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Keynote Lectures

Sustainability of personalised medicine*

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Resum. Per aconseguir l'equilibri econòmic, hi ha una equació molt bàsica que diu que els ingressos han de superar les despeses. Tot i que la crisi financera ha fet que la despesa en sanitat hagi caigut dràsticament des de l'any 2010, el consum públic dels recursos d'assistència sanitària continua creixent. L'única manera d'aconseguir l'equilibri és que la despesa en nous recursos quedi compensada per guanys futurs. Pot satisfer la medicina personalitzada aquesta necessitat? De moment, hi ha poques evidències que facin pensar que la medicina personalitzada reduirà els costos sanitaris pel fet de reduir els costos dels medicaments. En un escenari de medicina personalitzada per als propers anys, els ingressos seran, en el millor dels casos, neutres, mentre que les despeses per al diagnòstic i la prevenció augmentaran i el tractament tindrà, com a molt, un efecte neutral.

Paraules clau: medicina personalitzada · sostenibilitat · farmacogenètica · medicaments orfes · mecanismes de fixació dels preus dels medicaments

Summary. To achieve sustainability, there is a very basic equation that says that income has to be equal to or greater than expenditure. Despite the financial crisis, that lead expenditure in healthcare to fall sharply since 2010, consumption of healthcare resources continues to grow. The only way to achieve equilibrium is for expenditure on new resources to be balanced by future gains. But can personalised medicine meet this need? At the moment, there is little reason to think that personalised medicine will reduce healthcare costs by reducing drug costs. In a personalised medicine scenario, income will, at best, most likely be neutral in the coming years whereas expenditures for diagnostics and prevention will increase and treatment will, at best, have a neutral effect.

Keywords: personalised medicine · sustainability · pharmacogenetics · orphan drugs · drug pricing mechanisms

The current environment

The following are some thoughts that I would like to share on the sustainability of personalised medicine. I present my personal view because unfortunately there have been very few studies on this topic.

To achieve sustainability, there is a very basic equation that says that income has to be equal to or greater than expenditure. The same applies for a good or commodity in question, so that,

$$\text{Income} \geq \text{Expenditure} \quad \text{(eq. 1)}$$
$$\text{Income} \geq \text{Price} \times \text{Quantity} \quad \text{(eq. 2)}$$

If we look at the cost of sequencing a complete genome, we see that it is steadily decreasing. According to Moore's Law, which describes the trend of a computer processor doubling in complexity, generally translating into greater practical computing performance every two years accompanied by a decrease in cost, then sequencing costs (which depend to a great extent on computer hardware, computational tools, and other technological developments) should likewise progressively become much lower (Fig.1) [4]. The Google-launched initiative 23andMe, Inc., for example, has reduced the cost of sequencing an entire human genome from US$299 in 2012, to just US$99 in 2013. Thus, with regard to equation 2, price is no longer the limiting factor; instead, it will soon be quantity.

According to the OECD, while health spending grew, on average, close to 5 % from 2000 to 2009, expenditures in healthcare fell sharply in 2010 and remained flat in OECD countries in 2011 as the economic crisis continued to have a particularly strong impact in those European counties hardest hit by it (Fig. 2). But if we look at the standardised units of parity purchasing power, standardised to US$ to facilitate international comparisons, we

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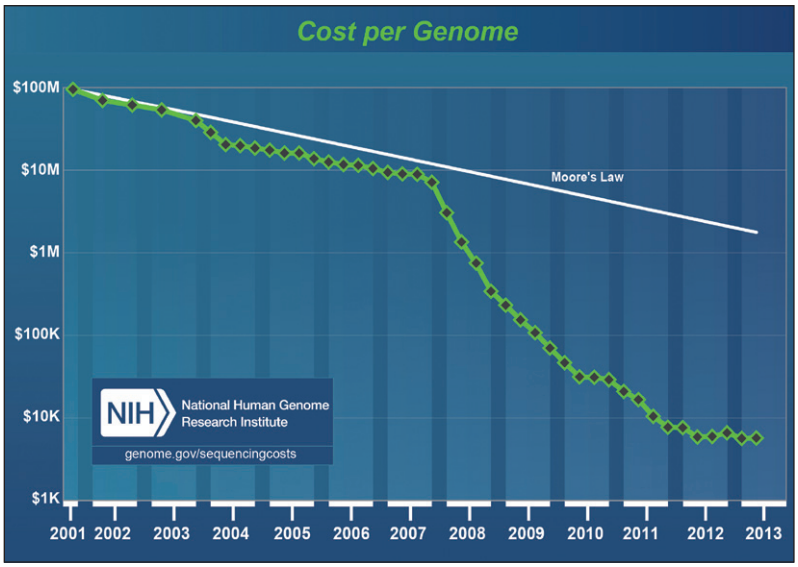

Fig. 1. Cost of sequencing a human-sized genome and hypothetical data reflecting Moore's Law. The costs include: labour, sequencing equipment, IT activities related to sequence production, shotgun library construction, and indirect costs. There is a profound outpace of Moore's Law in 2008 when sequencing centres transitioned to 'second-/next-generation' DNA sequencing technologies. Source: National Human Genome Research Institute [4].

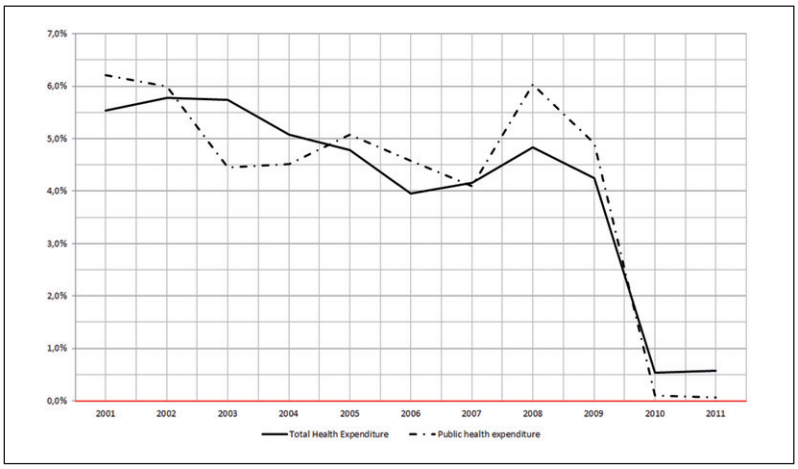

Fig. 2. Average OECD health expenditure growth rates in real terms, 2000–2011, public and total. Source: OECD Health Data 2013 [5].

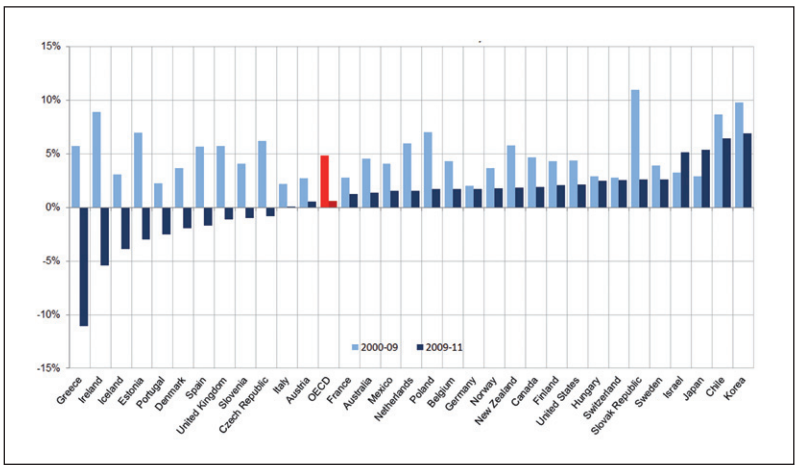

Fig. 3. Average annual growth in health spending across OECD countries in real terms, 2000–2011. Source: OECD Health Data 2013, [5].

see that healthcare expenditures have actually increased in recent years (Fig. 3). In other words, despite the financial crisis, consumption of healthcare resources is growing. If this has a real impact on resource availability, then the only way to achieve equilibrium is for expenditures on new resources to be balanced by future gains. But can personalised medicine meet this need?

$$\text{Income} \geq \text{Price} \times (\text{increased cost of new technology} - \text{future savings}) \quad \text{(eq. 3)}$$

Market size forecast: the supply side

If we look at the supply side and try to assess the size of the market, it becomes immediately clear that the numbers for the core of P4 medicine (personalised, preventive, predictive, and participatory medicine), i.e., personalised medical care, nutrition and wellness, are very, very large. Moreover, the 2015 predictions for this market are even larger (Fig. 4). The figure for the market size in 2012 is approximately U$208 billion [7]. But we have to con-

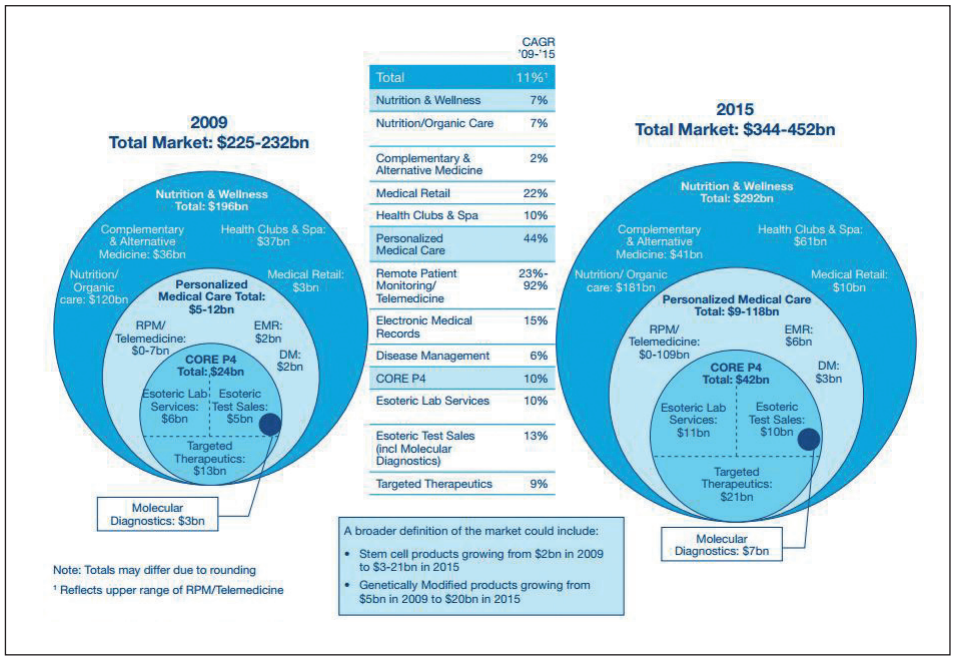

Fig. 4. Personalised medicine market size, 2009 and 2015. Source: PricewaterhouseCoopers analysis [7].

sider that much of this sum includes mergers and acquisitions, infrastructure construction for personalised medicine (new labs, and the hiring of skilled staff), with a far smaller amount devoted to drug costs and direct healthcare provision.

Pharmacogenetics and public expenditure on drugs

A look at the phamacogenetics aspect of personalised medicine, the equivalent of its Holy Grail, quickly shows that: (i) there are many diseases for which a particular drug is ineffective (Table 1) and (ii) there are many diseases that have a genetic component, reflecting genetic mutations that may be targetable by specific drugs. These observations provide the scientific rationale underlying the claim that personalised medicine can lower drug costs. But we should also consider how drug prices are set: the smaller the target population, the higher the price.

Imagine a newly developed drug that will cure twice as many people or will cure the same number of people but only half of the population must be treated. There is no doubt that the price of that drug will be twice the current standard. Accordingly, there is little reason to think that personalised medicine will reduce healthcare costs by reducing drug costs. In this sense, we can learn a lot from the market for orphan drugs, i.e., drugs developed specifically to treat rare medical conditions (orphan diseases). The orphan drug market shares several features with personalised medicine. Moreover, substitution is not possible. In some diseases, treating a subpopulation responsive to the drug does not mean that other populations will not be treated, nor does it mean that whenever this drug fails—because it will still fail—other drugs will not be used, such that, ultimately, the drug armamentarium for certain diseases will expand. Finally, there is the J-curve effect on drug substitution, in which relatively efficient drugs are withdrawn to incorporate more effective (though less efficient)

Table 1. Average percentage of the patient population for which a particular drug is ineffective

Disease	Patient population for which a particular drug is ineffective (%)
Anti-depressants (SSRIs)	38
Asthma	40
Diabetes	43
Arthritis	50
Alzheimer's	70
Cancer	75

Source of data: [4].

ones, but since price is supposed to be proportional to volume, the overall drug costs increase.

In Spain, the healthcare drug bill has decreased since 2003, reflecting the targeting of drug prices. However, the prescription trend has remained unchanged or is even slightly higher than before. Thus, by replacing cheaper drugs for more expensive ones, the impact will be even greater. A good example of this is *Trastuzumab*, a drug that targets breast cancer with a particular genetic biomarker. But while the incidence of breast cancer has decreased over the last decade, the use of *Trastuzumab* has increased. Why this is so merits investigation.

As the European Science Foundation has stated, "[a] realistic expectation could thus be cost containment rather than reduction, along with improved public health and quality of life. In other words, personalised medicine might be reasonably expected to generate a more efficient, rational use of resources. A more realistic promise is thus an improved return on investment." [2]

Another important consideration on the supply side is market segmentation. Again, comparison with the orphan dis-

ease market is appropriate [6]. In the view of some pharmaceutical companies, the identification of a gene that determines some features of a disease defines a separate disease with very low incidence, which accordingly should benefit from the privileges granted orphan drugs. This strategy has been around for a few years, but its practice should be scrutinised. For example, atrial fibrillation is the most common cardiac arrhythmia. If, based on genetic findings, it were to qualify as an orphan disease, the impact on healthcare costs would be enormous. The same is true for chronic pulmonary disease, and the combined impact of these two diseases on healthcare costs would be insurmountable.

Market expectations and value

From the business side, the pharmaceutical industry has a huge stake in genetic diseases, but its business model is not affected by supply and demand. Take the example of Roche, which a few years ago sought to buy the genetic diagnostics firm Illumina. In 2010, the share price of Illumina had fallen significantly, but as rumours of the purchase circulated, the share value increased steeply and then continued to fluctuate. Meanwhile, the value of Roche's shares remained stable. While the investment was likely to be quite profitable, the gene diagnostics industry is very unstable. Indeed, in 2012, the value of genetics or genetics-based companies was either stable or decreased slightly. For the major players in the pharmaceutical industry, the value of the genetics market is not clear, but it is innovation-based and therefore potentially highly profitable down the road.

It is highly likely that most biotechnology companies will fail in the very short run, so their business model is largely based on rapid growth followed by the sale of the company. This demands that the company generates high short-term profits to guarantee its eventual sale. The figures for failure in the biotechnology business are illustrative: if failure is defined as liquidating all assets, with investors losing most or all of the money they invested in the company, then the failure rate for start-ups is 30–40 %; if failure is defined as the failure to see a return on investment, then the failure rate is 70–80 %; if failure is defined as the failure to meet projections, then the failure rate is a spectacular 90–95 %. The biotechnology bubble is expanding very fast, supported by enormous sums of money, but its burst seems inevitable.

Creating value: the demand side

On the demand side are the buyers, which basically means the various countries, as purchasers of healthcare products. As they say, beauty is in the eye of the beholder, and this is true for value as well. Value is subjective and related to individual willingness to pay a price that is more than the cost of production. Value is related to several factors: novelty, appropriateness, competitive advantage, dynamic capabilities, organizational knowledge, etc. Furthermore, buyers must have the knowledge to recognise the value of the object of interest. In the case of genetics-based and personalised medicine, the buyer has to be trained in its evaluation, despite the many uncertainties regarding the therapeutic impact on disease. Because basically buyers do not purchase genes, they purchase diseases and their treatment.

However, the major issue is that personalised medicine is, as defined by Pricewaterhouse Coopers, "a holistic, individual model of care that examines each individual's unique makeup and designs appropriate strategies for maintaining wellness and treating illness. " In most developed countries, we have been successful at building health systems that are not individual, but rather that are based on risk sharing. Individualised medicine goes against that idea, moving from the fundamental goal of population-based, public benefit to non-risk-sharing among individuals. This is an important consideration because there will be obvious consequences in the attempts to bridge this gap.

The main concerns of regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), are efficacy, quality, and safety, whereas those of purchasers, on the demand side, are related to a drug's efficacy, e.g., whether an appropriate adjustment on the supply side is needed to meet the health needs of citizens, or whether a comprehensive or reasonable range of

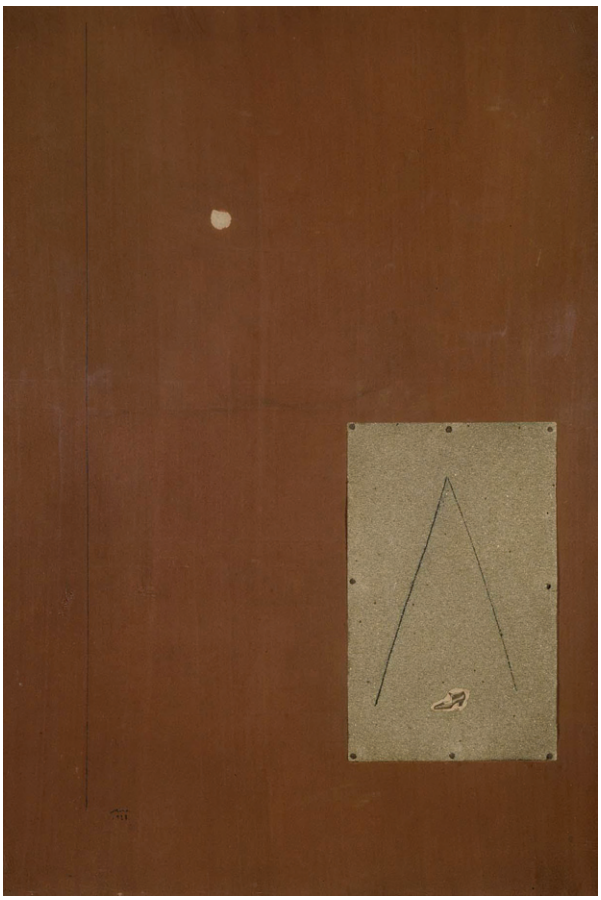

Fig. 5. Danseuse espagnole I (Spanish dancer I, 1928), by Joan Miró (Barcelona, Spain, 1893–Palma de Mallorca, Spain, 1983). Source: Reina Sofía National Art Museum, Madrid [http://www.museoreinasofia.es/en/collection/artwork/danseuse-espagnole-i-spanish-dancer-i].

services should be offered. Consider the painting by Joan Miró shown in Fig. 5. It is the minimal expression of a dancer, and a good reminder of the aim of public health: the minimum amount of healthcare provision that will achieve the appropriate level of care while taking into account opportunity cost, equity, and combinations thereof.

The health policy implications

Understanding the macroscopic (ethical, legal, and social) implications of genomic medicine requires an analysis of the ways in which genetic information and genetic approaches to disease affect people individually, both within their families and communities and in their social and working lives. Genomic medicine presents particular challenges to clinicians regarding their ethical and professional responsibilities [1]. At the microscopic level there are pharmacogenetics and pharmacogenomics implications, since patients vary in their drug responsiveness. Within a tumour, for example, some drug-targetable genes might be expressed and others not.

It is too soon to evaluate the link between personalised medicine and its impact on the population. In the word of Ioannidis, "[…] the ambitious enterprise of personalised medicine has to meet many challenges: a torrent of information with poor research and reporting standards, and a poor replication record; intrinsic difficulties in the predictive modelling; a lack of systematization; subtle effects of small magnitude; a disconnect between the science and its understanding by health practitioners and the general public; uncertainty even in the types of outcomes that we want to employ this information for, if at all; and even risks of causing more harm than good in some circumstances." [3]

So we return to the basic equation,

$$\text{income} \geq \text{price} * (\sum \text{diagnostic} + \text{prevention} + \text{treatment use}) \quad \text{(eq. 4)}$$

Should diagnosis, prevention, and treatment compensate for the expected increased costs? Whenever new diagnostic tools and treatments enter the market, there is an increase in the target population as new cases are detected, which implies higher diagnostic costs. Furthermore, in this newly discriminated population, we can ask: What is the cost of the new treatment? What is the cost of the side effects? What is the cost of the use of healthcare resources? The new diagnostic tools must also be incorporated into the payment system, as specified by the Diagnostic Related Group. Table 2 shows the comparative costs of different procedures related to colorectal cancer for Spain. The cost KRAS determination is a fifth of that of total colectomy. How can we incorporate the cost of that genetic test into our current system? In terms of diagnosis and prediction, if the genetic risk of every 20-year old in Spain (455,824 people as of October 2012) is determined, at US$99 per test [9], this comes to a total of approximately 40 million Euros per year. This is an unsustainable figure by itself, and does not even take into account the consequences of a positive test. Moreover, there are issues related to insurance, reimbursement, and population segmentation.

Table 2. Comparative cost of different procedures related to colorectal cancer diagnostic and treatment in Spain.

Procedure	Cost (€)
Total colonoscopy or ileoscopy, biopsy	210.89
Rectosigmoidoscopy, biopsy	84.36
Hemicolectomies by laparotomy	940.80
Total colectomy	1282.91
Complicated biopsy	86.38
Intraoperative biopsy	172.76
Simple biopsy, macro- and microscopic study	69.11
Detection of KRAS[a]	200.00

[a]A biomarker for colon cancer. Source of data: Nomenclator, Medical Association of Barcelona (COMB) [www.comb.cat].

How to adapt?

Current European Health Policy is based on redistribution. Personalised medicine may impose future difficulties in ensuring equity. For individuals at high risk, moral hazard tells us that they will overuse the system, whereas individuals at low risk will choose to opt out of the system, to avoid paying for the risk of others. This is a real threat to Bismarckian models (used in Germany, France, Belgium, and the Netherlands), in which the health insurance system is financed jointly by employers and employees through payroll deductions such that everyone is covered and profit-making is forbidden, and doctors and hospitals tend to be private. In this case, there would be a need to further redistribute risks. There would also be profound financial, legal, and ethical implications in: the use of genetics information, insurance de-linked to genetic testing, controlling the shift from private to public because of high risks/costs, profit-making, higher transaction costs incurred by private insurance to check risks, etc.

How can prices be controlled? Mostly through risk-sharing schemes, although the tools needed to assess outcomes are highly complex. The Velcade experience in the UK is an example of the very high transaction costs. Also, risk-sharing is not efficient without budget limits. It is much cheaper to incorporate uncertainty in the selling price: paying for performance within a disease group, for procedures, for capitation systems (should they include some form of redistribution), etc.? With the currently available technology, IT systems could be used to carry out observational studies and analyse potential phenotypic correlations. By gathering information on age, sex, place of residence, places visited, and other information that is already available, complex IT solutions can be applied to obtain a similar risk profile as that promised by genetic testing.

This is something that insurance companies are well aware of. So rather than engage in something for which there is no link between cost and consequence, there may be other sources of relevant information.

Conclusions

There is a divide between populations and individuals, there is a high level of uncertainty, and there are macroeconomic consequences. Does that mean we should not invest in personalised medicine? No, just that it may be too early to reap its benefits. So why invest in uncertainty? First, to reduce uncertainty. Second, because it means investing in research and thus in the technology that comes with it, and that means creating wealth while educating society. I believe that we should invest even if we do not really know what the result will be. But, by investing in a cluster of businesses, not only in genetics or personalised medicine, we are investing in an ecosystem that may ultimately deliver benefits, and perhaps not only to the healthcare system.

As to whether personalised medicine will be sustainable, income will, at best, most likely be neutral in the coming years whereas expenditures for diagnostics and prevention will increase and treatment will, at best, have a neutral effect. The implementation of personalised medicine requires the confluence of several sectors: insurance coverage and reimbursement, genetic privacy and legal protection, medical education, healthcare information technology, and regulation. The full implementation and standardization of personalised medicine can only be achieved when there has been a recognition of value, the enactment of policy or legislation, and pilot studies and sufficient precedent in all these sectors.

References

1. Clayton EW (2003) Ethical, Legal, and Social Implications of Genomic Medicine. N Engl J Med 349:562-569
2. European Science Foundation (2012) Personalised Medicine for the European Citizen. Towards a more precise medicine for the diagnosis, treatment and prevention of disease
3. Ioannidis JPA (2009) Limits to forecasting in personalized medicine: an overview. International Journal of Forecasting 25:773-783
4. National Human Genome Research Institute [http://genome.gov/sequencingcosts]
5. OECD Health Data 2013 [http://www.oecd.org/health/healthdata]
6. Orphanet. The portal for rare diseases and orphan drugs [www.orpha.net]
7. PricewaterhouseCoopers (2009) The New Science of Personalised Medicine: Translating the promise into practice [http://www.pwc.com/us/en/healthcare/publications/personalized-medicine.jhtml].
8. Spear BB, Heath-Chiozzi Margo, Huff J (2001) Clinical application of pharmacogenetics. Trends in Molecular Medicine 7:201-204
9. 23andMe [www.23andme.com]