

Personalised Medicine: is it an Oil-Rush or Oil-Spill?

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1 Introduction and Background

Personalised medicine, also known as 'precision' or 'stratified' medicine, targets treatment by using genetics and/or biomarkers to identify patients or subgroups of patients who have distinct mechanisms of disease or who may respond to treatment in a particular way. The goal is to provide more effective care, which potentially not only benefits the patient but also improves the efficiency of the healthcare system. This comes at the cost of adapting the regulatory environment so it is fit for purpose, and raising some difficult issues with product pricing.

This more tailored approach is producing important changes in drug development, regulation and use. Mullard (2020; see Figure 1) suggests the growing importance of personalised medicine. The lighter blue portion of the bars are traditional chemical entities; the darker blue are biologics, and an increasing proportion of those are personalised medicines. By 2019, more than 260 drugs approved by the FDA included genomic information in the official labelling for use (Mehta, 2020).

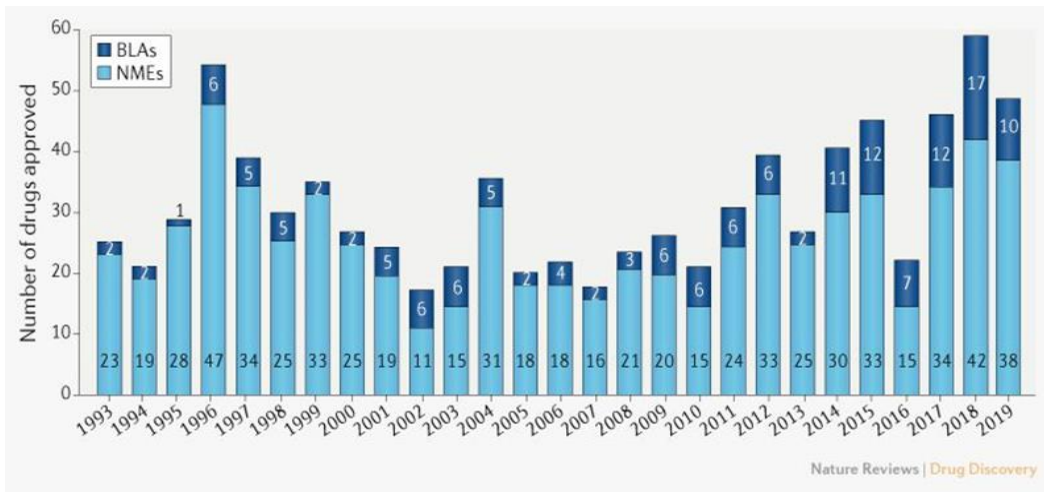


FIGURE 1. YEARLY APPROVALS OF NMEs AND BLAs BY THE FDA, 1993-2019

Source: Mullard, 2020

Developing treatment based on aspects of genomics means that the target populations are better defined and usually smaller. To realize a return on the cost of Research and Development (R&D), drug prices tend to be higher for these niche markets than for traditional medicines. Many personalised medicine drugs qualify as ‘orphan’ drugs, making them eligible for special treatment under legislation in most of the developed world, including expedited review of licencing applications and possibly longer patent life and/or marketing exclusivity. The growing number of orphan product designations in the EU since 2000 is shown in Figure 2 (Copenhagen Economics, 2018). Assuming that a substantial proportion of these are targeted, genomic-based products, the change that is occurring as a result of this focus is clear. Statistics are similar for the USA.

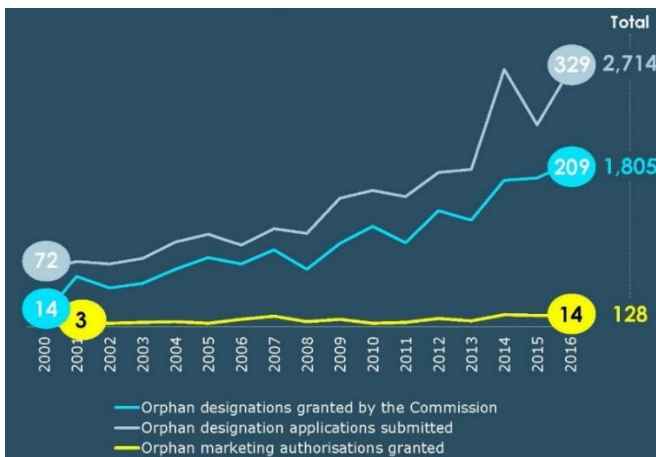


FIGURE 2. NUMBER OF EU APPLICATIONS FOR ORPHAN DESIGNATION SUBMITTED AND GRANTED, AS WELL AS NUMBER OF ORPHAN MARKETING AUTHORISATIONS GRANTED, 2000-2016

Source: Copenhagen Economics, 2018, p. 60.

The greater number of drugs being developed under orphan status may be affecting trends in development time. Figure 3 (Copenhagen Economics, 2018) tracks the time from the first patent anywhere in the EU to the first marketing authorisation anywhere in the EU for the decade 1996–2016. Although several factors contribute to development time – including changes in the review process itself – average development time appears to be decreasing. This may be due at least in part to faster reviews under the orphan product designation.

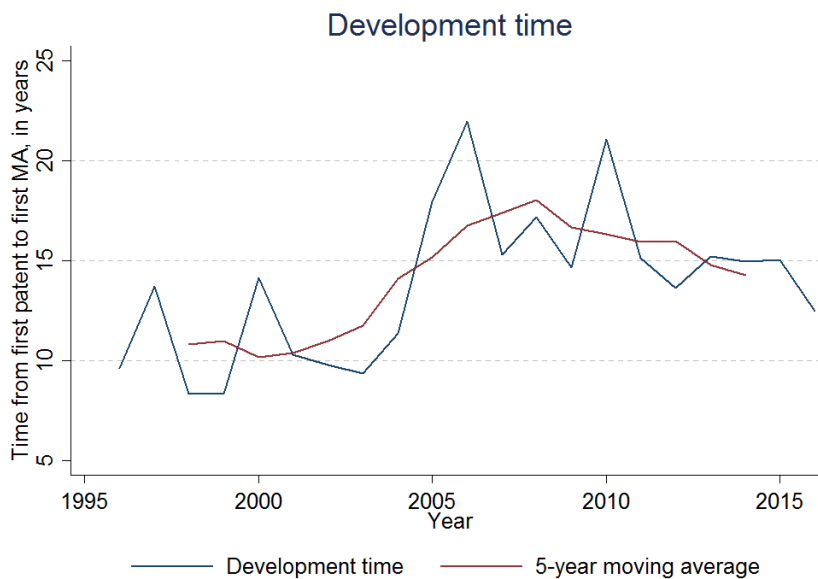


FIGURE 3. AVERAGE TIME FROM PATENT TO MARKETING AUTHORISATION IN THE EU, 1996-2016

Source: Copenhagen Economics, 2018, p. 66.

The effect of regulation on total development time is an important consideration. Recent research has demonstrated that increases in regulation do increase the time required for a drug to receive marketing approval. Introduction to the market is affected by other variables, such as price regulation and competition, but the effect of drug approval regulation has been shown as an independent influence that lengthens time to market (Costa-Font, McGuire and Varol, 2015; Cockburn, Lanjouw and Schankerman, 2016). The latter study did demonstrate that strong patent protection can help mitigate the effect. However, the patent clock is ticking during development and a stringent regulatory process can seriously erode patent protection. Figure 4 (Copenhagen Economics, 2018) suggests that patent protection continues to decline in the EU, a trend observable worldwide.



FIGURE 4. AVERAGE EFFECTIVE PATIENT PROTECTION AFTER MARKETING IN THE EU, 1996-2016

Source: Copenhagen Economics, 2018, p. 73.

The length of effective patent protection, or market exclusivity, is important because incentives for R&D will decline if innovators believe that the period of exclusivity will be insufficient to recoup enough of their R&D costs to fund further innovation. R&D is an expensive endeavour. Researchers continue to disagree about just what the average cost is, or has been, but most would agree that it is nearly \$1 billion for most drugs, and considerably more than that for some, as the return for successful drugs covers the losses incurred when R&D fails to give rise to a marketable product. A portion of that cost is directly affected by regulation; again, researchers disagree on just what that proportion might be, but it is substantial.

2 The Effects of Personalised Medicine on Health Care and Economics

The human genome is made up of 23 chromosome pairs that contain DNA, arranged in the now-famous double helix structure. That structure of nucleotides contains information in two sets of paired bases. A 'locus' is a specific position of a DNA sequence on a pair of chromosomes. Genes are sequences of nucleotide base pairs that code RNA and proteins that regulate bodily structure and functions. Most genes are non-variant, i.e. part of being human, but others can vary and affect how the body behaves.

The rate of advance in understanding how genes may affect behaviour is remarkable. The human genome project provided a wealth of information about structure but understanding how genetic variation produces problems became possible only in the past decade. Genetic variation can be traced to two types of mutations. The first are simple mutations where a base pair is substituted with another base pair, creating a single nucleotide polymorphism (SNP). The second type of mutation is repeated segments of DNA, across segments, not just at the points where the base pairs come together. Most research to date has been focused on SNPs; technology for understanding repeat polymorphisms is still at an early stage but developing fast. Most interventions, moreover, currently work by blocking or disrupting the transmission of genetic information rather than by altering the genes themselves.



Being able to identify what sets off the transmission of information, or what alters genes to relay faulty information, is extremely complex. Some diseases are more complex than others, involving a greater number of genetic mutations and biologic intricacy. Common mutations, which might apply to large number of patients, explain a relatively small percentage of gene variations. To complicate matters further, non-protein coding mutations may regulate protein-coding genes. Seemingly unrelated 'peripheral' genes also may affect disease through cellular networks. This all means that genetic mutations rarely map clearly onto a disease, so discovering how to switch off or retarget or otherwise 'fix' genes is a difficult and daunting challenge.

Much of the research to date seeks to discover correlations between genetic information and disease response. Such correlations are not necessarily causal, so treatment based on such associations will not necessarily produce a cure. Such a treatment might not work at all in a large portion of the population with a particular genetic anomaly, although it might produce dramatic improvements in some patients. The average gain, then, might be small overall but highly important for a minority. As an example, ipilimumab was approved by the FDA in 2011 for the treatment of stage 4 melanoma. Although it increased life expectancy by a median of three months, some patients were cleared of the disease entirely — even at stage 4. The treatment unquestionably has an effect, then, but the effect varies substantially across the population.

Analysis of possible associations produces some interesting research. In a study published in 2011 (Beauchamp, et al.), the authors use the data from the Framingham epidemiological study of 8,500 individuals, using SNPs. The focus was on whether genetic structure somehow predicts educational ability. After adjusting for variable bias, the n was about 7,500 individuals. The study included a set of principal component analysis and linear regressions on educational outcomes: the outcome variable, educational attainment, was regressed against the independent variables, these independent variables being different correlates of this SNP information. Various analyses used some stratification of the population, for example across males and females, using hundreds of thousands of combinations of SNPs. The study did find some indicative statistical relationships, which may or may not be causal. Although such inductive studies may find associations, assuming causation is quite another question.

Indeed, in general the human genome project, which ran from about 1990 to 2003, created immense excitement with thousands of papers published on "mapping" the human genome. Some predicted that genetic variation would soon uncover associations with specific diseases and outcomes. Excessive enthusiasm, however, often produces correlations that are overstated, or just wrong. Ioannidis and Trikalinos (2007) evaluated meta-analyses of clinical studies of neuroleptic treatments and found a 'clear or possible excess' of statistical significance in six of eight large meta-analyses and in the wide domain of neuroleptic treatments. In other words, genomic research often was more wishful thinking than reliable science.

The first important success was ipilimumab, with 3.6 months improvement in overall median (not mean) survival and a 36 percent improvement in progression-free survival. Some patients clearly respond better than others and some remain disease free at 12 or 15 years. The active mechanism is known — blocking inhibitory signals mediated by CTLA4 molecules to allow enhanced T cell responses. Why this works in some patients and not others, however, is unclear.

HOW CLINICAL RESEARCH IS CHANGING

The new genetic based technology for finding treatments has had a far-ranging impact on R&D. Rather than identifying a target mechanism for a disease and designing a drug around that mechanism, personalised medicine based on genomics has generally adopted an inductive approach. Taking immuno-oncology as an example, the cellular responses produced by specific agents are analysed using statistical algorithms. The approach uses principal-component type models to examine correlations between large numbers of potentially predictive biomarkers and cellular responses. This involves, for example, examining SNPs across many proteins at one level



and many molecular structures at another to determine which combinations of proteins and molecules are affected by the specific monoclonal antibody (MAB) to produce an immuno-response that attacks cancer cells. It is, therefore, based on an identification of statistical correlations which may identify causal pathways. Of course, the correlations may not be reflective of causal effects.

If a significant immuno-response effect is found, the particular combination is then tested in a small number of patients. If the effect of the MAB is maintained in patients, then testing enters the R&D Phase II and, if results at this point are positive, the rest of the testing process may proceed under accelerated approval procedures. This shortens the review process and therefore the time required to gain marketing approval.

Clinical research is not quite the same for immuno-oncology agents as for traditional cancer therapies and a positive effect is somewhat open to interpretation. Responses to immuno-oncology agents are generally based on their effect on immune response, rather than the direct killing of cancer cells. Determining the extent of effect takes longer because the immuno-response takes some time, which means that either clinical trials must be longer or intermediate endpoints must be used. The process is further complicated because it can be difficult to assess response using standard measures of positive response – e.g. of tumour size, and patients respond differently, as noted above—some individuals may be responders, while some remain non-responders.

Tracking effectiveness over time also can be a challenge; progression-free survival may last for a time, then the cancer reappears. Surrogate markers, moreover, may not correlate well enough with actual clinical outcome. The complexity and uncertainty of monitoring and demonstrating positive effect is evident in the variation among regulatory agencies in accepted endpoints. Disagreement continues over what constitutes adequate tumour response and how to measure different levels of response. Another layer of complication is added when the same therapy is licenced for different indications with various outcomes.

Data analysis in clinical trials is also more complicated for MABs. In traditional clinical trials, data usually are analysed using proportional hazard models, which focus on treatment differences across control and intervention groups. An important purpose is to better define response in subpopulations. However, for some gene-based therapies, response is not necessarily proportional and a small number of responders may have long-lasting effects. A non-proportional response may mean that the cure effect increases over time, an outcome that can be known with certainty only if all patients are followed for a long time.

To use an actual therapy as an example, Kazandjian et al. (2016) compares overall survival for nivolumab and docetaxel for non-small-cell lung cancer (see Figure 5). Note that early on nivolumab is not as effective as docetaxel because it takes time for the immuno-response to have an effect, a common finding in this area. Graphs for progression-free survival for these treatments show a similar cross-over. What is clear is that response is not proportional, so traditional statistical analyses (based on proportional hazards) may not be appropriate and data must be collected out far enough to capture any true positive treatment effect.

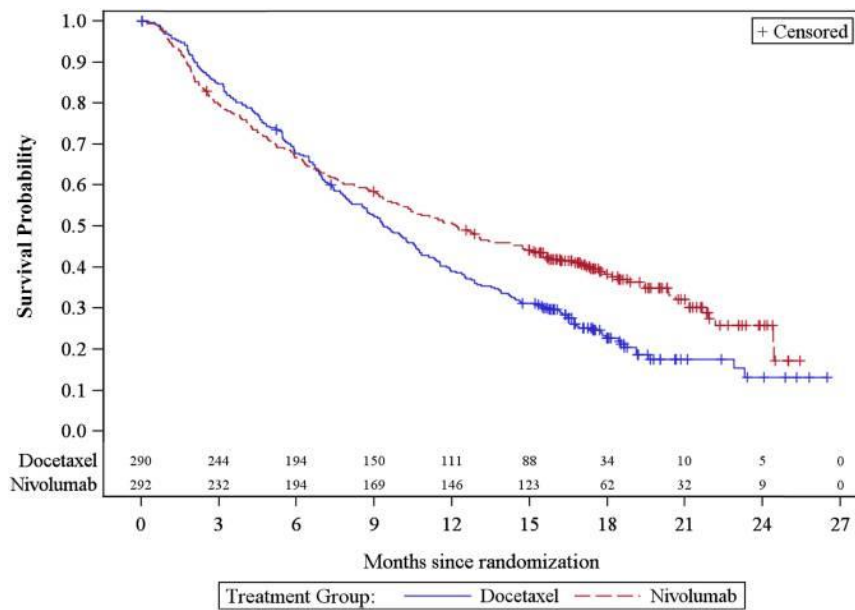


FIGURE 5. KAPLAN-MEIER SURVIVAL CURVES IN MONTHS

Source: Kazandjian et al. (2016)

Other analytical challenges are presented by this general statistical approach. For example, the appropriate “p-value” used to differentiate the effect in the treatment and control populations will be affected by the number of hypotheses that need to be tested in using SNP algorithms to identify response correlations. In clinical trials, proportional hazard tests usually employ a logrank test, similar to a chi-squared test versus expected values, to test for differences in survival curves. Multiple testing requires adjustment to such tests. Statistical approaches also have to account for the lag phenomenon. Developments in this area are relatively recent. One common adjustment is through the Karrison test, accepted as valid only in 2015, which seeks to display true positives when an effect is delayed. Trials also are changing as more therapies are being developed as combinations, which presents additional challenges in recommending dosage, timing and frequency of treatment.

Not surprising the effect-lag characteristic of MAB therapy substantially increases the cost of clinical trials if conventional approaches are implemented. This is one reason why trial design is changing, and target outcomes often are intermediate rather than final. Progression-free survival, for example, has again become an acceptable outcome for determining the value of a new therapy in the last decade; longer trials based on final clinical outcomes not only increase expense, but also can delay marketing and timeliness of access to important therapies. Other potential changes include adaptive trials design that allows the control group to change over time as the immuno-response changes, which in turn has implications for sample size calculations and trial cost.

THE ECONOMICS OF PERSONALISED MEDICINE

Personalised medicine can produce remarkable results, but the R&D process and the resulting products are costly. Some analyses suggest that returns to R&D expenditure are exceptionally high for MAB products, but that this primarily reflects high product prices (see Prasad and Mailankody, 2017).

Often, added to the cost of the therapy itself is the cost of diagnostic tests, which are important in determining how patients respond. Such tests can be crucial in improving both targeting and

outcomes. For example, in colon cancer, genetic testing has been used to identify likely true positive responders before treatment. This increases the proportion of those treated who benefit but adds the cost of a diagnostic test. The ability to target treatment also constrains potential market size and may discourage entrants into the market. Figure 6, taken from Berndt and Trusheim (2017), is a hypothetical case illustrating how a use of a diagnostic can affect treatment efficacy and market size. In this example of 100,000 patients, if you use all patients little information is gained, but as the testing cut-off is increased to include more and more responders the sensitivity of the test falls as the response increases and the specificity of the test increases. Of course, this is illustrative as the sensitivity and specificity of a test is not normally known *a priori*, but it shows how companion diagnostics leverages clinical efficacy.

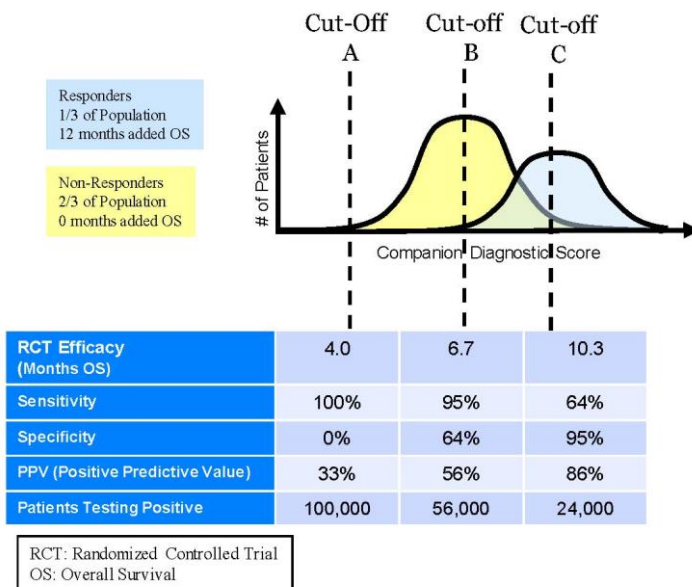


FIGURE 6. HOW COMPANION DIAGNOSTICS AFFECT OBSERVED EFFICACY

Source: Berndt and Trusheim (2017)

PRICING AND WHO PAYS

If price is a function of efficacy, different prices can be set for different 'bundles', i.e. test or treatment alone, or test and treatment together. If diagnostic testing is important for targeting, a key issue is who pays and how. The first step, of course, is to determine whether and in what instances diagnostic testing is worthwhile. This depends in part on sensitivity and specificity, i.e. how well a diagnostic test identifies responders and non-responders. Decisions become more difficult when diagnostic tests for MAB treatment of the same condition differ; results may or may not be comparable enough to clearly guide pricing.

The first entrant into the market will be at a disadvantage if pricing combines testing and treatment. It may be possible to separate testing from treatment and perhaps the health system should pay for testing since diagnostic screening and ongoing testing ensures better population targeting and more efficient care.

Further complications arise when the same therapy is used for different indications. Economists in this instance would argue for price discrimination, which allows markets to be served that might not be served otherwise. How to discriminate, however, is an issue when final outcomes are only achieved after a lengthy time so that surrogate endpoints become unavoidable – e.g. progression-free survival rather than overall survival. Overall survival can be modelled, but models are not necessarily more accurate than progression-free survival data. Other bases for differential pricing

might include disease prevalence or the proportion of responders to non-responders, but again data on these characteristics are rarely available.

Screening and testing are perhaps even more difficult to price discriminately. Some medical experts argue that family history is possibly a better predictor of response than diagnostic tests, at least for some inherited diseases. Given the cost of therapy for that example – over €1.5 million per annum for one MAB – knowing response probability clearly is important and likely worth the cost of diagnostic testing, at least for some potential patients.

Not all patients, however, will act on information gained from genetic screening. BRCA1/2 mutation carriers provide an example. The women who carry those genes have a considerably higher risk of breast and ovarian cancer, which can be eliminated through surgery. A study done in the northwest of England (Evans et al., 2009) reported the number of women who opted for surgery up to seven years after having been found to carry a BRCA mutation. Uptake was significantly related to lifetime risk and age, and decisions were made up to several years after initial diagnosis. The rate of surgeries was, however, only 40% for mastectomy and 45% for salpingo-oophorectomy. Counselling appeared to have some effect on decisions, increasing the likelihood of surgery. Risk tolerance, however, evidently also varied significantly across the sample.

The issue of identifiable responders presents a challenge to all types of insurance schemes that involve health. Insurance premiums are calculated on the probability of becoming ill multiplied by the average price of the treatment plus some loading factor. As the probability of becoming ill gets close to 100%, insurance collapses. Only public funding then remains as an option for covering costs.

The life insurance market provides an illustration of the impact of the availability of genetic testing on insurers. In Britain, insurers will not write a policy if the value of the policy is more than £500,000 and the individual seeking life insurance has Huntington disease. Huntington is one of the few diseases that can be pinpointed genetically. Applicants are asked about family history, of course, and those at risk may be required to be tested. For policies below £500,000, those that test positive for the gene are not excluded.

That diagnosis may change the proclivity to buy insurance has been demonstrated by research in the US; 4% of women with the BRCA1/2 mutation increased life insurance cover and none was denied coverage (Anderson et al., 2003). Genetic testing may also encourage some patients to purchase long-term care insurance. A study in the US found that Huntington disease patients, for example, were five times more likely to purchase long-term care insurance (Oster et al., 2010). The issue of access to insurance has prompted several countries to legally ban the use of genetic testing information in underwriting; countries without a ban may impose strict regulation.

With respect to the effect on health budgets, total costs are a combination of the size of the population at risk that is detected by a test, the test costs, the treatment cost, and the take-up, i.e. whether patients opt for treatment. Test cost can be quite important, depending on population size, i.e. the number of people screened. For rare conditions, when treatment cost is high, a low-cost test reduces budget impact by eliminating expensive treatment of no benefit, assuming test specificity is high. For a common condition, where treatment cost is high, but treatment take-up is low, even a low-cost test may not reduce treatment budget impact if no treatment results in high future (discounted) costs, even when test specificity is high. Regulators might find it useful to ask for information on diagnostic specificity and sensitivity, and about responders and non-responders. But even with better information, making treatment mandatory is unlikely.

Genetic testing raises equity concerns. Lower income individuals have lower rates of diagnostic testing and lower rates of treatment uptake. Targeting via diagnostic testing can increase demand among lower income groups, possibly beneficial for patients but also a potentially greater cost

burden. Genetic testing also may shift emphasis within health care, particularly when screening can identify potentially effective preventative measures.

3 Conclusions

Personalised medicine holds much promise, but it is a complicated undertaking and, at this point, still only a concept for most diseases. It has, and will continue to have, an important impact on the nature of scientific investigation, the nature of clinical trials, and the nature of drug regulation. The role of the public sector almost inevitably will increase. Screening on a large enough scale for more common diseases requires public sector involvement. Private insurance, under existing approaches, is ill suited to personalised medicine because of issues of potentially small numbers and adverse selection, which have important implications for risk spreading (the basis of all insurance cover).

Personalised medicine affects pricing because of the high cost of R&D and discussions will continue about the appropriate balance between private and public sector sponsorship. Pricing also is affected by the prospect of bundling diagnostics with treatment and the possibility of differential pricing. Volume, i.e. the treatment consumed, is affected by this bundling but unpredictably. Moreover, not everyone wants information about health status and even those who do may not seek treatment as a result, particularly if it requires difficult trade-offs between treatment and quality of life. The mix and provision of health care provision will be affected if personalised medicine can increase the effectiveness of prevention or offer real cures going forward.

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