a stage long before they are currently detectable. These techniques will also be crucial in successful follow-up. A patient who has a predisposition to a certain cancer process will be monitored regularly and treatment offered when necessary. Not all cancers will be diagnosed in these earliest of stages — some patients will inevitably fall through the screening net. Nevertheless, there will be opportunities to offer less invasive treatment than at present. Surgery and radiotherapy will continue but in greatly modified form as a result of developments in imaging. Most significantly, surgery will become part of integrated care. Removal of tumours or even whole organs will remain necessary on occasion. However, the surgeon will be supported by 3-D imaging, by radio-labelling techniques to guide incisions and by robotic instruments. And although many of the new treatments made possible by improved imaging will be biologically driven, there will still be a role for radiotherapy — the most potent DNA damaging agent — to treat cancer with great geographical accuracy. The targeting of radiotherapy will be greatly enhanced enabling treatment to be more precise.

In addition to the reconfiguration and merging of the skills of clinicians, the delivery of care will also change. Minimally invasive treatments will reduce the need for long stays in hospital. As more patients are diagnosed with cancer, the need to provide the care close to where patients live will be both desirable and possible — and, as this report will show later — expected. The prospect of highly sophisticated scanning equipment and mobile surgical units being transported to where they are required is not unrealistic. Technicians, surgical assistants and nurses would provide the hands-on care, while technical support will be provided by the new breed of clinician — a disease-specific imaging specialist working from a remote site. Cost control will be an essential component of the diagnostic phase. Healthcare payers will create sophisticated systems to evaluate the economic benefits of innovative imaging and tissue analysis technology.

Table 3: Delivering new diagnostics for personalised therapy

Radiology and pathology will merge into cancer imaging
Dynamic imaging will create a changing image of biochemical abnormalities
Cancer will be detected prior to disease spread from primary site
Greater precision in surgery and radiotherapy will be used for precancer
Molecular signatures will determine treatment choice
Cost control will be essential for healthcare payers to avoid inefficient diagnostics

New treatment approaches

Future cancer care will be driven by the least invasive therapy consistent with long-term survival. Eradication, although still desirable, will no longer be the primary aim of treatment. Cancers will be identified earlier and the disease process regulated in a similar way to chronic diseases such as diabetes. Surgery and radiotherapy will still have a role but how much will depend on the type of cancer a patient has and the stage at which disease is identified. It will also depend on how well the drugs being developed today perform in the future.

Cancer treatment will be shaped by a new generation of drugs. What this new generation will look like will critically depend on the relative success of agents currently in development and the willingness to pay for innovation. Over the next three to five years, we will understand more fully what benefits compounds such as kinase inhibitors are likely to provide. It is estimated that there are about 500 drugs currently being tested in clinical trials. Of these, around 300 inhibit specific molecular targets (12). But this number is set to rise dramatically. 2,000 compounds will be available to enter clinical trials by 2007 and 5,000 by 2010. Many of these drug candidates will be directed at the same molecular targets and industry is racing to screen those most likely to make it through in the development process. Tremendous pressures are coming from the loss of patent protection from the majority of high-cost

chemotherapy drugs by 2008. Unless new premium-priced innovative drugs are available cancer drug provision will come from global generic manufacturers currently gearing up for this change.

So what will these drug candidates look like? Small molecules are the main focus of current research — most of which are designed to target specific gene products that control the biological processes associated with cancer such as signal transduction, angiogenesis, cell cycle control, apoptosis, inflammation, invasion and differentiation. Treatment strategies involving monoclonal antibodies, cancer vaccines and gene therapy are also being explored. Although we do not know exactly what these targeted agents will look like there is growing confidence that they will work. More uncertain is their overall efficacy at prolonging survival. Many could just be expensive palliatives. In future advances will be driven by a better biological understanding of the disease process (Figure 2).

Already we are seeing the emergence of drugs targeted at a molecular level — trastuzumab, directed at the HER2 protein, imatinib which targets the Bcr-Abl tyrosine kinase, and gefitinib and erlotinib, directed at EGFR tyrosine kinase. These therapies will be used across a range of cancers. What will be important in future is whether a person's cancer has particular biological or genetic characteristics. Traditional categories will continue to be broken down and genetic profiling will enable treatment to be targeted at the right patients. Patients will understand that treatment options are dependent on their genetic profile. The risks and benefits of treatment will be much more predictable than today.

Table 4: Drivers of molecular therapeutics

HGP and bioinformatics
Expression vectors for target production
<i>In silico</i> drug design
Robotic high throughput screening
Combinatorial chemistry
Platform approach to drug discovery
Huge increase in number of molecular targets

Therapies will emerge through our knowledge of the human genome and the use of sophisticated bioinformatics. Targeted imaging agents will be used to deliver therapy at screening or diagnosis. Monitoring cancer patients will also change as technology allows the disease process to be tracked much more closely. Treatment strategies will reflect this and drug resistance will become much more predictable. Biomarkers will allow those treating people with cancer to measure if a drug is working on its target. If it is not, an alternative treatment strategy will be sought. Tumour regression will become less important as clinicians look for molecular patterns of disease and its short term response to novel agents. Eventually only those patients showing a validated surrogate response will continue with treatment so speeding up and increasing the statistical power of pivotal studies (Figure 3).

There will be more of a focus on therapies designed to prevent cancer. A tangible risk indicator and risk reducing therapy, along the lines of cholesterol and statins, would allow people to monitor their risk and intervene. Delivering treatment early in the disease process will also be possible because subtle changes in cellular activity will be detectable. This will lead to less aggressive treatment. The role of industry in the development of new therapies will continue to change. Smaller more specialised companies linked to universities, will increasingly deliver drug candidates and innovative diagnostics to 'Big Pharma' to develop and market.

People will be used to living with risk and will have much more knowledge about their propensity for disease. Programmes will enable people to determine their own predisposition to cancer. This in turn will encourage health-changing behaviour and will lead people to seek out information about the treatment options available to them. Patients will also be more involved in decision making as medicine becomes more personalised. Indeed, doctors may find themselves directed by well-informed patients. This, and an environment in which patients are able to demonstrate choice, will help drive innovation towards those who will benefit. However, inequity based on education, wealth and access will continue.

Table 5: The uncertainty of novel drugs for cancer

Will the new generation of small molecule kinase inhibitors really make a difference or just be expensive palliation?
How will big pharma cope with most high value cytotoxics becoming generic by 2008?
Can expensive late stage attrition really be avoided in cancer drug development?
How will sophisticated molecular diagnostic services be provided?
Will effective surrogates for cancer preventive agents emerge?
Will patient choice involve cost considerations in guiding therapy?

The development of personalised medicine

The era of molecularly personalised medicine for cancer has already begun. Herceptin can only work in erbB2 positive breast cancer. Similarly the humanised monoclonal antibody Rituximab can only bind to CD20 expressing lymphoma cells. Molecular phenotyping prior to drug use is now accepted clinical practice. But this is just the beginning. It is likely that increasing use of sophisticated diagnostics will revolutionise we use all our therapies. Figure 4 examines the six diagnostics needed for effective cancer care. Each is important for different parts of controlling cancer. To those involved in drug development the three most important are identifying

pharmacodynamic biomarkers, validating effective early surrogates of tumour response and the predictive reclassification of disease. This last diagnostic has two strands. Firstly, it can be used to predict the relative aggression of the disease so selecting patients for more intensive therapy and secondly it can be used to identify those patients who are likely to respond to a specific molecularly targeting agent. Figure 5 considers the likely impact versus the technological uncertainty behind them. So toxicity prediction is of low uncertainty as it is already available for some drugs but really of very little impact. Effective surrogates look less certain at the moment but would have a huge clinical impact. Figure 6 looks at two future scenarios over a 15 year timeframe – one conservative and one optimistic. Inevitably the real future will be somewhere in between – with some unpredicted step changes leading to greater successes than expected and some failures.

It is likely that the next decade will be focused on getting more information from smaller and smaller pieces of tumour tissue. Molecular histopathology will be the core discipline. Eventually developments in functional imaging and perhaps serum proteomics will drive non tissue based methods of obtaining the same information. The potential technologies are listed below.

- Genetics
- Genomics
- Proteomics
- Peptidomics
- Metabolomics
- Methylomics
- Acetylomics
- Integromics
- Histopathology
- Immunohistochemistry
- Serum markers

Each has its own start-up costs, running costs, throughput capacity, accuracy, potential for automation, data handling problems, drawbacks and of course utility. The holistic technologies such as gene expression analysis or proteomics generate huge amounts of raw data that need to be sifted for patterns. But the inter-sample variability can be massive leading to false conclusions. Furthermore promising observations using relatively small sample cohorts have a tendency to disappear as the sample size increases. Ultimately it is likely that the holistic approach using complex number crunching techniques will be superseded by precision assays for defined biochemical constituents just as in current clinical chemistry. Those biomarkers that can be used as early response surrogates will have huge value in reducing the costs of targeted therapy as drugs can be stopped in non – responding patients. It is likely that eventually biomarkers will be used at every stage on cancer from diagnosis to palliative care.

Table 6: The clinical use of biomarkers

Diagnosis of early disease including molecular precancer
Providing prognostic information to chose appropriate therapy
Identifying drug sensitivity so the right drug goes to the right patient
Early surrogate markers of tumour response
Monitoring quality of response
Monitoring effectiveness of adjuvant therapy
Monitoring chronic drug dosage
Monitoring length of drug administration

Barriers to innovation

Innovation in cancer treatment is inevitable (13): its nature and intensity critically influenced by the way innovation is rewarded. However, there are certain prerequisites for the introduction of new therapies. First, innovation has to be translated into usable therapies. These therapies must be deliverable, to the right biological target, and to the right patient in a way that

is acceptable by patient, healthcare professional and society. Innovation must also be marketed successfully so that professionals, patients and those picking up the cost understand the potential benefits. Those making the investment in research will inevitably create a market for innovation even if the benefits achieved are minimal. The explosion of new therapies in cancer care is going to continue and pricing of these drugs will remain high. The cost of cancer drugs in 2005 is estimated to be \$24bn globally, of which \$15bn is spent in the United States. If effective drugs emerge from the research and development pipeline, the cancer drug market could reach \$300bn globally by 2025, with this cost spreading more widely around the world (Figure 5).

But parallel to this explosion in therapies and increase in costs, a number of confounding factors will make markets smaller (14). The technology will be there to reveal which patients will not respond to therapy so making blockbuster drugs history. Doctors will know the precise stage of the disease process at which treatment is necessary. And as cancer transforms into a chronic disease, people will have more co-morbidities, which will bring associated drug-drug interactions and an increase in care requirements.

How do we balance this equation? The pharmaceutical companies will not necessarily want to do the studies to fragment their market. Research leading to rational rationing will need to be driven by the payers of health care. There is a risk that pharmaceutical companies will stop developing drugs for cancer and focus instead on therapeutic areas where there is less individual variation and therefore more scope for profit. Furthermore, development costs are rising. Ten years ago, the average cost of developing a new cancer drug was around \$400m. Now it is \$1bn. At this rate of growth, the cost of developing a new drug could soon reach \$2bn, an amount unsustainable in a shrinking market. With this in mind, the process of developing drugs needs to be made faster.

However, instead of research being made simpler, changes in legislation concerned with privacy and prior consent are making it more difficult. The EU Clinical Trials Directive will make quick hypothesis testing trials impossible. Other challenges exist, as well, such as obtaining consent for new uses of existing human tissue—following political anxiety when consent for removing

and storing tissues had not been obtained in the early years of the 21st century. However, surveys have shown that patients who gave consent for tissue to be used for one purpose were happy for it to be used for another. They do not wish to be reminded of their cancer years later. To overcome these constraints regulators will have to start accepting surrogate markers rather than clinical outcomes when approving therapies. Outcome studies may well move to post-registration surveillance of a drug's efficacy similar to cholesterol lowering agents today.

The rise of personalised medicine will mean the temptation to over-treat will disappear. Doctors and patients will know whether a particular treatment is justified. The evidence will be there to support their decisions. As a consequence of this, treatment failure — with all its associated costs — will be less common.

Table 7: Barriers to innovation

The drug industry will continue to compete for investment in a competitive, capitalist environment
Blockbuster drugs drive profit — niche products are unattractive in today's market
Personalised therapies are difficult for today's industry machine
Surrogate endpoints will be essential to register new drugs
Novel providers will emerge providing both diagnostic and therapy services
Payers will seek robust justification for the use of high cost agents

Patient's experience

Two separate developments will determine the patient's experience of cancer care in future. Increasing expectations of patients as consumers will lead health services to become much more responsive to the individual, in the way that other service industries have already become. Targeted approaches to diagnosis and treatment will individualise care. People will have higher personal expectations, be less deferential to professionals and more willing to

seek alternative care providers if dissatisfied. As a result, patients will be more involved in their care. They will take more responsibility for decisions rather than accepting a paternalistic “doctor knows best” approach. This will partly be fuelled by the internet and competitive provider systems. By 2025 the overwhelming majority of people in their 70s and 80s will be familiar with using the internet to access information through the massive computing power that they will carry personally (15).

With patients having access to so much health information, they will need someone to interpret the huge volumes available, helping them assess the risks and benefits as well as determining what is relevant to them. These patient brokers will be compassionate but independent advocates who will act as patients’ champions, guiding them through the system. They will be helped by intelligent algorithms to ensure patients understand screening and the implications of early diagnosis. They will spell out what genetic susceptibility means and guide patients through the treatment options. Patients and health professionals will have confidence in computer-aided decision making because they will have evidence that the programmes work.

How the service will be designed around patients’ needs and expectations will be determined by the improved treatments available and their individualisation. Care in the early stages will be provided near to where patients live. Even the most sophisticated diagnostic machinery or robotic surgeon will be mobile so much of this intervention will be carried out by technicians and nurses, with the most highly-trained professionals in audio-visual contact from a distant base. When cancer centres developed mid 20th century, the diseases were relatively rare, and survival was low. Although distressing for patients when they were referred to a centre, their existence concentrated expertise. Cancer will be commonly accepted chronic conditions that even when inpatient care is required, patients will be able to choose many places in the world where they will receive care at a “cancer hotel”. But for many patients even that option will not be necessary. Most new drugs will be given orally, so patients will be treated in their communities (16). However, this approach to cancer and other concomitant chronic conditions will place a huge burden on social services and families. Systems will be put in place to

manage the ongoing control of these diseases and conditions — psychologically as well as physically. Pain relief and the control of other symptoms associated with cancer treatment will be much improved.

Today, 70 per cent of the cancer budget is spent on care associated with the last six months of people's lives. Although many recognised that such treatment was more to do with the management of fear rather than the management of cancer, medical professionals have relatively few treatment options available and there was limited awareness of which patients would benefit. There is also an institutional reluctance to destroy patients' hopes that led to confusion between the limits of conventional medicines and reluctance to face the inevitable — by both patients and their families and doctors. There is a widespread perception that if patients were continuing to be offered anti-cancer treatment there was the possibility that their health might be restored.

With better treatments, consumers of services will be able to focus on quality of life. Much of the fear now associated with cancer will be mitigated. Demand for treatments with few side effects or lower toxicity will be high, even if there are only quite modest survival gains. The transition between active and palliative care is often sudden, but in future, because patients will be in much greater control of their situation, the change in gear will not be as apparent (17).

Table 8: Experiencing cancer in future

Patient brokers will guide people with cancer through the system
Choice will be real and will involve cost decisions
Patients will make a contribution to their care costs
Complementary therapies will be widely available and well regulated
Themed death chosen by patients will be possible

Conclusion

Cancer will become incidental to day to day living. Cancers will not necessarily be eradicated but that will not cause patients the anxiety that it does today. People will have far greater control over their medical destinies. Patients in all socio-economic groups will be better informed. In addition, surgery and chemotherapy will not be rationed on grounds of age since all interventions will be less damaging — psychologically as well as physically. Patients will want to know more about the likely progression of their cancer and how different treatments will affect it. We can already see the beginnings of patient empowered risk analysis using relatively crude, mainly clinical data driven programmes for the choice of adjuvant therapy after breast cancer surgery (www.adjuvantonline.com). Eventually this concept will apply to most clinical situations and be driven by far more sophisticated measurements of biomarkers in clinical samples and their changes following treatment.

How true this picture will be will depend on whether the technological innovations will emerge. Will people, for example, really live in smart houses where their televisions play a critical role in monitoring their health and well-being. It is also dependent on health care professionals working alongside each other, valuing the input of carers who, even more than today, will provide voluntary support because of the number of people in older age groups compared with those of working age. The reality for cancer care may be rather different. The ideal will exist for a minority of patients, but the majority may not have access to the full range of services. Old people, having been relatively poor all their lives, may suffer from cancer and a huge range of co-morbidities that will limit their quality of life. Looking after them all — rich and poor — will place great strains on younger people: will there be enough of them to provide the care? As with all health issues the question of access will be determined by cost and political will. In 2005 a cancer patient consumes about £25,000 worth of direct medical care costs with 70 per cent spent in the last six months of life. Conservatively, with patients living with cancer, rather than dying from it, and with access to new technologies this could reach £100,000 per patient per year by 2025. Figure 7 shows the current annual cost of currently marketed targeted therapies. In theory cancer

care could absorb an ever-increasing proportion of the health care budget. Would this be a reflection of what patients want? Probably "yes". Surveys reveal that three quarters of the population believed cancer care should be the NHS priority with no other disease area even a close second.

But to achieve that expenditure — and assuming that part of the health service will be funded from taxation — the tax rate might have to rise to 60 per cent. Inevitably, there will be conflicting demands on resources: the choice may be drugs or care costs. And how are the costs computed? Although the technology will be expensive, it will be used more judiciously since it will be better targeted. Another argument suggests that when patients are empowered they use less and fewer expensive medicines, in effect lowering the overall costs. An extension of that argument is that although costs will increase for treating each individual patient, the overall costs will decrease because more care will be delivered at home. But because people will live longer the life-time costs of cancer care will rise along with co-morbidity costs. Politicians will be faced with a real dilemma: if the prevalence of cancer increases, the cost of delivering innovative care could be massive. Will cancer care need to be rationed in a draconian way?

One dilemma for the future will be the political power of old people. More will be living longer and their chronic problems will not necessarily incapacitate them physically or mentally. This educated gerontocracy will have high expectations that will have been sharpened through the first two decades of the 21st century and they will not tolerate the standards of care now offered to many old people. They will wield considerable influence. Will a tax-based health system be able to fund their expectations? Politicians will have to consider the alignment between patients' requirements, and taxpayers' and voters' wishes. Figure 8 shows the four components of cancer's future — innovation, delivery, finances and society.

Whatever system is put in place there is the prospect of a major socio-economic division in cancer care. A small percentage of the elderly population will have made suitable provision for their retirement— both in terms of health and welfare, but the vast majority will not be properly prepared. Policy-makers need to start planning now as they are doing for the looming pensions crisis.

The most productive way forward is to start involving cancer patient and health advocacy groups in the debate, to ensure that difficult decisions are reached by consensus. Societal change will create new challenges in the provision of care. A decline in hierarchical religious structures, a reduction in family integrity through increasing divorce, greater international mobility and the increased selfishness of a consumer driven culture will leave many lonely and with no psychological crutch to lean on at the onset of serious illness. There will be a global shortage of carers — the unskilled, low paid but essential component of any health delivery system. The richer parts of the world are now harnessing this from the poorer but eventually the supply of this precious human capital will evaporate.

New financial structures will emerge with novel consortia from the pharmaceutical, financial and healthcare sectors enabling people to buy into the level of care they wish to pay for. Cancer, cardiovascular disease and dementia will be controlled and join today's list of chronic diseases such as diabetes, asthma and hypertension. Hospitals will become attractive health hotels run by competing private sector providers. Global franchises will provide speciality therapies through these structures similar to the internationally branded shops in today's malls. Governments will have long ceased to deliver care. Britain's NHS, one of the last centralised systems to disappear, will convert to UK Health — a regulator and safety net insurer by the end of this decade.

This vision presents huge financial challenges for all societies – rich and poor. The only way to reduce cancer care costs will be to ensure that expensive medicines are only given to patients who are predicted to really benefit from them and to confirm their response as soon as possible. Molecular signatures to guide therapy choice will be sought after by those paying for care. Over 55% of cancer drugs are sold in the USA which houses less than 5% of the world's population. It is significant that the Food and Drug Administration, the National Cancer Institute have this year teamed up with the Centre for Medicare Services to form the Oncology Biomarker Quantification Initiative (OBQI). Regulator, researcher and payor are working together for the first time to reduce the overall costs by the development of novel strategies for

patient selection. This suggests the death knell of the blockbuster approach to cancer drugs with its multimillion dollar advertising and marketing strategy.

The ability of technology to improve cancer care is assured. But this will come at a price — the direct costs of providing it and the costs of looking after the increasingly elderly population it will produce. We will eventually simply run out of things to die from. New ethical and moral dilemmas will arise as we seek the holy grail of compressed morbidity. Living long and dying fast will become the mantra of 21st century medicine.

Figure legends

1. Chemotherapy for advanced cancer. There are three groups of cancer. The first is frequently cured by drugs with a high complete response (CR); the second where although there is a high CR but most patients relapse with resistant disease and a third group where CR is rare. 5% of cancer patients are in the first group, 40% in the second and 55% in the third.
2. Predicted New Drug Application dates for molecular therapies in the USA. The years 2005-2010 will see an explosion of novel therapies coming into clinical use outside the research setting. The costs to healthcare payors will be huge unless better methods can be developed to select the correct drugs for the correct patients.
3. The future of cancer drug development. Drugs will enter patients for the first time accompanied by effective biomarkers. These will be used to choose the maximum effective dose (MED). They will also be used to identify surrogate markers of response so selecting patients early in pivotal studies to either continue or stop a specific trial. This will enhance the speed and statistical power of pivotal studies. In addition continued laboratory research will be used to create diagnostic kits to identify signatures of response.
4. Cancer diagnostics for personalised medicine. There are six areas where diagnostics will be helpful in personalising cancer medicine.
5. The impact of cancer diagnostics versus their relative uncertainty over a 20 year horizon. Personalised medicine has the highest impact and will almost certainly be in routine practice by 2020.
6. A pessimistic and optimistic prediction for cancer diagnostics in 2020. The baseline predictions are for little real change. Given the current efforts in this area this seems unlikely.
7. The high annual costs of molecularly targeted drugs. Included here are the costs of administration and its supervision. As cancer therapy becomes more successful the prevalence of the disease will increase further increasing its overall cost.
8. The four building blocks of cancer's future — innovation, society, delivery and finances. Cancer is predominantly a disease of retired relatively

low taxpayers so putting the financial burden increasingly on younger people in society. If costs escalate then at some point resistance will come.

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