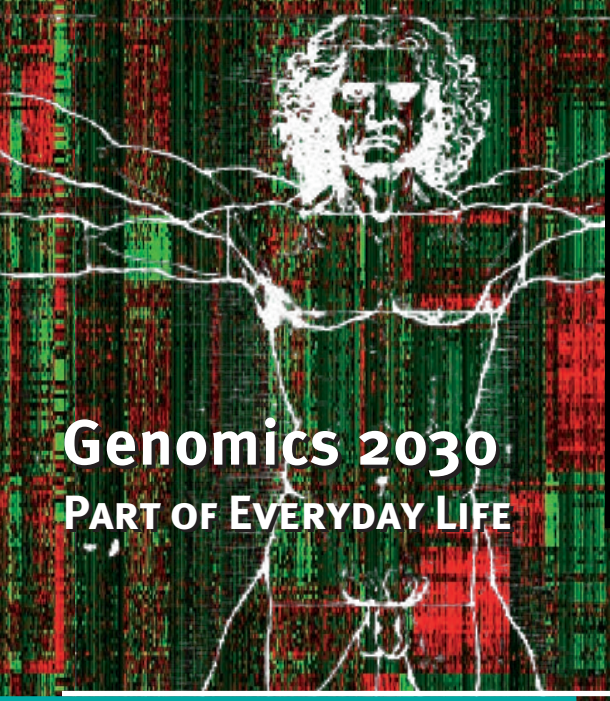
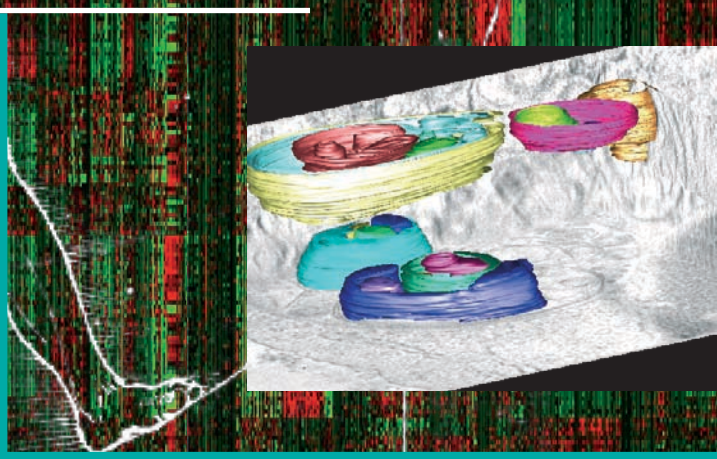


Genomics 2030

Part of Everyday Life



Edited by Mark de Graef

STT 70

STT Netherlands
Study Centre for
Technology Trends

Genomics 2030:

Part of Everyday Life

STT Netherlands
Study Centre for
Technology Trends

The Netherlands Study Centre for Technology Trends (STT) was founded in 1968 by the Royal Institution of Engineers (KIVI). STT/Beweton has the following aims:

- To evaluate technological trends from the viewpoint of the engineering sciences and to explore their interaction with other developments in society as a whole.
- To give wide publicity to its findings as a contribution to a more integrated picture of the future of society in the Netherlands and elsewhere.

STT/Beweton addresses itself to industry, government, science, and the interested layman.

STT/Beweton is established at Prinsessegracht 23, The Hague.
The Netherlands.
Correspondence address:
P.O. Box 30424
2500 GK The Hague
The Netherlands
Telephone +31 70 302 98 30
E-mail: info@stt.nl
Website: www.stt.nl

Genomics 2030:
Part of Everyday Life

Edited by Mark de Graef
Co-edited by Theo Verrips

2005

STT/Beweton
The Hague, The Netherlands

Colophon

English translating and proofreading Justine Stoop, The Hague
Editor Mark de Graef, Amsterdam
Co-editor Theo Verrips, Utrecht
Book design Salabim Design Consultancy BNO, Rotterdam
Cover design Salabim Design Consultancy BNO, Rotterdam
Printing DeltaHage bv, The Hague

Cover illustrations

- L. Da Vinci, Vitruvian Man, c. 1490.
- Combined fMRI and DTI in a normal subject. A) Fiber bundles originating from a ROI corresponding to the activation site of Wernicke's area: Wernicke is anatomically interconnected with the temporal pole, cerebellum, parietal lobe, perirolandic region, and frontal areas. B) DTI fibre tracking between Wernicke's and Broca's regions: depiction of the classical direct arcuate fasciculus. From: B. Thomas, S. Sunaert. Diffusion Tensor Imaging: Technique, Clinical and Research Applications. *Rivista di Neuroradiologia*, 18, 2005.
- A model of Lysosomal membranes in a Tomogram of a Cell by Dr W. Geerts, Department Cellular Architecture and Dynamics, Utrecht University.
- Part of Figure 1 from the chapter DNA Microarrays for Treatment Development in Cancer by Prof Dr B. Löwenberg.

ISBN-10: 90-809613-2-9
ISBN-13: 978-90-809613-2-6
STT/Beweton Publication no 70
NUR 950
Key words genomics, healthcare, food, converging technologies, medical imaging, nanotechnology

This study has been financially supported by the Netherlands Genomics Initiative (NGI), The Hague, The Netherlands.

Contents

	Prologue	10
	General Introduction	
	Genomics between Technology and Health Care Theo de Vries	14
Part I	**Technology**	20
	A Short History of Genomics Gertjan B. van Ommen	20
	Micro- and Nanotechnology for Genomics Helene M.A. Andersson, Albert van den Berg	36
	Myths and Miracles of Medical Imaging Sjaak Deckers	42
	e-Science in Life Sciences Bob Hertzberger	48

Part II **Impact on Society** 62

Introduction 62
Mark de Graef

Genomics 2030: Part of Everyday Life 64
Theo Verrips

Pharmacogenomics and Everyday Health Care 72
Dick Willems

Molecular Imaging 78
Sjaak Deckers

Living the Future 80
Peter Streng

Development of a PDMS Spotting Device for Confined Protein Arrays 86
Bianca Beusink, Richard B.M. Schasfoort

Consumer Acceptance of Nutrigenomics-Based Food Technology 88
Amber Ronteltap, Hans van Trijp

Genomics for consumers? 98
Frans van Dam

Microneedles Coupled to a Microanalysis Chip for Lithium Measurement in Blood 104
Albert van den Berg, Elwin Vrouwe

Genomics: Towards a More Comprehensive View on Human Life 106
Hub Zwart

DNA Microarrays for Treatment Development in Cancer 114
Bob Löwenberg

Report Discussion Meeting Consumers and Manufacturers 120

Report Discussion Meeting General Practitioners (GPs) 126

Report Discussion Meeting Associations of Patients 132

Report Discussion Meeting Technologists 138

Part III **Visions on the Future** 144

Molecular Medicine — A Revolution in Health Care 144
Hans Hofstraat

Final Thoughts and Recommendations 154
Theo Verrips, Mark de Graef

Survey Organization 158

Project Cooperation 160

STT Publications 164

Financial Support STT/Beweton 170

Prologue

In a recent report[1] of the Dutch government body for economic planning CPB, an analysis was made for the costs of health care and (public) pensions under the following premises:

- A large part of the expenditure in health care is related to the remaining life span rather than to age.
- Life expectancy might increase much faster in future than assumed in general.
- Health might much improve in the future.

The conclusion for the 15 EU countries is that the current fiscal and social security regulations cannot be maintained.

However, the report does not take into account scientific and technological breakthroughs, although scientific and technological developments are to be found in the figures the CPB has used in order to map the historical development of the costs connected with health care.

1 Can we Afford to Live Longer in Better Health? CPB Document 85, June 2005.

The effects of real breakthroughs in our scientific and technological knowledge on life expectancy are huge. For instance, it is generally assumed that better hygiene, antibiotics and much improved surgery were the most important factors for the increase of life expectancy in the 20th century.

In the 21st century, technological and scientific developments that earn the designation 'breakthrough' will also occur. Micro system technology, ICT and countless new biochemical and molecular techniques have led to the clarification of the human genome, a sort of blueprint of man as a biological being. In the world of science, a large number of genomics activities are now based on this; in the Netherlands these are combined in the Netherlands Genomics Initiative.

There are also developments in physics that allow us to map without operations the state of our body with always greater accuracy. In the 20th century it was mainly X-rays with which our insides could be looked at; nowadays there is a whole range of new methods, such as CT, fMRI and PET. These techniques will make it possible to detect these deviations in good time, and because the chance of being cured almost always increases when the deviation is detected at an earlier stage this will have a strongly positive effect on health. In addition, our understanding of diseases on molecular and cellular levels, such as cardiovascular diseases and cancer, and processes such as aging will increase, also thanks to genomics research.

These breakthroughs will probably generate only a slight increase in life expectancy, but — even more important — they may significantly contribute to maintaining the quality of life for (aging) persons and by doing so make important social and economic contributions to society.

In the STT/Beweton study 'Genomics 2030: Part of Everyday Life' there are a number of essays about the current en future scientific and technological breakthroughs written by Dutch experts from various disciplines, from consumer science to non-invasive techniques, from system biology to 'laboratory on a chip'. Apart from the technological developments themselves, the impact of these developments on society will be discussed from various perspectives by patients, consumers and health care workers.

The Hague, October 2005

Ir R.M.J. van der Meer
Chairman STT/Beweton

Mrs Prof Dr H. Maassen van den Brink
Chairman Consultative Committee of Sector Councils
for research and development COS

Prof Dr Ir P. Folstar
Director The Netherlands Genomics Initiative

GENERAL INTRODUCTION

Genomics between Technology and Health Care

Theo de Vries[1]

General

"*I predict that, by the year 2030, gene-based therapy will have revolutionised the practice of medicine*." This remark (and similar statements) of W. French Anderson [French Anderson, 1999] in the late 1990s led to many speculations about the possibilities of this new technology. In the meantime, six years have gone by. Speculations are only slowly replaced by insights and expectations based on facts.

This book concerns such a new technology. Facts will be presented aiming to feed the debate on genomics. This is necessary, for discussions are, and were, often much too abstract; many people lacked the essential basic facts. That nevertheless a discussion was started, was frequently caused by a wide spectrum of expectations ranging from all sorts of gloomy scenarios to ideas about radical changes in health care, where they were caused by expectations about unprecedented predicting possibilities attributed to genomics. For that matter, such discussions occur quite regularly in health care. Often, their outcome is similar. Therefore it is wise to first put into perspective an essay on new technologies in health care. First, a brief history.

1 Prof Dr Ir T. de Vries, Twente University, Enschede, The Netherlands.

Fantasies in the past

From our current point of view, the 1960s and 1970s gave rise to many unrestrained fantasies. They were fed by the big successes in medical science that were quite often world news. In 1966, several possibilities were described to substantially influence the brain and accordingly the behaviour of people with medication, and this before the year 2000 [Krech, 1966]. The futurologists Kahn and Wiener examined this seriously a year later. They saw big possibilities to influence the brain as a result of the knowledge acquired by analysing the secrets of RNA and DNA structures [Kahn and Wiener, 1967]. Not only did these ideas live in the United States, in the Netherlands similar insights were passed on: direct stimulation of the brain, pharmacological improvement of the memory, and the like, were expected before the year 2000 [Hattinga Verschuere, 1971]. These fantasies could perhaps still be ascribed to the belief in the success of technology during the Cold War, but the ideas about the transplantation of organs or replacing them by all sorts of substitutes were different. These were considered as real developments in the 1960s, maybe even before the year 2000. The belief in technological progress was very much alive, sceptics were hardly believed.

Manipulation of hereditary material was discussed very seriously [Hattinga Verschuere, 1971]. The results were considered to be very clear. The result, influencing the quality of offspring, was seen as a reality in the near future. These speculations rapidly changed into wild fantasies. Often, they were taken very seriously, as shown by a quote from 1966, for instance, that caused a great deal of controversy in the Washington Post. The text reads more or less as follows: "*Within 10-15 years, a housewife will be able to visit a new type of institution and examine a row of packages as if she were looking for flower seeds. Then, she will choose her baby on the basis of the label. Each package contains a frozen one-day-old embryo. The label states the expected colours of hair and eyes and the child's IQ (...)*" [Washington Post, 1966; Kaiser Aluminum News, 1966].

... and today's fantasies

The above ideas are ascribed much too easily to the fanciful 1960s. In the years around the turn of the century, similar insights existed that have been described excellently in Francis Fukuyama's book 'The New Man' [Fukuyama, 2002]. He describes three scenarios that might unfold within one or two generations.

The first scenario also concerns the influencing of behaviour. Many have heard of Prozac and Ritalin, medication that is effective in respect to characteristics such as self-respect and ability to concentrate. A drawback is that they can

have undesirable side-effects. It is probable that by adapting them specifically to the user's genetic make-up, these side-effects can be almost entirely prevented. Unhappy people can become happy, introvert ones extravert, and so on. The second scenario concerns replacing tissues and organs. Not by all sorts of transplantations but by application of the results of stem cell research. This appears to make it possible in the future to regenerate almost all body tissues. In the last scenario, the line of Kahn and Wiener is further extended into the future. Fukuyama also considers influencing the quality of offspring as a realistic option. In his opinion, rich people can afford to have embryos checked on a regular basis before they are implanted. As a consequence, the social background of young people can be told to an increasing extent from their looks and intelligence [De Vries, 2005].

These three scenarios of Fukuyama's have a surprisingly large similarity with the perceptions of forty years ago. There is an ever increasing technological imperative in health care on our way towards the horizon — without ever reaching it.

Objections

Whoever thinks that this optimism is widely shared, however, will be disappointed. Little by little, doubts are being expressed about the possibilities of technology in medical science and in connected sciences. For instance, in the year 1979, the biologist Glass came with an argument that was confronting at that time about the progress of science. He stated that the development of science had more or less reached its apex and that the pace of new findings would only decrease. He acknowledged that much could still be learned, but that in his opinion real breakthroughs would only decrease [Glass, 1979]. Glass is not alone in his pessimism. Le Fanu, a physician, presumes that we are confronted with a decline in the number of developments [Le Fanu, 1999]. This point of view is extremely interesting, because he draws our attention to a number of inhibiting factors that appear to be becoming more and more manifest in medicine. Le Fanu, but he is not alone in this, thus provides a necessary counterbalance — necessary in order to keep both feet on the ground. For that matter, Le Fanu acknowledges the successes achieved in medical science in the past century. He cites developments such as penicillin, cortisone, open-heart surgery, MRI, liver transplantations, and so on. In his opinion, all these developments are hardly the result of systematic scientific research but more likely of seizing opportunities, of perceptivity, of doggedness and perseverance. After the 1970s, says Le Fanu, these have been increasingly lacking, and the abundance of ideas is decreasing. New developments become more and more scientifically-oriented, also as a consequence of the thalidomide affair, resulting in delays in the production of new concepts. And indeed, we

see a worldwide decrease of, for instance, new pharmaceutical products — in ten years a decrease of more than 20% [Efpia, 2003]. At the same time, the R&D costs have doubled in this industry over the same period, in spite of the recession affecting a large number of economies.

There is more going on

The paradox mentioned lets us presume that there is more going on. Traditional R&D techniques are being abandoned, a trend of computer-related research techniques is emerging, which is making 'wet chemistry' partially redundant. But this is not all. New knowledge is emerging by way of alliances with all kinds of genomics and 'baby biotech' companies; convergence of disciplines (nanotech, biotech and infotech) is more and more common. This appears to be giving rise to new research cultures both within and outside the pharmaceutical industry. There is every indication that in the near future the downward movement of the number of medical innovations will stop. Reorientation of scientific research is the decisive factor in this context.

It is no longer unthinkable that researchers have almost solved the mystery of how cancer develops. Findings of the Human Genome Project played an important role in this. It is clear that much progress has been made and that it is probable that in approximately ten years various forms of cancer will be reduced to chronic diseases, like diabetes [Workman, 2004].

The importance of nanotechnology for medical scientific research is rapidly increasing. In the meantime, nanotechnology has become a (political) spearhead. In 2004, the United States government alone spent twice as much on research as in the most expensive years of the Human Genome Project. Apart from direct economic importance (new materials and products), acquired conceptions will be very useful in research into medicines, in medical diagnoses and in important analyses. For instance, sensors on a nanoscale will be useful in tracing infections within the next three to five years [Economist, 2004].

All new developments point to a type of health care increasingly centred on the patient. Treatment will increasingly take place outside hospitals. The trend to more and more treatments in outpatients' departments or in the patient's private environment has begun: cyber-medicine and 'hospital at home'. ICT will be of crucial importance in this instance. This trend will not be over for a long time.

What about the patient?

The influence new technologies will ultimately have on the patient and on the health care system is far from clear. However, it does appear to be probable

that developments will lead to 'personalised medicine'. This development appears to respond to the individualism and increasing consumerism in health care. The latter only seems to be the case, because it can be assumed that at the same time the egalitarian aspect of health care — an important aspect of consumerism — will be considerably eroded by new developments. The following is a construed example [De Vries, 2005]:
New developments indicate that future pharmaceutical products will become more and more specific. The number of cancerous disorders the patients are confronted with will increase, because diversity at a molecular level is very extensive: for each type of cancer a separate approach will have to be selected. This means that the markets for medication will become considerably smaller. The consequence will be that the industry will only focus on subtypes of frequently occurring disorders. Less frequently occurring disorders can be dealt with but will often not be developed for market technical reasons. Prices will considerably increase, not only because of the smaller markets but initially also because of the necessary research that has to be done with smaller populations.

The consequence will be that very effective but also very expensive drugs will be created. The most attractive markets for the industry are the elderly — as for numbers and effectively anticipated demand. Then it is the question whether the health care system can produce the solidarity to finance qualitatively superior drugs (including expensive maintenance doses). It must be feared that in this field important social issues will occur. The solidarity will not only be limited to the price but also to the question whether the available knowledge must or can be applied for less frequently occurring disorders. To maintain an egalitarian system as in the Netherlands, it is essential that new technologies are always tested for their consequences for the health care system — it is hardly possible to exclude the technologies, but a careful introduction process can prevent many problems.

The ever increasing demand for health care

The Dutch population is growing old. Growing old means an increasing consumption of health care, which is a reason for a number of organisations to study the consequences of this phenomenon. In the meantime, several views have been published, many of them ending in negative scenarios. For instance, it has been calculated that there will be shortages in particular with regard to family doctors, nurses and attendants — shortages to the extent of 23% in 2020 are probable [SCP, 2004].[2] In many scenarios, the influence of technology hardly plays a role, many confine themselves to continue the existing demand for health care, taking into account the expected developments of a number of important diseases, another and maybe better use of the labour

2 In many scenarios, for that matter, the fact is ignored that the Netherlands are quite a young country and that the countries surrounding it have already reached the number of senior citizens it expects to have about 2020. The Dutch might also look to these countries for solutions.

factor. Up to now, the latter has not been the case, except for some exceptions. The Dutch Central Planning Office (CPB) considers the technology factor as one of the causes of the future increase of the health care demand [Folmer, 2001]. It is debatable whether this also applies to new technologies — there are reasons to make subtle distinctions in this context. Genomics, nanotechnology and information technology can in principle be used to ensure access to health care for all, but it is questionable whether market realities will correspond with this. A continuous assessment of this issue will remain relevant in future.

References

- Economist (2004). A Survey of Nanotechnology. *The Economist*. January 1. pp 1-15
- Efpia (2003). *The Pharmaceutical Industry in Figures — 2003*. Update p 4
- Fanu, J Le (1999). *The Rise and Fall of Modern Medicine*. Little, Brown and Company
- Folmer, K et al (2001). *Een scenario voor zorguitgaven 2003-2006*. CPB-Document, No 7
- French Anderson, W (1999). Gene Therapies. In: E Griffith (ed.). *Predictions, 30 Great Minds on the Future*. Oxford University Press. pp 12-21
- Fukuyama, F (2002). *De nieuwe mens. Onze wereld na de biotechnologische revolutie*. Olympus. p 23 et seq.
- Glass, B (1979). Milestones and Rates of Growth in the Development of Biology. *Quarterly of Biology*. March. pp 31-53
- Hattinga Verschuere, JCM (1971). *Patiënt, ziekenhuis, gezondheidszorg op weg naar 2000*. Agon Elsevier. pp 36-52
- Hattinga Verschuere, JCM (1971). *Patiënt, ziekenhuis, gezondheidszorg op weg naar 2000*. Agon Elsevier. pp 36-37
- Kahn, H, AJ Wiener (1967). *The Year 2000*. Macmillan Company. p 111
- Kaiser Aluminum News (1966). Forseeing the Unforseeable, No 6. p 22. In: H Kahn, AJ Wiener (1967). *The Year 2000*. Macmillan Company
- Krech, D (1966). Controlling the Mind Controllers. *Think*. July-August. pp 3-7
- SCP (2004). *In zicht van de toekomst*. Sociaal Cultureel Planbureau. p 436
- Vries, T de (2005). *Technologie en zorg: Wie wordt er beter van*? Farewell Speech. University Utrecht, The Netherlands
- Washington Post (1966). October 31. In: H Kahn, AJ Wiener (1967). *The Year 2000*. Macmillan Company
- Workman, P (2004). Inhibiting the Phosphoinositide 3-Kinase Pathway for Cancer Treatment. *Biochem. Soc. Trans*, No 32. pp 393–396

A Short History of Genomics

Gertjan B. van Ommen[1]

The beginning: clinical cytogenetics

The application of genetics in diagnostic health care was primed by the discovery by Tjio and Levan in 1956 of the correct number of 46 chromosomes in humans: 22 pairs of autosomes (1-22) and two sex chromosomes, two X chromosomes in females and an X chromosome and a Y chromosome in males. In 1959 Lejeune found that Down's syndrome was caused by an extra chromosome 21 [Lejeune et al, 1959]. Subsequently, chromosomal rearrangements were discovered to cause some hematological malignancies, such as the Philadelphia chromosome in leukaemia. In 1960, the first nomenclature standardisation was decided upon in Denver. The field of chromosome analysis, 'Cytogenetics', then rapidly blossomed with the identification of many chromosome abnormalities in malformation syndromes.

The discovery of chromosome banding by the group of Zech in 1968 [Caspersson et al, 1968] not only improved insight and resolution, but greatly aided their identification, expanding the diagnostic use of cytogenetics. In 1971, in Paris, the chromosome classification and nomenclature were refined, and in 1976 a new high-resolution banding method [Yunis, 1976] furthered detailed resolution, leading to a final nomenclature (ISCN) in a further Paris conference in 1978.

1 Prof Dr G.B. van Ommen, Head of the Department of Human Genetics of the Center of Human and Clinical Genetics/Director of the Center for Medical Systems Biology, Leiden University Medical Center, The Netherlands.

The first diagnostic applications of cytogenetics involved identification of chromosomal abnormalities in malformation and leukaemia, i.e. 'postnatal' applications. Soon, however, the potential prevention of Down's syndrome and other malformations was tabled, and prenatal diagnosis based on metaphase chromosome patterns made its entry in the early '70's. This caused some national and international discussions, both on the ethical aspects of preventive health care and on the exercise of quality control. A major role in this discussion in the Netherlands was played by Prof Galjaard, head of Clinical Genetics of Erasmus University in Rotterdam. One of his most widely known phrases, also one of his book titles, was 'Better to prevent than not to cure' [Galjaard et al, 1974]. The process of the emerging clinical impact of genetics has been well-described in Nelis's thesis [Nelis, 1998].

DNA markers take off

In the mid 1970s, with the advent of recombinant DNA technology, the first research was done on human genes at the DNA level. This led to the unexpected discovery in 1977, among others by Jeffreys and Flavell [Jeffreys and Flavell, 1977], then doing research on the haemoglobin genes in Borst's group in Amsterdam, that genes in higher organisms were segmented into short coding segments, 'exons', separated by large non-coding segments, 'introns', which had to be removed from the gene transcripts by a process called 'splicing'. This typically caused chromosomal genes to be many times larger than expected, often 10-100 times as large.

In particular research carried out on the haemoglobin genes had clinical implications. Mutations of these genes were found to be the cause of thalassaemia and sickle cell anaemia, the major hereditary blood diseases of the developing world. The high frequency of hereditary blood diseases in tropical and subtropical areas is caused by the selective advantage of malaria resistance in gene carriers. Thus, developing a proper diagnosis, permitting preventive strategies and ultimately even a therapy, were, and still are, much sought after.

The clinical diagnostic usefulness of DNA diagnosis for haemoglobin disorders was established in a crucial paper by Kan and Dozy in 1978, showing that an easily detectable sequence variant in the non-coding region of the globin gene, being in itself harmless, was mapped close to the sickle cell mutation and co-segregated as a 'linked marker' with the mutation through families [Kan and Dozy, 1978b]. This was indeed a first case of what we nowadays call SNPs or 'single nucleotide polymorphisms'.

In particular those variants were of major practical value that altered the recognition site of restriction enzymes which cleave DNA at a specific sequence. These polymorphisms could be easily recognized using the molecular biology tools then available, as they changed the size of the DNA fragments produced.

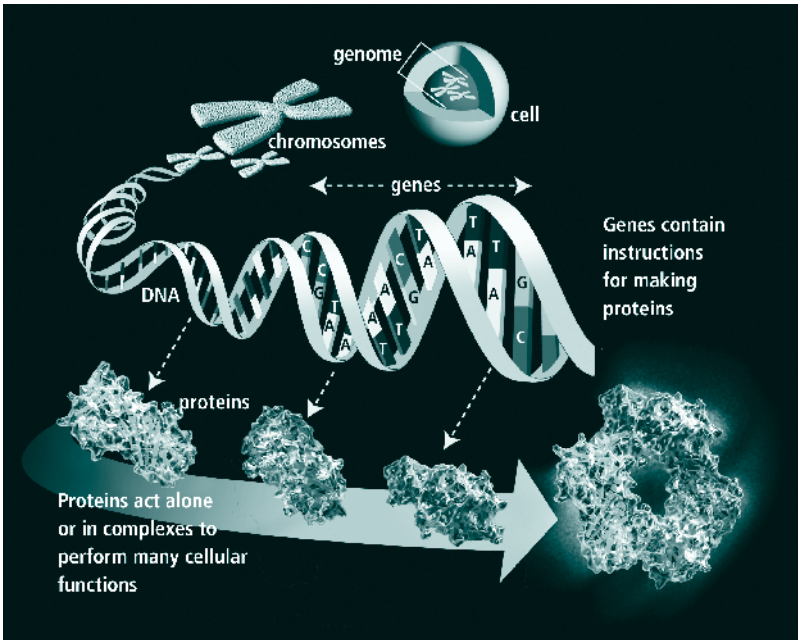


Figure 1

From the cell to protein machines

Cells are the fundamental working units of every living system. All the instructions needed to direct their activities are contained within the chemical DNA (deoxyribonucleic acid).

DNA from all organisms is made up of the same chemical and physical components. The DNA sequence is the particular side-by-side arrangement of bases along the DNA strand (e.g., ATTCCGGA). This order spells out the exact instructions required to create a particular organism with its own unique traits.

The genome is an organism's complete set of DNA. Genomes vary widely in size: the smallest known genome for a free-living organism (a bacterium) contains about 600,000 DNA base pairs, while human and mouse genomes have some 3 billion. Except for mature red blood cells, all human cells contain a complete genome.

DNA in the human genome is arranged into 24 distinct chromosomes – physically separate molecules that range in length from about 50 million to 250 million base pairs. A few types of major chromosomal abnormalities, including missing or extra copies or gross breaks and rejoinings (translocations), can be detected by microscopic examination. Most changes in DNA, however, are more subtle and require a closer analysis of the DNA molecule to find perhaps single-base differences.

Each chromosome contains many genes, the basic physical and functional units of heredity. Genes are specific sequences of bases that encode instructions on how to make proteins. Genes comprise only about 2% of the human genome; the remainder consists of noncoding regions, whose functions may include providing chromosomal structural integrity and regulating

The sickle mutation itself was hard to find because it did not affect a restriction site, but this closely linked, neutral variation was useful to track down the faulty gene and diagnose the sickle mutation nearby [Kan and Dozy, 1978a].

In 1980, Botstein et al [Botstein et al, 1980] generalised this finding and floated the idea of establishing a complete genetic map of all the human chromosomes, by first identifying a large number of these restriction fragment length polymorphisms, RFLPs, covering the entire human genome, and then by using these ubiquitous, DNA-based variants as genetic markers to establish their genetic linkage distance in pairs as well as in groups. Geneticists worldwide immediately recognised the power of this approach, and the first systematic, DNA-based genome mapping effort began, yielding several, increasingly refined, genetic maps of the human genome [Donis-Keller, 1987; Weissenbach et al, 1992; Murray et al, 1994].

By 1980-81, the Leiden cytogeneticist Pearson considered that recombinant DNA technology presented an alternative to the cytogenetic microscope and would offer a much more refined tool to 'count chromosomes', using specific DNA sequences. Pearson and his co-worker Bakker set out to clone a large number of human DNA segments and map them to different human chromosomes. Spurred by the rising popularity of the RFLP markers, this effort was adapted to turn these cloned human DNA segments into tools, 'probes', in order to detect RFLPs. This activity was so successful that in the mid 1980s about half of all RFLP markers available to the genetics community, listed in the reports of the biannual 'Human Gene Mapping' (HGM) workshops, were developed in Leiden [Skolnick et al, 1984; Willard et al, 1985; Pearson et al, 1987].

where, when, and in what quantity proteins are made. The human genome is estimated to contain 30,000 to 40,000 genes. Although genes get a lot of attention, it's the proteins that perform most life functions and even make up the majority of cellular structures. Proteins are large, complex molecules made up of smaller subunits called amino acids. Chemical properties that distinguish the 20 different amino acids cause the protein chains to fold up into specific three-dimensional structures that define their particular functions in the cell.
Image credit: U.S. Department of Energy Human Genome Program, www.ornl.gov/hgmis.

DNA diagnostics: tracking the disease

In those years, DNA sequencing technology was still in its infancy, the fruit of laborious, fundamental research into mutations in cloned genes. The introduction of RFLPs as easy tools to follow genetic heredity signalled the breakthrough of sequence-specific DNA analysis in the clinical diagnostic arena. While for haemoglobin the genes were known before the diagnostic marker was used, the enormous power of the new marker technology lay in the very fact that these linked markers also permitted the diagnosis of unknown disease genes, as soon as they were shown to co-segregate with any (set of) diagnostically useful markers.

In 1982-83, the groups of Davies in Oxford and Pearson in Leiden described the first RFLP markers linked to the X-chromosomal Duchenne Muscular Dystrophy (DMD) gene [Murray et al, 1982; Davies et al, 1983]. Immediately thereafter, they teamed up with the Ropers group in Freiburg to perform the first DMD carrier detection [Wieacker et al, 1983]. In 1985, the Pearson group in turn allowed the others to make history with a prenatal DMD diagnosis, the first prenatal diagnosis ever by linked DNA markers, for an as yet unknown gene [Bakker et al, 1985].

Within a few years, RFLP linkages were reported in many major, severe genetic diseases, like Huntington disease [Gusella et al, 1983], polycystic kidney disease [Reeders et al, 1985], cystic fibrosis [Kerem et al, 1989; Riordan et al, 1989; Rommens et al, 1989] and spinal muscular atrophy [Melki et al, 1990; Brzustowicz et al, 1990]. Also several hereditary cancer syndromes were mapped, like retinoblastoma [Cavenee et al, 1983], and one form of colon cancer [Solomon et al, 1987]. Not only did these findings pinpoint the disease gene on the emerging genetic map — spurring the further hunt for the culprit gene and its precise mutations — but the discoveries immediately made sensitive and specific prenatal or presymptomatic diagnosis possible. In most cases, this was the first diagnostic option ever available to gene carriers, who had until then only found out about their being carriers by developing the disease, or having — and often losing — children with the disease.

The stepwise improvement of the genetic map eventually brought the discovery of many disease genes proper, and the nature of their mutations, often after historic chases. The diseases in which some mutations were caused by chromosomal deletions or rearrangements, like Duchenne [Kunkel et al, 1985; Koening et al, 1987; Monaco et al, 1986] and haemophilia [Lakich et al, 1993], yielded their secrets more rapidly, because at the end of the course DNA markers began to show alterations or deletions, flagging the end game. In contrast, the hunt for the genes causing cystic fibrosis and Huntington disease took a long time (the latter 10 years!) and required the development of sophisticated but laborious statistical mapping and cloning procedures. However, these statistical and long-range methodologies turned out to be very important in their

own right, in the next phase, i.e. the complete mapping of our genes in the Human Genome Project.

The next major breakthrough was the invention of the 'Polymerase Chain Reaction' (PCR) in 1985 [Saiki et al, 1985]. This made unlimited amplification of any desired DNA sequence possible and tremendously facilitated disease gene research and the causal elucidation of an even larger number of rare diseases and single-base mutations. In the decade to follow, PCR was the key tool making DNA diagnostics possible that was of major clinical value, with refined, mutation-specific diagnoses for currently approximately 1,500 Mendelian genetic diseases and hereditary cancer syndromes, proper guiding genetic counselling, increasing parental choices, improving psychological preparedness, and often alleviating concern.

In the Netherlands, 23,000 DNA diagnoses were performed in 8 genetic centres for 990 disease loci in 2004. Most importantly, in the quantitative sense, DNA diagnosis of different forms of hereditary breast cancer and colon cancer, and hereditary cardiovascular diseases has profoundly affected the lives of high-risk individuals and families. This has brought timely and targeted preventive surgical interventions to the cancer gene carriers and targeted medical prevention in familial hypercholesterolaemia. Moreover — an often overlooked, major benefit — it has freed an even larger amount of non-carrier relatives from further severe worrying about their future.

Novel mechanisms with clinical relevance

During this energetic search for the causes of severe genetic diseases, a large number of remarkable gene structures and unknown genetic processes were discovered, such as the unprecedented 2.5 Mb size of the DMD gene [Van Ommen et al, 1987], thus making it the largest target for deletions and duplications in the human genome [Den Dunnen et al, 1989], or the trinucleotide expansion or 'unstable DNA' in Huntington disease [The Huntington's Disease Collaborative Research Group, 1993], fragile X syndrome [Verkerk et al, 1991] and myotonic dystrophy [Brook et al, 1992; Harley et al, 1992; Mahadevan et al, 1992], causing these diseases to become increasingly severe in next generations. This so-called 'anticipation' had been dismissed for decades as an observational artefact, but was revisited and convincingly argued in 1989 by Howeler [Howeler et al, 1989], thus also anticipating the molecular mechanism of the triplet expansion diseases.

Another major novelty was the phenomenon of 'genetic imprinting', a parent-of-origin effect. Some diseases only became manifest if the disease gene was inherited from the father, while in other diseases this was the case for the maternal gene [Nicholls et al, 1989; Heutink et al, 1992]. These findings were to highlight a phenomenon which has since spurred the research field of epigenetic (i.e. non-DNA-based) heredity [Ferguson-Smith et al, 1993]: the chemical

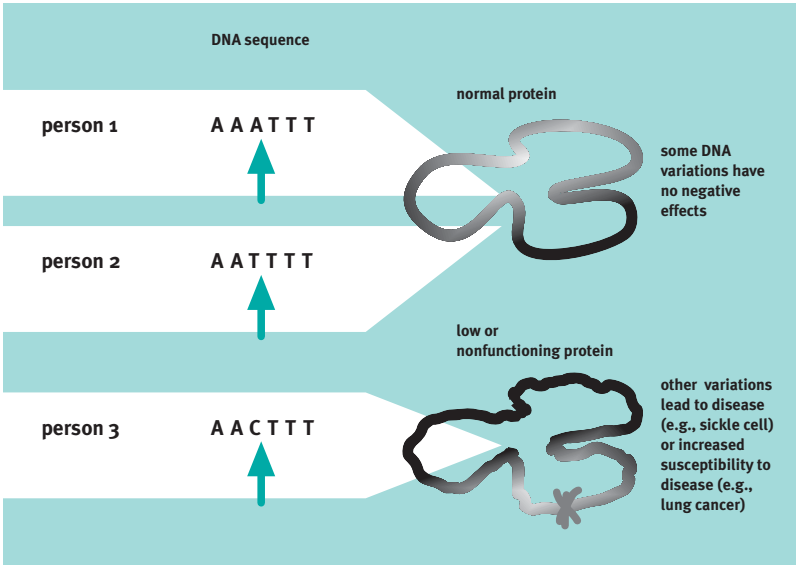


Figure 2
Health or Disease?
Each DNA molecule contains many genes – the basic physical and functional units of heredity. A gene is a specific sequence of nucleotide bases, whose sequences carry the information required for constructing proteins, which provide the structural components of cells and tissues as well as enzymes for essential biochemical reactions. The human genome is estimated to comprise more than 30,000 genes.
All living organisms are composed largely of proteins which are coded for by genes. Proteins are large, complex molecules made up of long chains of subunits called amino acids. Twenty different kinds of amino acids are usually found in proteins. Within the gene, each specific sequence of three DNA bases (codons) directs the cells protein-synthesizing machinery to add specific amino acids. For example, the base sequence ATG codes for the amino acid methionine. Since 3 bases code for 1 amino acid, the protein coded by an average-sized gene (3000 bp) will contain 1000 amino acids. The DNA code is thus a series of codons that specify which amino acids are required to make up specific proteins.
Some variations in a person's genetic code will have no effect on the protein that is produced, others can lead to a disease or an increased susceptibility to a disease.
Image credit: U.S. Department of Energy Human Genome Program, www.ornl.gov/hgmis.

'marking up' of gene regions — often much larger chromosomal domains — by DNA modifications, typically methylation, causing the genomic DNA to be silenced as regards gene expression. This silencing, once established, is then faithfully copied throughout development and growth into the descendant tissue cells. It is only erased in sperm and egg cells, so that the next generation starts with a 'clean slate'. Even the completeness of this erasure is not fully confirmed, which might allow for a modest degree of multigenerational 'epigenetics', interesting from an evolutionary perspective [Pembrey, 2002; Kaati et al, 2002].

From genes to the genome

As implied above, the disease gene studies soon expanded from genes to much larger segments of the genome. The DMD gene, by its sheer size of 2.5 Mb, can be just as well considered to be a small genome. The hunt for this gene and the other early 'hot targets' greatly stimulated the development of 'long-range' genomic technologies. Thus, 'Chromosome jumping', 'Pulsed Field Gel Electrophoresis' (PFGE), and cloning in yeast and bacterial artificial chromosomes (YACs and BACs) appeared in 1984-87. PFGE first made the sizing of the DMD gene [Van Ommen et al, 1986; Burmeister and Lehrach, 1986] and reporting its large fraction (>50%) of deletions [Den Dunnen et al, 1987] possible. For mapping and cloning of the genes connected with Huntington, cystic fibrosis and many other genes the long-range techniques were also very useful. Even nowadays, PFGE is diagnostically used for Facioscapulohumeral Muscular Dystrophy (FSHD). For this frequent, dominant muscle disease, no culprit gene has yet been found, more than 13 years after its location and finding the causal mutations [Wijmenga et al, 1990; Wijmenga et al, 1992].

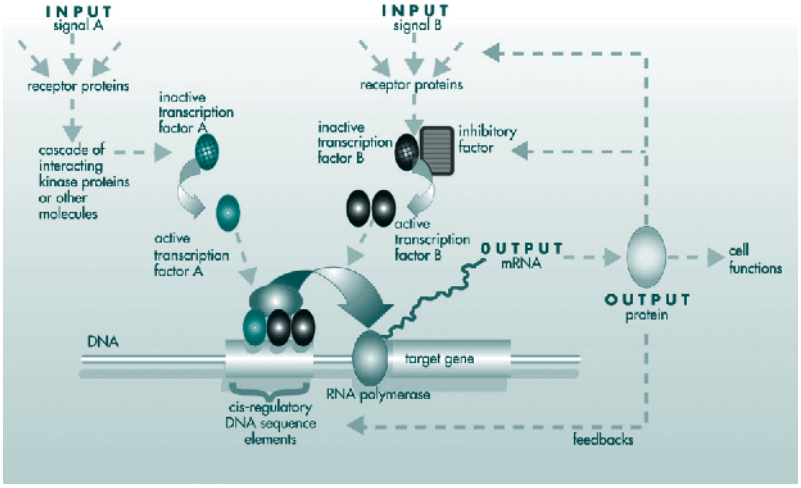


Figure 3

Gene Regulatory Network (GRN)

GRNs are remarkably diverse in their structure, but several basic properties are illustrated in this figure. In this example, two different signals impinge on a single target gene where the cis-regulatory elements provide for an integrated output in response to the two inputs. Signal molecule A triggers the conversion of inactive transcription factor A (green oval) into an active form that binds directly to the target gene's cis-regulatory sequence. The process for signal B is more complex. Signal B triggers the separation of inactive B (black oval) from an inhibitory factor (black rectangle). B is then free to form an active complex that binds to the active A transcription factor on the cis-regulatory sequence. The net output is expression of the target gene at a level determined by the action of factors A and B. In this way, cis-regulatory DNA sequences, together with the proteins that assemble on them, integrate information from multiple signaling inputs to produce an appropriately regulated readout. A more realistic network might contain multiple target genes regulated by signal A alone, others by signal B alone, and still others by the pair of A and B.

Image credit: U.S. Department of Energy Genomics: GTL Program, doegenomestolife.org.

FSHD has gained notoriety as a disease with a mainly epigenetic cause [Van Overveld et al, 2003]: the apparent (in)activation of a genomic region near the tip of the chromosome 4 long-arm.

Similarly, linkage techniques made the construction of connected, regional genetic maps around adjacent disease loci possible. Taken together, the transition from isolation of disease genes towards wholesale genome mapping, cloning and sequencing was much more gradual indeed than is commonly perceived.

HUGO

The large impact of DNA diagnostics, brought about by disease gene mapping, did not escape health politicians, and early in the 1980s the two main US funding agencies NIH (National Institute of Health) and DOE (Department of Energy) were already heavily involved in gene mapping and actively fuelled the debate on how to initiate and coordinate the next phase of mapping and sequencing the entire human genome [Congress of the US Office of Technology Assessment, 2005]. While many opponents at the time feared the decrease of funding for basic research, proponents drew attention to the major benefits for health care and health-related science and industry [Dulbecco, 1986].

In the late 1980s, the human gene mapping community itself also shifted its main focus from mapping the disease genes to generating interconnected maps of genes and genetic markers. In 1987, Donis-Keller published the first complete genetic map of the human genome [Donis-Keller, 1987]. In those days, heated debates were held about the best ways for unambiguous map ordering, and how to maintain — or better, achieve — order, nomenclature and quality control of the rising tide of cloned DNA segments. As cloning strat-

egies increasingly grazed technological limits, these segments indeed often contained internal deletions or artificially linked remote parts of the genome. At that time, the Human Genome Organisation (HUGO) was founded at the first Cold Spring Harbor Human Genome Mapping meeting in 1988. Its aim was to foster collaboration between the human genome scientists and provide a forum for discussion, assist with coordination and achieve consensus on strategies and nomenclature issues, as well as to initiate and stimulate considerations on ethical and intellectual property issues. HUGO's first president was the venerable and highly reputed Victor McKusick, whose 'Mendelian Inheritance of Man' (MIM, then just going online as OMIM: http://www.ncbi.nlm.nih.gov/omim/) was the bible of all human and clinical geneticists. Unfortunately, the 'academic' format of HUGO membership with a stringent ballot gave the organisation a somewhat elitist start and slow spreading. Only from 1995 onwards this approach was left in favour of open membership. Still, many HUGO activities have made major contributions throughout the years, particularly the statements of its Ethics and Intellectual Property committees and the widely accepted disentangling work of HUGO's Nomenclature Committee [Van Ommen et al, 1998]. Also the independent, international stature of HUGO allowed it to get support to organise a variety of regional, publicly and privately sponsored, topical workshops and its yearly HGM meeting. The latter, held in cities worldwide, has long been the scientific focal point of the gene mapping community.

... and the Human Genome Project

It was crystal clear to the proponents of a coordinated human genome project, however, that this well-meaning, but modestly funded organisation, that had been self-appointed by the scientific community and was trying to master a debate which ranged as widely as map orders, clinical phenotypes, gene names, ethics and gene patents, lacked the funding and power to get the systematic, industrial high-throughput task done of mapping our genes and sequencing the entire genome. Thus, basically side by side with the HUGO activities, major funds were allotted, often competitively, by leading figures to embark on the main project: mapping and sequencing our genes and eventually the genome. Contributors to this gene phase of isolating, cataloguing and mapping extensive sets of gene clones were governmental parties, such as NIH and DOE in the US, the EU and other countries, charities like Wellcome Trust in the UK and AFM in France. In this gene mapping phase, roughly from 1989-1994, also private companies like Human Genome Sequences, Incyte and Merck came on stage.

It is interesting to observe that the first party to actually file a patent series on ~2000 human genes in 1992 was NIH, the US governmental research body, then employing the well-known 'gene hunter' Craig Venter, whereas it was the

large private pharmaceutical company Merck, in a heavily guarded, densely packed side room at the 1994 HGM Meeting in Washington, which challenged gene patenting by allotting $ 100 million to an academic consortium to get as many gene sequences rapidly out in the public domain.

The end game

In the early 1990s the preparatory work of obtaining the whole genome in order to make its systematic sequencing focused on the generation of overlapping 'physical' maps possible by using large-insert DNA clones of various sources. Several of these comprehensive maps were published. In addition, the sequencing of several smaller genomes such as E. coli and yeast was undertaken. Interesting socio-scientific experiments took place, such as the local community-based sequencing of yeast chromosomes in a EU-funded project. The single genome sequencing project that had the biggest impact on the Human Genome Project, however, was the sequencing of C. elegans by the collaborating groups of Sulston in Cambridge, UK, and Waterston at Washington University, St Louis, US. This forged the ties between two leading figures in the subsequent human genome project, who made the joint pioneering of large-scale data processing, storage and analysis possible. But more importantly, it also caused the crucial intervention of Sulston and Waterston at a Cold Spring Harbor meeting, claiming that the time to get going, to start sequencing the human genome in earnest, "*was now, not some time in the distant future*." The tools were there, and the need for efficiency would force the costs to decrease only when it had actually been started. This plea by two eminent scientists with hands-on experience caused, more than any other event, the funding agencies to get their act together and get going.
On the other hand, even amongst this highly focused community of large genome centres, the ideas on how to proceed, which technologies to prioritise, what quality requirements to adhere to, the standards of public access, and how to generate fully quality-controlled and ethically-consented, comprehensive libraries of cloned human DNA, caused major debates. Consequently, in the spring of 1998, the field fell apart, and a private company, Celera Genomics, was founded by Craig Venter, claiming that it would do the job all by itself and be finished in two years. In the concern that this might cause major accessibility and gene patenting problems, the publicly funded parties followed suit and stated a similar target for early 2000. The next two years saw an incredible increase of focus, restraint as well as scale-up of applied technology, and coordination of tools, bioinformatics and policies, in particular in the 'Bermuda rules' for public availability. The two competing parties each followed a different strategy, with the public consortium applying a (mainly BAC) clone by clone basis, and Celera using a 'whole genome shotgun' (WGS) approach. The sequence of the public consortium became part of the public

domain on a 24-h basis, whereas Celera's sequence was first made available to paid subscribers. In 1998, Celera's WGS method worked with the genome of D. melanogaster, the fruit fly. In the race for the human genome, the public sequence and clone information was utilised on an ongoing basis by Celera to resolve positioning issues. The two parties simultaneously declared the sequence finished on a historic presentation in the US White House on 26 June 2000. The two papers were published in 2001 [Lander et al, 2001; Venter et al, 2001]. Although this sequence already made a large amount of interesting biological questions to be phrased and answered possible, it still took 3 years to generate a much improved finished sequence [Nature, 2004], and even now there are a few percentages of inaccessible regions due to complicated repetitive and/or unclonable, unstable sequences [She et al, 2004].

Comparative genomics

Now that the sequence exists, much work need to be done to find out function and regulation. This is largely done by studying similarities and differences between related genes in humans, and between humans and their ancestors, the sequences of which are now being unravelled with amazing speed, including those of mouse [Waterston et al, 2002], rat [Gibbs et al, 2004], puffer [Jaillon et al, 2004] and many more to come soon, including man's nearest relative, the chimpanzee [Ruvolo, 2004; Olson and Varki, 2004]. It is commonly accepted that comparing the genomes of closely and distantly related species in order to find evolutionary conserved elements will pinpoint items of importance, in which nature has apparently invested in order to safeguard them against rapid, random evolutionary change. In fact, this is the electronic equivalent of the 'zoo-blots' that were so useful in the mid 1980s to identify potentially coding sequences in genomic fragments in which linkage research made it clear to geneticists that a disease gene had to lie in hiding [Monaco et al, 1986]. In this process of functional annotation, the previously obtained disease-related maps and phenotypic clinical knowledge created by the clinical-genetics community has also to be integrated, as this valuable information has been temporarily disregarded to a large extent in the high-throughput phase of the genome project.

Therefore, many discoveries are still waiting to be made. Examples are the mechanisms of epigenetics, but also the role of regulatory sequences other than genes, which have recently emerged when comparing the many genomes now sequenced with each other. It is clear that sequence conservation goes far beyond what we have thus far identified as genes. So-called 'conserved non-coding sequences' imply that many more, unknown languages are written into our genetic material [Nobrega et al, 2004]. The recently discovered variation in amounts and positions of segmental duplications in our genome [She et al, 2004; Fredman et al, 2004; Lafrate et al, 2004; Sebat et al, 2004;

Schmutz et al, 2004] will also have a major impact on our views on normal and pathological, multifactor heredity.

Pharmacogenomics and systems biology

To conclude, we have still a long way to go. Indeed, the closer we thought we would get to the 'original plan', predicting our future from our past, the clearer it becomes that we have all too easily overlooked the impact of the present: the interaction between our genetic makeup — unique for each individual — and the environment. In the near future we will have to learn much more about the crosstalk between our basic genetic wiring and our health status, our medication and nutrition, and probably also emotional status. These fields of 'pharmacogenomics' and 'nutrigenomics' are still wide-open and require closely integrated multidisciplinary research on many levels, from molecular genetics (genomics) to protein research (proteomics) to research on the metabolic processes in our cells and organs (metabolomics). The combined application of these approaches, termed 'systems biology', has to become one of the extensive growth areas of biomedical research if it is to deliver its full benefit to preventive and therapeutic health care.

References

- Bakker, E et al (1985). Prenatal Diagnosis and Carrier Detection of Duchenne Muscular Dystrophy with Closely Linked RFLPs. *Lancet*, 1. pp 655-658
- Botstein, D, RL White, M Skolnick, RW Davis (1980). Construction of a Genetic Linkage Map in Man Using Restriction Fragment Length Polymorfism. *Am. J. Hum. Genet*., 32. pp 314-331
- Brook, JD et al (1992). Molecular Basis of Myotonic Dystrophy: Expansion of a Trinucleotide (CTG) Repeat at the 3' End of a Transcript Encoding a Protein Kinase Family Member. *Cell*, 68. pp 799-808
- Brzustowicz, LM et al (1990). Genetic Mapping of Chronic Childhood-Onset Spinal Muscular Atrophy to Chromosome 5q11.2-13.3. *Nature*, 344. pp 540-541
- Burmeister, M, H Lehrach (1986). Long-Range Restriction Map around the Duchenne Muscular Dystrophy Gene. *Nature*, 324. pp 482-485
- Caspersson, T et al (1968). Chemical Differentiation along Metaphase Chromosomes. *Exp. Cell Res*., 49. pp 219-222
- Cavenee, WK et al (1983). Expression of Recessive Alleles by Chromosomal Mechanisms in Retinoblastoma. *Nature*, 305. pp 779-784
- Congress of the US Office of Technology Assessment (2005). *Mapping our Genes. Genome Projects: How Big, How Fast*? Johns Hopkins University Press, Baltimore-London

- Davies, KE et al (1983). Linkage Analysis of Two Cloned DNA Sequences Flanking the Duchenne Muscular Dystrophy Locus on the Short Arm of the Human X Chromosome. *Nucl. Acids Res*., 11. pp 2303-2312
- Dunnen, JT den, E Bakker, EG Breteler, PL Pearson, GJ van Ommen (1987). Direct Detection of More than 50% of the Duchenne Muscular Dystrophy Mutations by Field Inversion Gels. *Nature*, 329. pp 640-642
- Dunnen, JT den et al (1989). Topography of the DMD Gene: FIGE and cDNA Analysis of 194 Cases Reveals 115 Deletions and 13 Duplications. *Am. J. Hum. Gen*., 45. pp 835-847
- Donis-Keller, H (1987). A Genetic Linkage Map of the Human Genome. *Cell*, 51. pp 319-337
- Dulbecco, R (1986). A Turning Point in Cancer Research: Sequencing the Human Genome. *Science*, 231. pp 1055-1056
- Ferguson-Smith, AC, H Sasaki, BM Cattanach, MA Surani (1993). Parental-Origin-Specific Epigenetic Modification of the Mouse H19 Gene. *Nature*, 362. pp 751-755
- Fredman, D et al (2004). Complex SNP-Related Sequence Variation in Segmental Genome Duplications. *Nat. Genet*., 36. pp 861-866
- Galjaard, H, W Strubbe, B van Zijderveld (1974). *Voorkomen is beter dan niet genezen: Over preventie, vroegtijdige onderkenning en begeleiding van ernstig gehandicapten*. Uitgeverij Intro, Nijkerk, Nederland
- Gibbs, RA et al (2004). Genome Sequence of the Brown Norway Rat Yields Insights into Mammalian Evolution. *Nature*, 428. pp 493-521
- Gusella, JF et al (1983). A Polymorphic Marker Genetically Linked to Huntington's Disease. *Nature*, 306. pp 234-238
- Harley, HG et al (1992). Expansion of an Unstable DNA Region and Phenotypic Variation in Myotonic Dystrophy. *Nature*, 355. pp 545-546
- Heutink, P et al (1992). A Gene Subject to Genomic Imprinting and Responsible for Hereditary Paragangliomas Maps to Chromosome 11q23-qter. *Hum. Mol. Genet*., 1. pp 7-10
- Howeler, CJ, HF Busch, JP Geraedts, MF Niermeijer, A Staal (1989). Anticipation in Myotonic Dystrophy: Fact or Fiction? *Brain*, 112 (Pt 3). pp 779-797
- Lafrate, AJ et al (2004). Detection of Large-Scale Variation in the Human Genome. *Nat. Genet*., 36. pp 949-951
- Jaillon, O et al (2004). Genome Duplication in the Teleost Fish Tetraodon Nigroviridis Reveals the Early Vertebrate Proto-Karyotype. *Nature*, 431. pp 946-957
- Jeffreys, AJ, RA Flavell (1977). The Rabbit Beta-Globin Gene Contains a Large Insert in the Coding Sequence. *Cell*, 12. pp 1097-1108
- Kaati, G, LO Bygren, S Edvinsson (2002). Cardiovascular and Diabetes Mortality Determined by Nutrition during Parents' and Grandparents' Slow Growth Period. *Eur. J. Hum. Genet*., 10. pp 682-688

- Kan, YW, AM Dozy (1978a). Antenatal Diagnosis of Sickle-Cell Anaemia by D.N.A. Analysis of Amniotic-Fluid Cells. *Lancet*, 2. pp 910-912
- Kan, YW, AM Dozy (1978b). *Polymorphism of DNA Sequence Adjacent to Human Beta-Globin Structural Gene: Relationship to Sickle Mutation*. Proceedings National Academy of Science. USA 75. pp 5631-5635
- Kerem, B-S et al (1989). Identification of the Cystic Fibrosis Gene: Genetic Analysis. *Science*, 245. pp 1073-1080
- Koenig, M et al (1987). Complete Cloning of the Duchenne Muscular Dystrophy (DMD) cDNA and Preliminary Genomic Organization of the DMD Gene in Normal and Affected Individuals. *Cell*, 50. pp 509-517
- Kunkel, LM, AP Monaco, W Middlesworth, HD Ochs, SA Latt (1985). *Specific Cloning of DNA Fragments Absent from the DNA of a Male Patient with an X-Chromosome Deletion*. Proceedings National Academy of Science. USA 82. pp 4778-4782
- Lakich, D, HHJ Kazazian, SE Antonarakis, J Gitschier (1993). Inversions Disrupting the Factor VIII Gene are a Common Cause of Severe Haemophilia. *A. Nat. Genet*., 5. pp 236-241
- Lander, ES et al (2001). Initial Sequencing and Analysis of the Human Genome. *Nature*, 409. pp 860-921
- Lejeune, J, R Turpin, M Gautier (1959). Mongolism; a Chromosomal Disease (Trisomy). *Bull. Acad. Natl. Med*., 143. pp 256-265
- Mahadevan, M et al (1992). Myotonic Dystrophy Mutation: an Unstable CTG Repeat in the 3' Untranslated Region of the Gene. *Science*, 255. pp 1253-1255
- Melki, J et al (1990). Gene for Chronic Proximal Spinal Muscular Atrophies Maps to Chromosome 5q. *Nature*, 344. pp 767-768
- Monaco, AP et al (1986). Isolation of Candidate cDNAs for Portions of the Duchenne Muscular Dystrophy Gene. *Nature*, 323. pp 646-650
- Murray, JC et al (1994). A Comprehensive Human Linkage Map with centiM-organ Density. *Science*, 265. pp 2049-2054
- Murray, JM et al (1982). Linkage Relationship of a Cloned DNA Sequence on the Short Arm of the X Chromosome to Duchenne Muscular Dystrophy. *Nature*, 300. pp 69-71
- Nature (2004). Finishing the Euchromatic Sequence of the Human Genome. *Nature*, 431. pp 931-945
- Nelis, A (1998). *DNA-diagnostiek in Nederland: een regime-analyse van de ontwikkeling van de klinische genetica en DNA-diagnostische tests, 1970-1997*. PhD Thesis. Technical University Twente, Nederland
- Nicholls, RD, JH Knoll, MG Butler, S Karam, M Lalande (1989). Genetic Imprinting Suggested by Maternal Heterodisomy in Nondeletion Prader-Willi Syndrome. *Nature*, 342. pp 281-285

- Nobrega, MA, Y Zhu, I Plajzer-Frick, V Afzal, EM Rubin (2004). Megabase Deletions of Gene Deserts Result in Viable Mice. *Nature*, 431. pp 988-993
- Olson, MV, A Varki (2004). Genomics. The Chimpanzee Genome – a Bittersweet Celebration. *Science*, 305. pp 191-192
- Ommen, GJB van et al (1986). A Physical Map of 4 Million bp around the Duchenne Muscular Dystrophy Gene on the Human X-Chromosome. *Cell*, 47. pp 499-504
- Ommen, GJB van et al (1987). Long-Range Genomic Map of the Duchenne Muscular Dystrophy (DMD) Gene: Isolation and Use of J66 (DXS268), a Distal Intragenic Marker. *Genomics*, 1. pp 329-336
- Ommen, GJB van et al (1998). HUGO's Midlife Crisis: Life Begins at 40. *Nat. Genet.*, 19. pp 113-114
- Overveld, PG et al (2003). Hypomethylation of D4Z4 in 4q-Linked and Non-4q-Linked Facioscapulohumeral Muscular Dystrophy. *Nat. Genet.*, 35. pp 315-317
- Pearson, PL, KK Kidd, HF Willard (1987). Report of the Committee on Human Gene Mapping by Recombinant DNA Techniques. *Cytogenet. Cell Genet.*, 46. pp 390-566
- Pembrey, ME (2002). Time to Take Epigenetic Inheritance Seriously. *Eur. J. Hum. Genet.*, 10. pp 669-671
- Reeders, ST et al (1985). A Highly Polymorhic DNA Marker Linked to Adult Polycystic Kidney Disease on Chromosome 16. *Nature*, 317. pp 542-544
- Riordan, JR et al (1989). Identification of the Cystic Fibrosis Gene: Cloning and Characterization of Complementary DNA. *Science*, 245. pp 1066-1073
- Rommens, JM et al (1989). Identification of the Cystic Fibrosis Gene: Chromosome Walking and Jumping. *Science*, 245. pp 1059-1065
- Ruvolo, M (2004). Comparative Primate Genomics: the Year of the Chimpanzee. *Curr. Opin. Genet. Dev.*, 14. pp 650-656
- Saiki, RK et al (1985). Enzymatic Amplification of Beta-Globin Genomic Sequences and Restriction Site Analysis for Diagnosis of Sickle Cell Anaemia. *Science*, 230. pp 1350-1354
- Schmutz, J et al (2004). The DNA Sequence and Comparative Analysis of Human Chromosome 5. *Nature*, 431. pp 268-274
- Sebat, J et al (2004). Large-Scale Copy Number Polymorphism in the Human Genome. *Science*, 305. pp 525-528
- She, X et al (2004). Shotgun Sequence Assembly and Recent Segmental Duplications within the Human Genome. *Nature*, 431. pp 927-930
- Skolnick, MH, HF Willard, LA Menlove (1984). Report of the Committee on Human Gene Mapping by Recombinant DNA Techniques. *Cytogenet. Cell Genet.*, 37. pp 210-273
- Solomon, E et al (1987). Chromosome 5 Allele Loss in Human Colorectal Carcinomas. *Nature*, 328. pp 616-619

- The Huntington's Disease Collaborative Research Group (1993). A Novel Gene Containing a Trinucleotide Repeat that is Expanded and Unstable on Huntington's Disease Chromosomes. *Cell*, 72. pp 971-983
- Venter, JC et al (2001). The Sequence of the Human Genome. *Science*, 291. pp 1304-1351
- Verkerk, AJHM et al (1991). Identification of a Gene (FMR-1) Containing a CGG Repeat Coincident with a Breakpoint Cluster Region Exhibiting Length Variation in Fragile-X Syndrome. *Cell*, 65. pp 905-914
- Waterston, RH et al (2002). Initial Sequencing and Comparative Analysis of the Mouse Genome. *Nature*, 420. pp 520-562
- Weissenbach, J et al (1992). A Second-Generation Linkage Map of the Human Genome. *Nature*, 359. pp 794-801
- Wieacker, P, K Davies, PL Pearson, HH Ropers (1983). Carrier Detection in Duchenne Muscular Dystrophy by Use of Cloned DNA Sequences. *Lancet*, 1. pp 1325-1326
- Wijmenga, C et al (1990). Location of Facioscapulohumeral Muscular Dystrophy Gene on Chromosome 4. *Lancet*, 336. pp 651-653
- Wijmenga, C et al (1992). Chromosome 4q DNA Rearrangements Associated with Fascioscapulohumeral Muscular Dystrophy. *Nat. Genet*., 2. pp 26-30
- Willard, HF, MH Skolnick, PL Pearson, JL Mandel (1985). Report of the Committee on Human Gene Mapping by Recombinant DNA Techniques. *Cytogenet. Cell Genet*., 40. pp 360-489
- Yunis, JJ (1976). High Resolution of Human Chromosomes. *Science*, 191. pp 1268-1270

TECHNOLOGY

Micro- and Nanotechnology for Genomics

Helene M.A. Anderson[1], *Albert van den Berg*[2]

Conventional DNA sequencing technology has limitations in cost, speed, and sensitivity, with as a result that the demand for sequence information far exceeds current capacity. In order to meaningfully use the sequence information currently being generated, the emerging tidal wave of DNA sequence information must be coupled to increasingly faster, cheaper, and more powerful technologies for DNA analysis. Extrapolating from a clear trend over recent decades, these technologies will likely entail ever-smaller reaction scales and ultimately nano-technologies. Cost is the major driving force behind the development of new high throughput technologies. Microfluidics is a field of research involving the manipulation of fluids in micrometer sized channels. Microfluidics technology has basically taken advantage of the inherent properties of liquids and gases from the microscale domain and combined this with microfabrication technology developed from the semiconductor industry in order to build singular devices. One of the features of microfluidics is that it provides a unique access to the nanoworld of biomolecular chemistry, thus offering the capability to manipulate the very basic building blocks of life at the molecular scale where the basic processes of biology occur. The advantages conferred by such microfluidic systems over conventional systems are numerous, including: reduction of reagent volumes, fast response times, well-controlled reaction conditions, parallel processing, speed of separation, improved transfer of mass and heat, low dead volumes, little power consumption, portability, disposability, etc.

1 Prof Dr H.M.A. Andersson, University of Twente, Faculty of Electrical Engineering, Mathematics and Computer Science, BIOS chair, MESA+ Institute for Nanotechnology, Enschede, The Netherlands.

2 Prof Dr Ir A. van den Berg, Twente University, Faculty of Electrical Engineering, Mathematics and Computer Science, BIOS chair, MESA+ Institute for Nanotechnology, Enschede, The Netherlands.

Making explicit use of the unique microfluidic effects, the microfluidic concept has today evolved towards the development of promising miniaturised tools for analyzing biological samples in a way commonly referred as Lab-On-a-Chip (LOC). Applications of miniaturised systems in genetic analysis, clinical diagnostics, combinatorial chemistry, proteomics, drug discovery, and portable instrumentation provide the stimulators for the development towards LOC concepts. An even more futuristic prospect is offered by realising nanofluidic devices, i.e. structures with fluid flow in and around geometries with nanometer dimensions. These devices possess dimensions in the order of the size of (macro) molecules and offer exciting new possibilities for their manipulation and separating, but at this moment they are still at a research stage.
An example of a microfluidic device developed for DNA analysis is shown below, see Figure 1. It is a flow-through filter-chamber device with a volume of 0.5 nl. DNA synthesis was monitored in real time by consecutive flushing reagents through the target DNA captured in the reaction chamber of the microfluidic device. The setup enables reproducibly sequencing of at least six consecutive bases, which is sufficient for SNP applications [Andersson, 2001; Ahmadian, 2002].

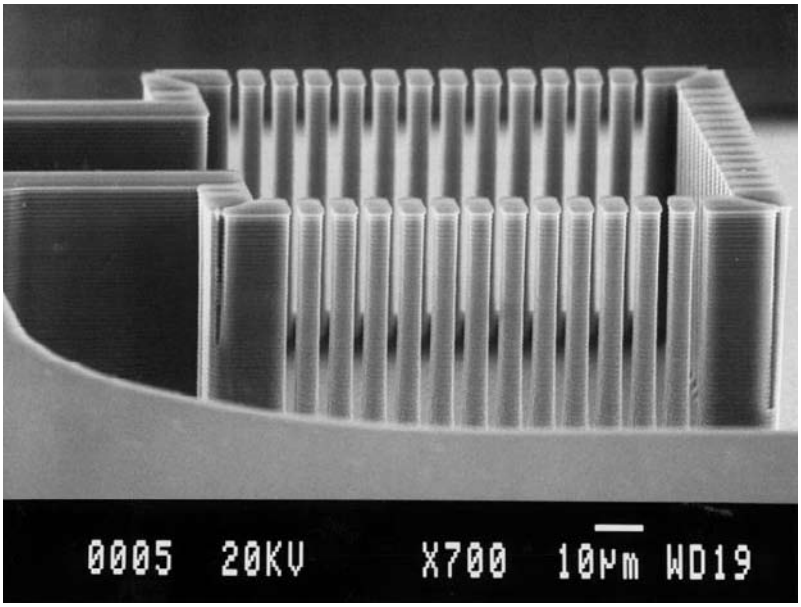


Figure 1
A filter-chamber device developed for bead based assays.

In Figure 2 a system for DNA analysis demonstrating the potential of integration is shown. This device is capable of DNA amplification or digestion, and labeling and separation of the resulting products. This compact system incorporates fluidics, pressure mobilization controlled temperature reaction chambers, sensors, gel electrophoresis and a fluorescence diode detector in one single unit [Burns, 1998].

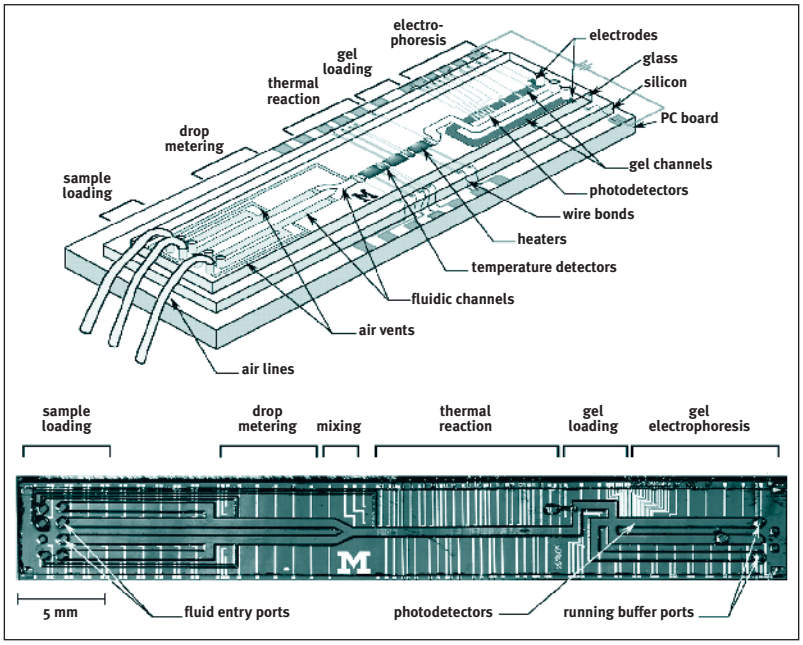


Figure 2
(Top) Schematic view of an integrated device with two liquid samples and electrophoresis gel present. (Bottom) Optical micrograph of the device seen from above.

It is clear that with the recent technological developments many life-science researchers obtain very powerful tools for detailed biological studies. A novel concept, Lab-In-a-Cell (LIC), has been described [Andersson, 2004] which combines the best of both worlds: the use of the biological 'unit', a cell, as a laboratory to perform complex biochemical operations, and advanced micro- and nanotechnological tools to access and analyse this laboratory and interface it with the outside world. Nowadays, many efforts are made trying to mimic the properties of single cells in order to design chips that are as efficient as cells. However, cells are nature's nanotechnology engineering at the scale of atoms and molecules and it will be very difficult (if not impossible) to create Lab-On-Chips that are as efficient as cells. It might therefore be better to vision chip solutions in which one single cell constitutes the core, the workhorse, and the chip is the interface that enables manipulation, characterization and communication, a Lab-In-a-Cell, see Figure 3. In Figure 4, one example of LIC is shown, in which single cells are trapped on chip and enable real time studies of cellular processes such as apoptosis which are currently not possible with the conventional technologies [Valero, 2005].

Many diseases are associated to a distortion of normal progression of cellular processes. Distortion of apoptosis (programmed cell death) is directly related to cancer (too little apoptosis) or neurodegenerative diseases such as Parkinson and Alzheimer (too much apoptosis). Therefore, it is of great relevance to be able to study these processes at single cell level. In drug development tests performed with drugs on individual cells may replace part of the animal tests. Analysis (of arrays) of individual cells may help medical doctors

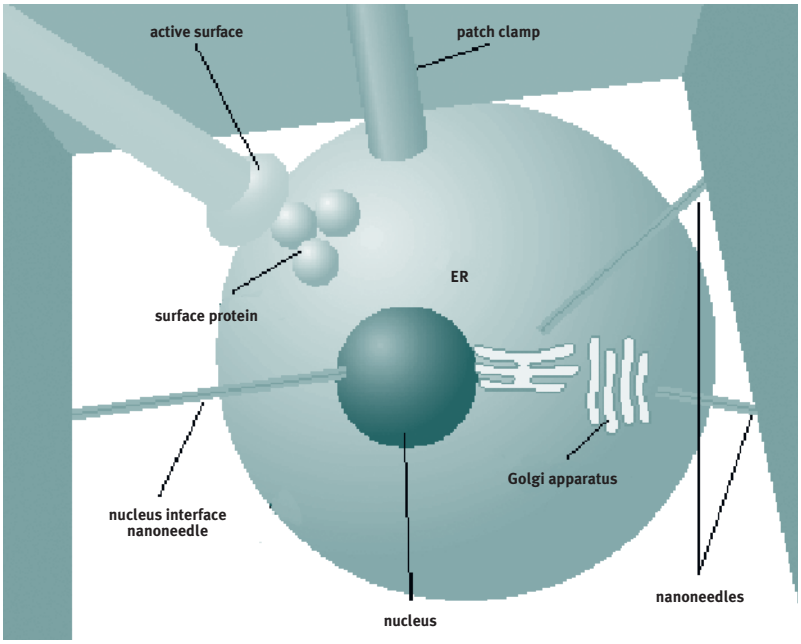


Figure 3
Conceptual drawing of the Lab-In-a-Cell [LIC] concept.

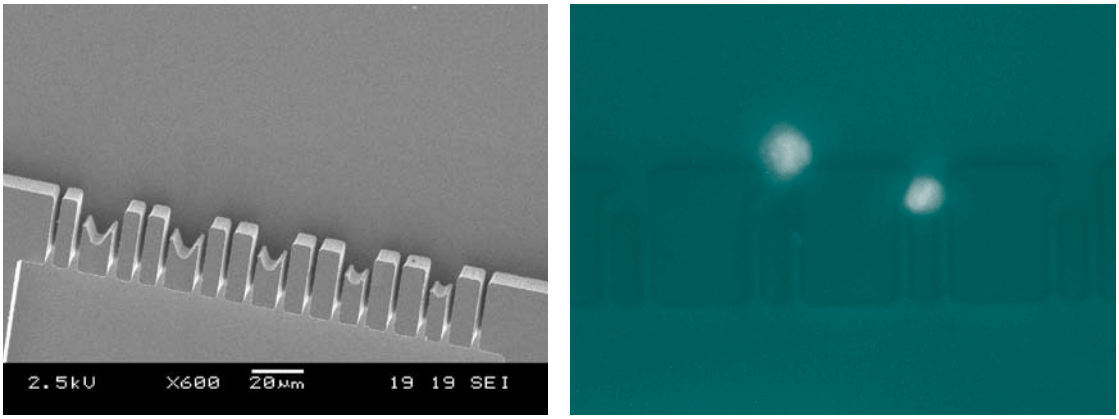


Figure 4
A single cell trap for real time studies of cellular processes.

in diagnosing diseases. Thus, the tools that have recently become available with micro- and nanotechnologies will help life-science researchers to better understand the origin of diseases, drug developers to develop better drugs and medical doctors to make improved diagnosis. As an example, instead of culturing certain bacterial cells for several days in order to investigate these cells, the few cells initially taken from a patient may be directly immobilised on a chip surface and assessed individually. This would dramatically speed up the diagnosis time, and illustrates the potential benefit of the LIC approach.

References

– Ahmadian, A, A Russom, H Andersson, M Uhlen, G Stemme, P Nilsson (2002). SNP Analysis by Allele-Specific Extension in a Micromachined Filter-

Chamber. *Biotechniques*, 32 (4). pp 748, 750, 752, 754
- Andersson, H, W van der Wijngaart, G Stemme (2001). Micromachined Filter-Chamber Array with Passive Valves for Biochemical Assays on Beads. *Electrophoresis*, 22. pp 249-257
- Andersson, H, A. van den Berg (2004). Lab-In-a-Cell: Using Individual Cells as Experimentation Platforms. *Current Opinion on Biotechnology*, 15. pp 1-6
- Burns, M, B Johnson, S Brahmasandra, K Handique, J Webster, M Krishnan, T Sammarco, P Man, D Jones, D Heldsinger, C Mastrangelo, D Burke (1998). An Integrated Nanoliter DNA Analysis Device. *Science*, 282. pp 484-487
- Valero, A, F Merino, F Wolbers, R Luttge, I Vermes, H Andersson, A van den Berg (2005). Apoptotic Cell Death Dynamics of HL60 Cells Studied Using a Microfluidic Cell Trap Device. *Lab on a Chip*, 5. The Royal Society of Chemistry. pp 49-55

Myths and Miracles of Medical Imaging

Sjaak Deckers[1]

Medical Imaging

Medical Imaging has been listed amongst the top-11 major revolutions of the past century, and for good reason! Starting in 1895 with W. Röntgen, who discovered X-rays, the field has moved into a number of modalities that together can obtain superb anatomical and functional information of the human body in a non-invasive way.

X-rays have evolved in various ways. Classical projection, nowadays with digital detection techniques, are used for chest X-rays and other relatively simple two-dimensional images. High-speed imaging at very low doses has opened up the new field of minimally invasive interventional procedures, like the dottering and stenting of cardio-vascular arteries. With CT scans, or Computed X-ray Tomography scans, invented by G. Hounsfield and others in the 1970s, high-resolution slices or full three-dimensional images can be made of the human anatomy in order to assess lung nodules, or blood perfusion in the human brain. Development of ultrasound, using sound waves, started already in the early 1920s, but has evolved into a modality with many applications and also beautiful images, for instance of human foetuses. Nuclear Medicine, both Single Photon Emission Computed Tomography (SPECT) and Position Emission Tomography (PET) have used nuclear techniques to image biological processes in the human body, like viability of the heart muscle or the biological activity of malignant lesions.

1 Dr S. Deckers, Philips Medical Systems, Corporate Technology Office, Eindhoven, The Netherlands.

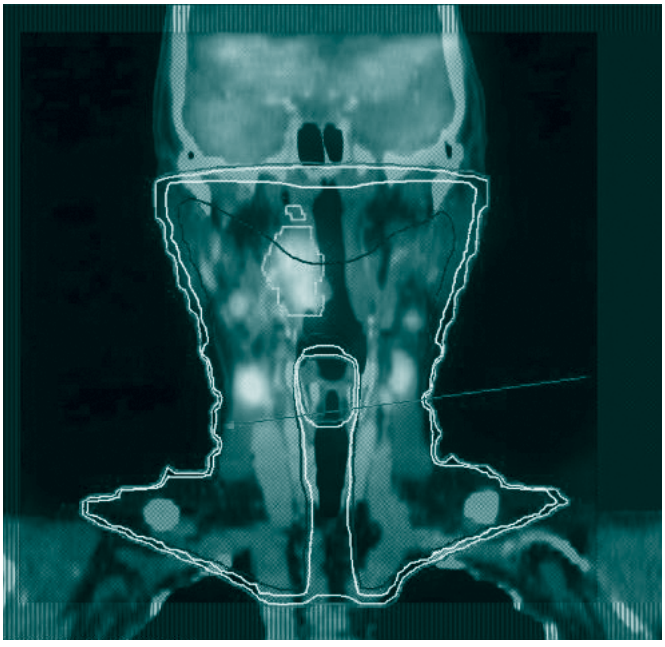
These past 30 years, Magnetic Resonance Imaging (MRI), where images are made using pulsed radio waves in a high magnetic field, has emerged as another modality that can provide high-resolution anatomical images without the ionizing radiation of CT and X-ray. With functional MRI, images can even be made of the place where thinking processes are located in the human brain thanks to increased activity and oxygen consumption of active regions in the brain.

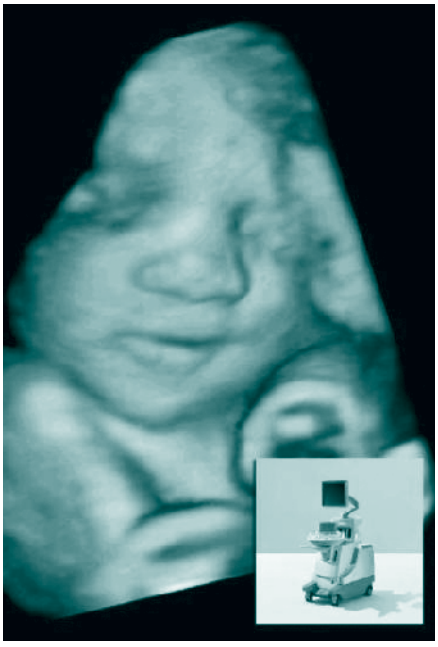
In recent years, combining various modalities to get the benefits of both has been a major trend for medical equipment vendors. Examples are integrated Ultrasound probes on a modern cathlab for interventional cardiovascular procedures, integrated PET-CT and SPECT-CT machines and integration of MRI and interventional X-ray systems in adjacent rooms using a patient transportation system. Another trend is the increasing use of contrast agents injected in the blood to enhance the contrast for improved imaging of the cardio-vascular system. Nuclear Medicine has always used contrast agents or radiopharmaceuticals for their imaging. But contrast agents have been developed for X-ray and CT, MRI and even for Ultrasound, in the form of microbubbles that enhance contrast.

Figure 1
PET image combined with a CT image, made with the PMS Gemini GXL, a hybrid PET-CT system, of the head and neck region of a patient with several lesions in the neck, with some radiation dose contours superimposed to guide the radiation therapy. Courtesy of Dr Bujenovic, Mary Bird Perkins, Cancer Center, Boca Raton, LA, USA.

Figure 2
Three-dimensional Ultrasound image showing face and upper torso of a 7-month-old foetus in the womb.

The latest trend in Medical Imaging is closely related to developments in the pharmaceutical and biotech industries, where more and more drugs are developed that very precisely aim biological targets like tumour cells or pathological events. This type of healthcare is also known as Molecular Medicine, or





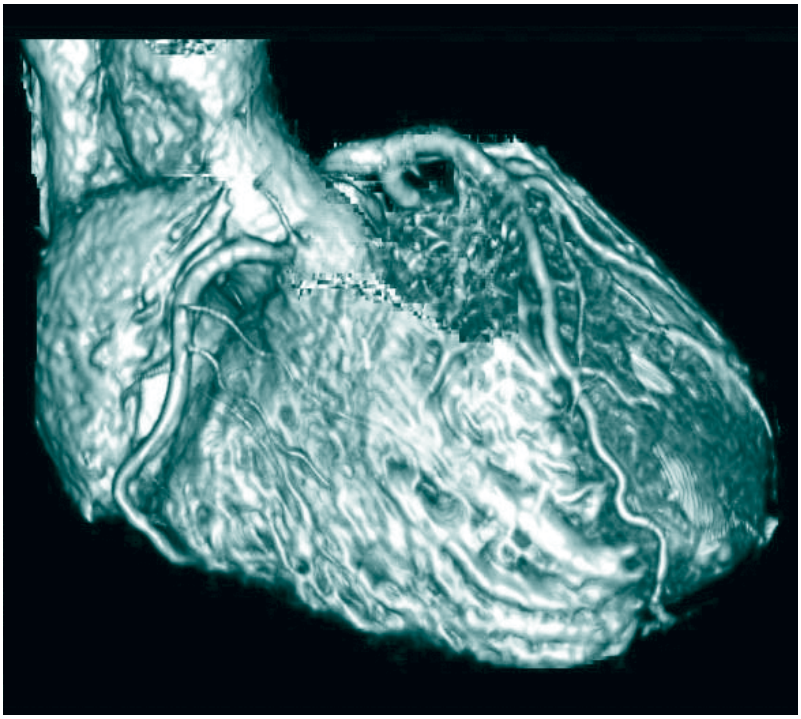


Figure 3
3D MRI image of the human heart, showing the aorta and coronaries.

Molecular Therapy. These developments can also be extrapolated to imaging, when biological processes are imaged, like amyloid plaques in early Alzheimer detection, or the viability of small lesions in tumour staging. One can even go further and try to detect pathologies *in vitro* in the blood or other body fluids by similar technologies, called Molecular Diagnostics.

Molecular Medicine (in this article abbreviated as MM), and adjacent terms as Molecular Imaging (MI), Molecular Diagnostics (MD) and Molecular Therapy (MT) show great promise for the future. These days many scientists can be found who claim future developments that will revolutionize our industry, opportunities that require investments, big investments, at once, fast, to prevent the competition from taking the lead. Let us try to separate the miracles from the myths.

Intermezzo

MM (Molecular Medicine) describes a current healthcare science that is more and more based on fundamental research regarding cells, proteins, genes and molecular pathways, in order to understand the real causes of diseases and to develop better drugs. Molecular processes leading to various types of cancer, neuro-degenerative disorders like Alzheimer, Parkinson, and cardio-vascular diseases are being unravelled with ever-increasing speed.

So as to better understand these developments some elementary biological knowledge is essential. All genetic properties of man, also called the human genome, with over 3 billion nuclear acid building blocks of 4 different 'colours', are coded into a few very long intricately folded molecules, called the DNA (Deoxyribo Nuclear Acid), present in the nucleus of virtually every cell in a human body. Pieces of this DNA, called genes, man has about 30,000 of them, contain a genetic code for making all proteins that a cell is made of. These genes can be transcribed into RNA molecules that leave the cell nucleus and are translated into proteins by miniature chemistry factories called ribosomes, who themselves are complex protein structures. There are 20 different protein building blocks called amino acids and each triplet of DNA building blocks codes for one of the proteins (or start/stop instructions for the ribosomes, with quite some redundancy). These proteins, called the proteome, take care of all biological processes in the cell, such as energy supply, proliferation, signalling, structural integrity, and all other functions of human cells and tissues. This order, from DNA to RNA to proteins, is often called the central dogma of modern biology (despite the fact that more and more refinements and deviations from the dogma are being discovered). An estimated 250,000 proteins or protein complexes can be active in a single human cell, such as membrane proteins coating the cell, skeleton-proteins for structural integrity, signalling pathway proteins to transport signals from the membrane to the cell nucleus, metabolic proteins turning food into fuel, and numerous proteins controlling the copying and proofreading of DNA for cell multiplication and transcription of DNA into RNA. In the cell membrane, there are also numerous receptor proteins to communicate with other cells by means of extra-cellular proteins, peptides (very small proteins), or other small molecules, often called ligands or biomarkers. These biomarkers are highly specific for the molecular shape of these receptors and fit unto these like a key in a lock.

Molecular Medicine

I would like to apologise for this tedious intermezzo, but it allows me to use some terms explained above. In recent years, large groups of oncology scientists have precisely discovered which successive genetic modifications are necessary to turn a human cell into a cancerous cell. For breast cancer, several inherited gene defects have been discovered that will accelerate these changes, resulting in a largely increased probability to get this disease. In addition, more and more subtle differences between tumour cells and normal cells are being found. Some tumours have much more signalling or metabolism-related receptors on their membrane. Slightly modified versions of the associated ligands for these receptors can be synthesised and used to bind to these receptors and therefore block, for instance, a proper inflow of nutrients to these tumour cells. Tamoxifen, Femara, Avastin, Rituxan, and Glivec (or Gleevec, for US readers or users) are recent examples of these molecular

drugs that are based on this principle. Many drug discovery programmes in biotech and pharmaceutical companies are based on this detailed knowledge having molecular biology as a basis, and the resulting drugs are also called smart or targeted drugs.

Molecular Imaging

Molecular Imaging is only a small part of this large MM domain. As early as since the discovery of X-rays over a hundred years ago, imaging has played an important role in diagnosis and treatment planning of many diseases: early diagnosis results in higher survival rates, and fast monitoring of the effectiveness of a therapy will also result in significant time gains. However, most current imaging methods, like X-ray, MRI or CT only show anatomical structures, broken bones, congested arteries or tumour masses. Other methods are able to image molecular differences between normal and diseased cells or tissue and to image biological processes. It is possible to label, for instance, glucose (sugar) molecules with 18F, which is slightly radioactive (for 2-3 hours), emitting positrons that can be detected using a PET scanner. The adsorption rate of this Fluoro-Deoxy-Glucose, or FDG, is proportional to the metabolic activity of a cell, and allows a doctor to see where in the body are places of increased metabolism, a tell-tale sign of tumour cells. A new experimental method is the use of 99mTc-labeled glucose, an agent used with SPECT, another nuclear technology that is cheaper than PET and very widely used nowadays in hospitals.

In order to use MRI for targeted imaging, people have made very small nano-particles filled with material with a high MR sensitivity, for example for the early detection of cardio-vascular diseases: in atherosclerosis, coronary or carotid arteries are clogged by a so-called plaque. In these plaques, there are newly grown blood vessels that express certain receptors not found on normal cells. When ligands to these plaque-specific receptors are attached to the outside of these nano-particles, these plaques can be imaged. One can go even one step further by adding a drug to these targeted particles so as to dissolve the plaque. Here MI and MT are merged into a joint targeted diagnosis and treatment procedure.

There are many ways to use imaging equipment for so-called functional imaging: correlate local oxygen consumption in the brain measured with MRI scanners to thinking processes; imaging the local changes in neurotransmitter concentration in the brain of patients with neurological diseases with nuclear technologies like PET or SPECT, or, using the same technologies or Ultrasound in order to register changes in heart muscle activity under physical stress.

A large uncertainty is still the developing speed of these agents, including all clinical trials and registration, before they are brought on the market. Current estimates still assume a tedious road ahead, with years of pre-clinical and clinical experiments. To conclude, there is a lot of truth in the miraculous promises of Molecular Imaging and Therapy, but expectations about when these products will hit the market are usually rather exaggerated.

e-Science in Life Sciences

Bob Hertzberger[1]

Introduction

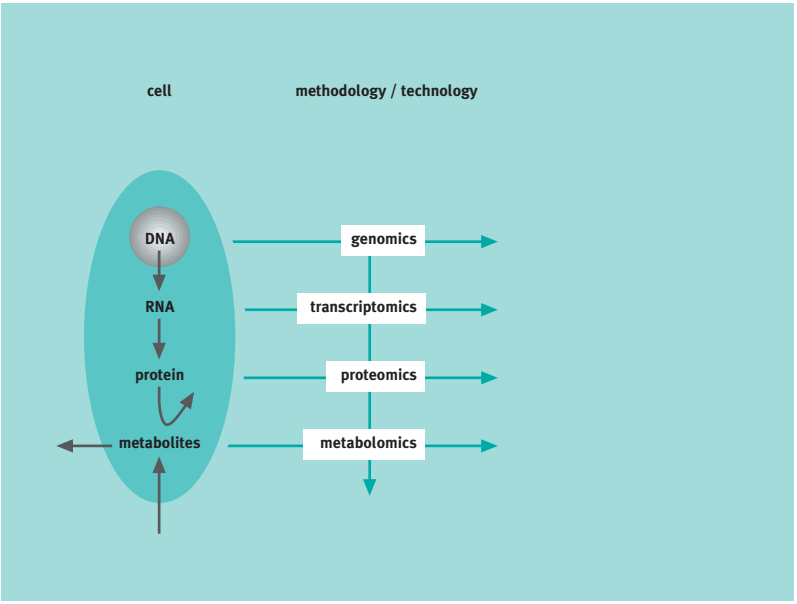
Internet and WEB are abundantly present in day-to-day life and networking and computing speed are improving at an impressive rate. The scientific community has been active to further exploit the pervasive computing power connected with regard to the Internet, also called the Grid. Nowadays, more and more attempts become visible to integrate WEB and Grid developments and apply them to various scientific domains often called e-Science.

In order to make e-Science work, a computing and networking environment has to be created that has to support the requirements of various scientific domains such as those of life sciences or high energy physics research.

When looking at current experimental sciences, one of the most important observations is that experiments become increasingly more complex due to the increase in detector resolution and automation as well as robotisation. For example, in biology the study of a particular genome is replaced by studying a large amount of genomes in what is called the genomics experiments which have been made possible via microarray equipment. Such high throughput experiments produce large quantities of data. An illustration of this so-called 'omics influence in life sciences' is illustrated in Figure 1.

1 Prof Dr L.O. Hertzberger, Computer Architecture and Parallel Systems Group, Department of Computer Science, University of Amsterdam, The Netherlands.

Figure 1
Omics methods in life sciences.



Such changes must have an impact on the way life science experiments are looked into, especially in the long run. Past experiments were hypothesis driven to evaluate existing hypothesis in order to complement this knowledge. Present experiments are based on data in order to acquire knowledge out of large amounts of data. This inevitably leads to a paradigm shift in life sciences. In such new experiments statistical techniques are applied so as to acquire new insights from the large data sets being produced.
Moreover, data sets of interest are not limited to one's own laboratory but are distributed all over the world. Therefore, it becomes necessary to have the methodology as well as the permission to access the interesting parts of other people's data sets, in order to complement one's own knowledge. This approach differs from those of the past and requires, beside other methods and techniques, another type of ICT based infrastructure.
The result of the increased complexity of experiments is an increase in amount and complexity of the data they produce. This is often called the 'application data crisis'. Some of the consequences are illustrated in Table 1.

Table 1
Some examples of the application data crisis.

Medical Imaging (fMRI)	~ 1 Gbyte per measurement (day)
Bio-informatics queries	~ 500 Gbyte per database
Satellite world imagery	~ 5 Tbyte per year
Current particle physics	~ 1 Pbyte per year
Future particle physics	~ 10-30 Pbyte per year

Another problem complicating this situation is the fact that data are often widely distributed.
In a field such as High Energy Physics the impact of new instrumentation was dramatic. In early experiments a particle beam was fired at a target and the resulting particles were studied via photos taken from a so-called 'bubble chamber'. In this situation only low density experiments could be performed. This situation changed when new instrumental techniques made so-called 'counter experiments' possible. However, these experiments produced much more data. It took a number of years before the big data sets resulting from these experiments could be processed in such a way that the scientifically important information could be extracted. In addition, these instrumental methods resulted into rethinking experiments in general and produced a completely new type of very high density, the so-called 'colliding beam experiments'. These developments had an impressive impact on the elementary particle field itself and produced numerous new insights.

I would not like to suggest here that a completely similar development in life sciences can be expected, but such developments certainly cannot be ruled out. In addition, understanding the potential of high throughput experimentation will undoubtedly require a rethinking of experiments themselves in a new design for experimentation.
One step forward would be to ensure that the heterogeneous data repositories resulting from these experiments could be made more easily available in a networked computer environment. This means that the experimental resources have to be made virtual. In such a way it will become possible to easily create data repositories and retrieve the relevant information whenever and wherever necessary. By doing so, an important step can be made towards collaborative experiments and e-Science.
It is to be expected that these developments will have a profound impact on life science experimentation, and the resulting profession and consequently will have an impact on future targets in health care. In addition, it will revolutionise the way in which information is used in the medical profession, whether in medical hospitals or by other medical practitioners.

e-Science objectives

WEB is about exchanging information that can be interpreted by man. The Grid is aiming at harnessing computer resources and making them available for sharing by virtualisation. In the case of science, this implies the sharing of computing power, data and information repositories, as well as expensive experimental facilities such as an fMRI for cognition research.
Not only coping with the data explosions, e-Science is also being targeted at enabling multidisciplinary research combining human expertise and knowl-

edge between domain scientists (such as biologists) and ICT scientists. Because the computer is becoming an integrated part of experiments it will require a different approach as to experimentation.

For e-Science to stimulate the scientific creativity and consequently being effective, the following requirements could be defined:

- Stimulating collaboration by sharing data and information.
- Improve re-use of data and information.
- Permission to search data and information from different modalities by using sensor data and information fusion.
- Realise the combination of real life and (model based) simulation experiments.

An example of the importance of sharing for collaboration can be found in the case of using fMRI for experimental cognition research mentioned before. A long debate about the usefulness of data-sharing using large repositories of data coming from cognition experiments was recently brought to an end, at least temporarily, by a Nature article showing the potential of such undertakings for neurosciences [Van Hove, 2004]. Based on a prototype implementation of such a database, it was outlined which advantages sharing studies for human cognition had for collaborative research, such as information sharing, independent experiment validation, training, etc.
In order to make the shared usage of data more successful, it is important to standardise protocols which inevitably will lead to more de facto rationalisation of the experimental process. This has the advantage that the experiment becomes more reproducible and comparable and allows better re-use of experimental results. Especially in the area of microarray experimentation this is an important issue, as the conditions under which the arrays are prepared are important when studying the results from other peoples experiments. This touches the issue of publications and what data to submit in order to support the claims made in an article in general.
The potential of combining real life with model-based simulation experiments can only be exploited in full if one realizes that it will be essential for the computational experiment that it can be validated. In the case of life sciences, this implies data from available databases that are well curated.

The combination of sensor detection modalities can be very important so as to get a better insight in a certain problem, such as the development of a certain illness. One example is the combination of data coming from transcriptomics (microarray-based) experiments with those coming from proteomics (mass spectroscopy-based) research. The combination of the data coming from these two different techniques could be used, for instance, to get a better insight in

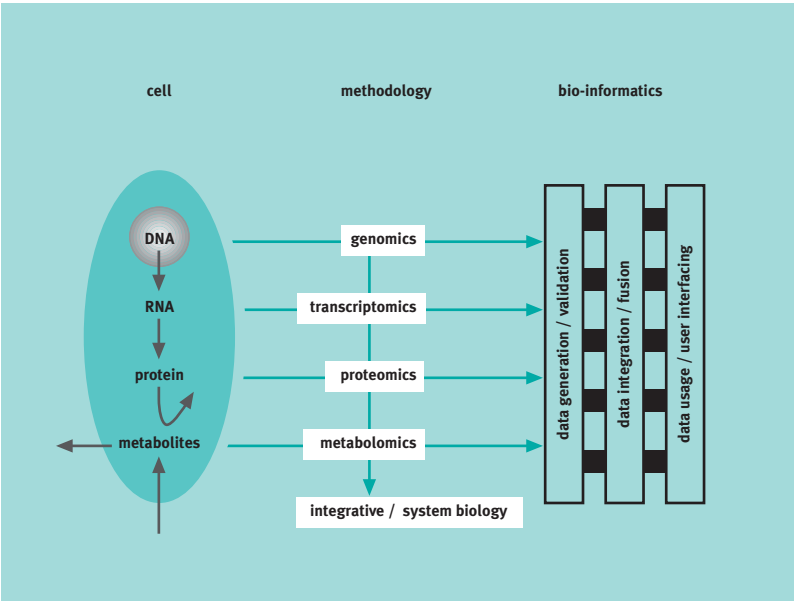
certain phenomena causing breast cancer. When doing so, it becomes important to have good possibilities to calibrate the datasets, otherwise the predicting values of the methodology cannot be fully exploited.
The result of all this will be the emergence of a considerable more widely distributed environment in health care in which the role of the various parties will change. In addition, the amount and complexity of medical data will considerably increase. Handling these data and extracting the correct information will make new demands on the medical methodology, a methodology in which ICT and ICT infrastructure will play a predominant role.
Because of this, e-Science should result in computer-aided support for the rapid prototyping of ideas and thus stimulating the creativity process. e-Science should be realised by creating and applying new methodologies and an ICT infrastructure stimulating this.
It should be realised that the same ICT infrastructure that has to be created for e-Science can also be used to form the basis for the development of new, more widely distributed applications in health care. One of the important requirements for the development of this infrastructure is that the results of application experiments done on top of this infrastructure can be rapidly back-propagated and tested in the form of new features of this infrastructure. Along these lines we have started our Virtual Laboratory for e-Science (VL-e) project [Virtual Lab e-Science, 2003].

Virtual Lab for e-Science (VL-e) research philosophy

The aim of the VL-e project is to do multidisciplinary research in different application domains in order to develop generic methodologies, as well as to develop the necessary ICT infrastructure.
As a result, our various application cases stimulate computer and computational science and engineering research. Bio-informatics that will play an essential role in handling and extracting biological and medical knowledge for the medical and pharmaceutical profession will be used here to further illustrate this point.
On the one hand, bio-informatics has the scientific responsibility to develop the underlying computational concepts and models in order to convert complex biological data into useful biological, chemical and pharmaceutical knowledge. On the other hand, it has the technological responsibility to manage and integrate huge amounts of heterogeneous data sources from high throughput experimentation, such as microarray and mass spectroscopy experiments. Bio-informatics is believed to be one of the most important enabling technologies necessary to develop new directions in biology, medicine and pharmacy.

In Figure 2, which is a further extension of Figure 1, the role of bio-informatics is further illustrated. Because genomics is critically dependent on information

Figure 2
The role of bio-informatics.

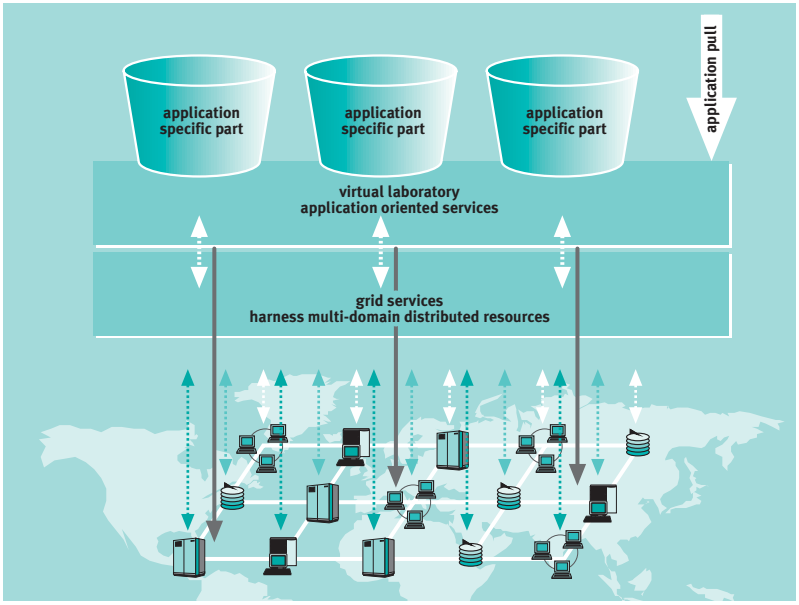


stored in internationally accessible databases, the need to handle large heterogeneous data repositories is essential. The access provision of these repositories depends on the availability of a good ICT infrastructure and illustrates the intertwining of bio-informatics and its infrastructure as well as the fact that bio-informatics is an e-Science.

So as to realise application-based research for the various domains, it became necessary in the VL-e project to develop a separate problem-solving environment for each of the research domains (see Figure 4). However, when studying the commonalities between these problem-solving environments for the different application cases, it became apparent that essentially two different parts could be distinguished. One part is application-specific for a particular domain. The other, in which such issues as visualisation, information management, workflow concepts, aspects of modelling and simulation, etc. have to be realised, is common for all and consequently generic in nature. For example, methods and software realising imaging for MEG (MagnetoEncefalogram), PET (Positron Emission Tomography) or MRI can be developed in such a way that they can be re-used and consequently can be made part of the virtual laboratory environment (see Figure 3). The VL-e project extensively uses the concept of a problem-solving environment which has a generic part and an application specific part.

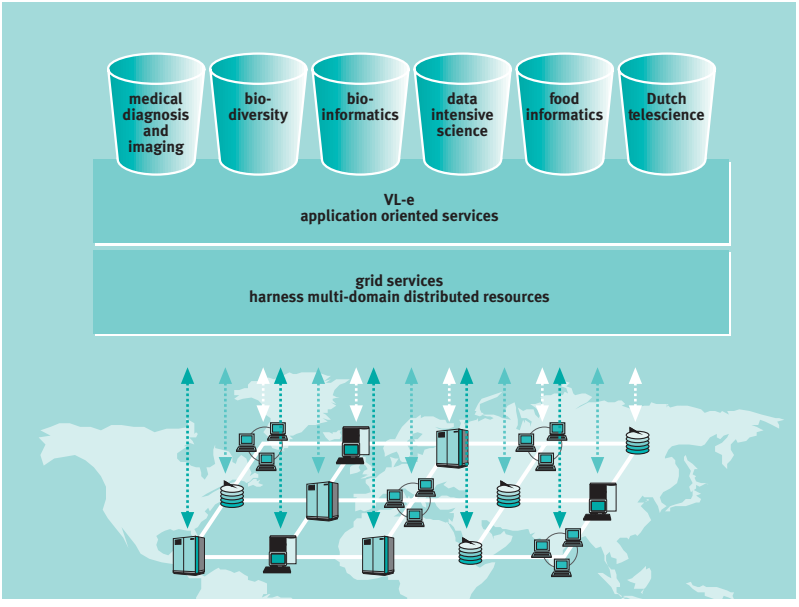
In Figure 4, the project and its various application cases are illustrated. The medical case mainly looks at fMRI applications for medical and cognition research. The biodiversity application has as a target the studying of the problem of integrating large amounts of small databases containing information about species.

Figure 3
Problem-solving environment.



The so-called Dutch Telescience Laboratory is specifically looking into the usage of proteomics apparatus like mass spectrometers and the way the pre-processing of the data has to be handled. Moreover, its aim is to build data repositories that can be shared. The role of bio-informatics has been discussed above. The Food Informatics case aims to develop an environment where food ontologies and their roles in improved designed food processing can be studied.

Figure 4
Various VL-e application domains.



The Data Intensive Science case studies the role of data handling and processing for experiments in high-energy particle physics as well as in astronomy. The fact is that the VL-e project intends to re-use software components wherever and whenever possible. This might have an impact on the design of the experiment [Belloum et al, 2003]. It has already been observed that design is important for experimentation when dealing with new types of instrumentation. The use of computer methodology as an integrated part of the experimental system can also be considered as a form of experimentation.

All factors discussed here lead to the necessity to further rationalise (and de facto standardise) the various steps undertaken when carrying out an experiment and consequently make it better reproducible and comparable.

In Figure 5, the issues that arise when designing an experiment in a virtual environment are illustrated. In this simple drawing, it is outlined that in all steps of the experimental process information is lost which plays an essential role when studying the results. In order to better capture this information, it will be necessary to formalise it in the form of protocols and capture it, among other things, via workflows and meta data. This has certain disadvantages because it might also limit the scientists in their creativity. On the other hand, the consequence of the use of a computer in an experiment is the necessity to explicitly describe steps in the computer-controlled experimentation process in order to improve reproducibility. The importance of this fact in the case of microarray and fMRI experimentation has already been illustrated.
So as to improve the quality of the protocols translating the experiment into

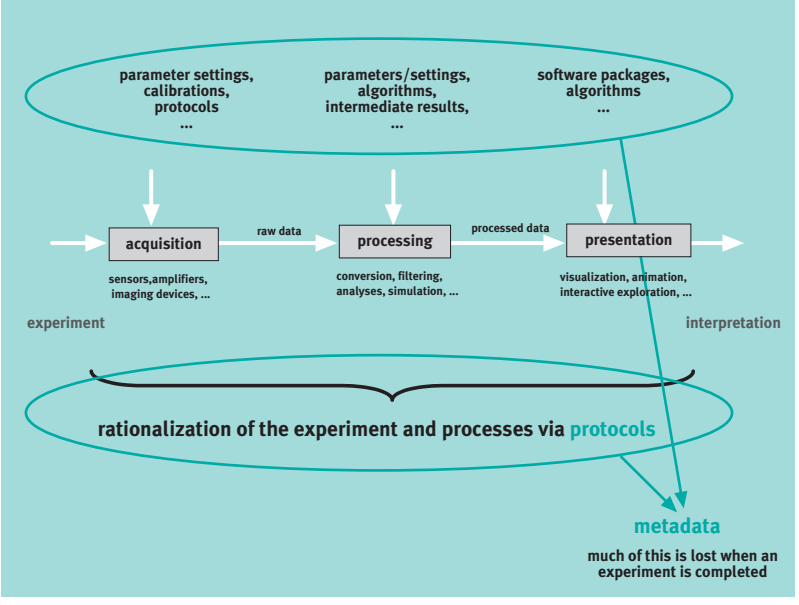
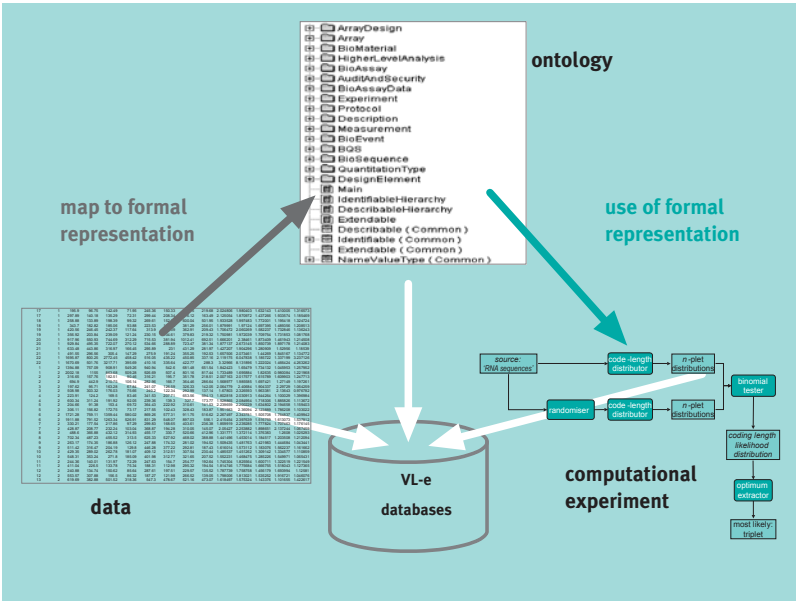


Figure 5
Reproducible experiment.

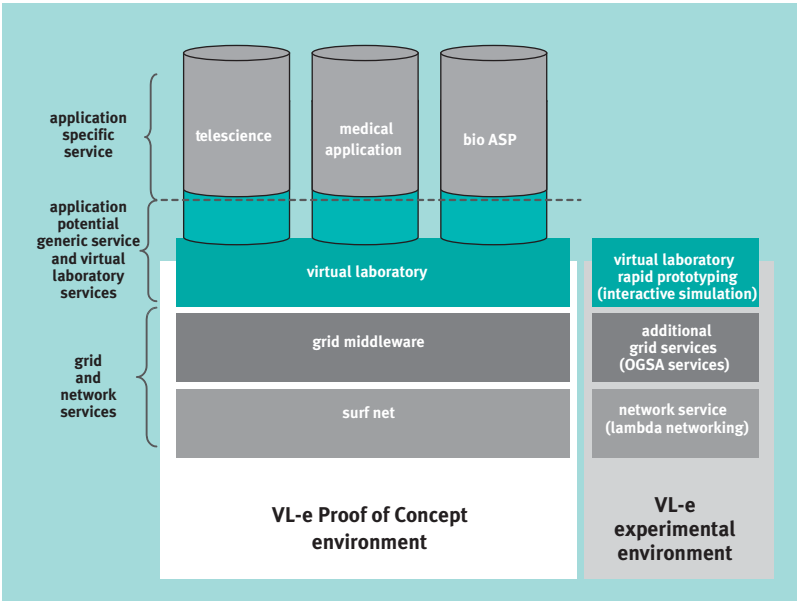
Figure 6
Use of ontologies for data modelling in bioinformatics.



computer-interpretable activities, they can be based on workflow definitions in order to help to re-create complex experiments into process flows. Such workflows can then play a role in the control over and the execution of a computer experiment. They can also be used as a basis to configure the various processing and data modules that are necessary for the interpretation and visualisation of experimental data. In order to define all these activities, ontologies can help to make knowledge about an experiment explicit in order to obtain a well-structured realisation of an experiment.
In Figure 6, an example of data modelling while using ontologies in microarray experiments is presented.

In the VL-e project it was found that the combination of application-based ICT based research as well as basic computer and computational science research required different computer-based environments. The reason for this was that the application-oriented research required an environment with a certain amount of stability that would severely limit both the creativity and the needs of the computer or computational science researchers. A researcher in bioinformatics for transcriptomics should be able to use the infrastructure and concentrate on his topic i.e. developing new software for microarray experiments analysis. This cannot be effected if there is not a certain level of stability in the underlying hardware and software of the ICT infrastructure.
On the other hand, a Rapid Prototyping Environment is necessary where computer, computational and domain-specific ICT scientists can conduct their experiments. In addition, new ideas in application-based virtual laboratory research might have an impact or might demand new facilities from the

Figure 7
Proof of Concept (PoC) and Rapid Prototyping Environments.



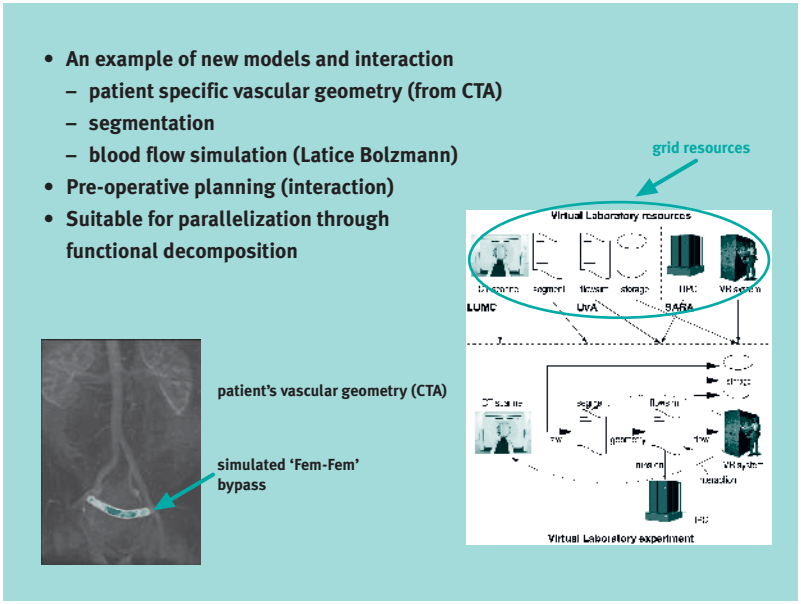
underlying ICT infrastructure. This can be tested in the Rapid Prototyping Environment. Therefore a distinction is made between the former and the latter — the more stable Proof of Concept (PoC) Environment (see Figure 7). One of the consequences of making this choice is the issue that software developed in the Rapid Prototyping Environment has to migrate towards the PoC and that consequently an authentication authority is required that will thoroughly test the software before it is accepted in the PoC.

e-Science example

One example of the use of the PoC is the problem-solving environment for Simulated Vascular Reconstruction [Belleman and Sulakov, 2002] with the aim to realise computer-aided design of a bypass operation in a virtual operating theatre (see Figure 8). It is a good example of model-based interaction and computational steering. A patient is put in a CT (Computed X-ray Tomography) scanner so as to obtain the geometry of the blood vessels under consideration. Thereupon, a simulation of the bloodstream through the vessels is obtained using Lattice Bolzmann methods. The CT scanner is located in Leiden, whereas the blood flow simulation is carried out on a grid system in Amsterdam.

Visualisation and interactive steering is realised in Amsterdam as well as in Leiden. This is an example of an application that has been realised on various locations and is carried out by different groups in the Netherlands working on the same problem, but each group on different aspects. It is also a nice example of how to realise multidisciplinary research.

Figure 8
Medical problem solving.



Consequences for the future

The question arises what the impact of the research developments described here will be on the everyday lives of practitioners in the medical profession and in the pharmaceutical and food industries in the future.
As illustrated before, the increase in complexity of the various detectors like PET, MEG, MRI that will be used in medical and pharmaceutical practice will have as a consequence that the amount of data will continue to explode. This explosion will be further fed by the emergence of ubiquitous small sensors that can be used to continuously observe patients as well as healthy individuals so as to monitor or prevent the development of illnesses. One condition for successful exploitation of this development is the necessity to harness the large heterogeneous and distributed sources of data and information that will result, so that useful and timely information can be extracted. Information that, for instance, might be used for a better prediction of the effects of drugs in order to improve the treatment of a disorder or so as to be used for prevention.

The consequence of these developments for hospitals will be that they will have to handle much more data as well as much more complex data than nowadays. It is the question whether the current data handling systems, which are largely centred around the centralised model of PACS (Picture Archiving and Communication System[2]) systems, will be sufficiently scalable so as to be able to handle this flood of heterogeneous data and meta data in the future. Moreover, it is the question whether current patient protocols are adequate to describe knowledge about a patient to the level where simple but time-

2 System used in hospitals to file medical images.

consuming processes can be automated, so that data can be reduced to information that can be used for primary processes such as diagnostics and treatment.

Modern ideas about personalised medicines based on ambient sensor availability can only be realised when the problem of data and information handling can be solved. In addition, the successful deployment of these developments is not only a data handling problem, but it will also require extensive and time-consuming research in order to create validated patient models characteristic for the development of all type of health risks.

These experiments will benefit from an e-Science research as well as an infrastructure as described here, targeting:

- A better methodology to handle and integrate large amounts of data and information originating from new diagnostics devices such as microarrays, proteomics arrays, mass spectrometers, CT, CAT (Computed Axial Tomography), MEG, PET, MRI etc. but also small sensory devices such as those for continuous blood pressure measuring.
- Improved models for predictions based on and validated by the information from these devices as well as on multi modal information integration.

If these problems can be solved this will create the possibility for a more personalised health care system — based on a considerable more widely distributed environment than nowadays — that can be used for prevention and treatment. In such a system, the role between hospitals, practitioners and other health care parties and (potential) patients will dramatically change in time. What such a system will look like, how quickly it will emerge and to which extent it will be accepted also depends on other than just technological factors such as organisational, economical and sociological ones.

Acknowledgements

This work described here has been carried out in the context of the Virtual Laboratory for e-Science Projects (www.vl-e.nl). This project is supported by a BSIK grant from the Dutch Ministry of Education, Culture and Science (OCenW) and is part of the ICT Innovation Program of the Ministry of Economic Affairs (EZ).

References

- Belleman, RG, R Sulakov (2002). High Performance Distributed Simulation for Interactive Vascular Reconstruction. In: PMA Sloot, CJK Tan, JJ Dongarra, AG Hoekstra (eds.). Computational Science-ICCS 2002. Proceedings Part III. Lecture Notes. *Computer Science,* 2331. Springer Verlag. pp 265-274

– Belloum, ASZ, DJ Groep, ZW Hendrikse, LO Hertzberger, V Korkhov, CTAM de Laat, D Vasunin (2003). VLAM-G: A Grid-Based Virtual Laboratory. *Future Generation Computer Systems*, 19 (2). pp 209-217
– Hove, DJ, ST Grafton, D Rockmore, MS Gazzaniga (2004). *Nature Neuroscience*, 7. pp 471-478
– Virtual Lab e-Science (2003). *Towards a new Science Paradigm*. A BSIK Proposal (www.vl-e.nl)

Introduction

Mark de Graef[1]

In the first part of this book, a description is given of part of the technology that should make it possible to actually apply the knowledge of genomics. A number of applications are already being or will shortly be used, such as, for instance, the use of microarrays for the characterisation of disease patterns; other applications will take more time. It has been established that these applications will influence society to a large extent. This influence will be different for all stakeholders. In its survey, STT/Beweton has tried to make visible some aspects of the influence these technologies (will) have on society and their accompanying opportunities and bottlenecks. The second part of the book focuses on their influence on society.

1 Dr M.R. de Graef, STT/Beweton, The Hague, The Netherlands.

In order to be able to write about the influence of these new technologies, Prof Verrips has written a view of the future from a technological point of view[2]. This view of the future was discussed by a number of homogeneous groups, namely general practitioners (GPs), patients, technologists and manufacturers/consumers in 2004. This has resulted in a collection of perspectives and clearly shows that the influence will not be the same for all of these groups (the reports of these meetings have been included at the end of the second part). Afterwards, a number of the participants in these discussion groups were asked to write down their personal perspectives of Verrips' view, and of their own vision of the future. These perspectives can also be found in the second part of this publication. The perspectives are alternated with a number of 'state of the art' technical examples ('Lab-On-a-Chip', microarray, ICT, and Medical Imaging). The pages of each of these chapters have a lighter blue background.

The final result is a kaleidoscope of perspectives from various points of view rather than a consensus of what the future will bring.

In the last part of the book, the even more distant future is glanced at. Here, an outlook is given where these new technological developments may lead to in the field of health care. Some final thoughts and recommendations for the future of genomics conclude this book.

2 See article of Verrips 'Genomics 2030: Part of Everyday Life' in Part II of this book.

Genomics 2030: Part of Everyday Life

Theo Verrips[1]

Introductory quotes

With two quotes of an article of Ginsburg [Ginsburg, 2001], I wish to introduce a number of aspects of our way of life in 2030.

Advances in human genome research are opening the door to a new paradigm for practicing medicine that promises to transform health care. Personalised medicine, the use of marker-assisted diagnosis and targeted therapies derived from an individual's molecular profile, will influence the way drugs are developed and medicine is practiced. In addition, patient care will be revolutionised through the use of novel molecular predisposition, screening, diagnostic, prognostic, pharmacogenomic and monitoring markers. Although numerous challenges need to be met to make personalised medicine a reality, this approach will replace the traditional trial-and-error practice of medicine in time.

1 Prof Dr Ir C.T. Verrips, Utrecht University, Utrecht/IOP Genomics, The Hague, The Netherlands.

Traditional medicine practice, which is based on trial and error, results both in under-treatment and over-treatment, multiple consultations, the need for drug monitoring, and frequent regimen changes. More than 100.000 deaths per year (USA figure) are attributed to adverse drug reactions. A personalised approach of tailored care for every individual based on his or her specific, molecular disease profiles will become standard. In the prototypical consultation of 2015, the physician will examine a patients' profile (stored on CD ROMs or equivalents): genetics, lifestyle as well as the results from objective molecular screening and monitoring tests. Algorithms derived from previous research efforts will be used to compute the likelihood that a patient develops a host of chronic diseases. At this junction, medicine will entirely focus on prevention. Lifestyle modifications and the use of prophylactic therapies will be recommended based on what is best for that patient so as to avoid any chronic disease they might be susceptible to. The 'surgery' of the future may itself be a virtual office; Internet consultations may supplant some of the direct contacts between patients and physicians. Patients will know about their own health and risk profiles and will be more active in directing their own health care.

Discussion

I would like to discuss the following aspects, not in any fixed order of priority.

A. Knowledge of the genome and influence on medicine and health care

In 2030, it will be possible to determine the complete genome of individuals for € 100-1000. Moreover, the other two layers of gene transcription regulation, RNA and epigenetics, will be understood in greater detail due to progress made in all types of 3D structural analysis methods. The effects of individual SNP's[2] and epigenetics on the probability of getting a certain disease will be known for more than 70% of the diseases known to us today. For these potential diseases for every stage of that individual's life, recommendations with respect to lifestyle, such as diets, preventive and curing personalised medicines, will be available. These recommendations will be based on algorithms developed in System Biology. The results of the genome determination will be held by the individual whose genome has been determined. Special user-friendly algorithms will be available to assist individuals to understand the influence of their genomes only on those aspects for which a preventive or curative personalised solution is available (called 'health agent', see B.). Although infectious diseases will still occur, the system biological approach and detailed knowledge of the strategies of infectious organisms will have resulted in a much more effective prevention against these invaders. In those rare cases that invaders have surprised the medical world, fast strategies will be developed in order to conquer these invaders efficiently. The extensive

2 Single Nucleotide Polymorphisms.

training in prevention for all individuals and the ICT/precision technology of food production processes will also have contributed significantly to the reduction of (large) epidemical outbreaks.

Different perspectives[3]

1 The cause of only less then 30% of diseases, mainly single gene diseases, will be known. SNP[4] analysis has proved to be too expensive and therefore the determination of the genome of individuals has not taken place and as a consequence no personalised treatment for prevention and cure will be available.
2 Technically, it (A.) can be realised, but because of lack of clear communication and education, the public will not accept personalised prevention and cure.
3 The costs for personalised prevention and cure will be too high for a large part of the public.

B. The health agent as a key player in health care

In 2030, people's houses will have an ICT infrastructure that is more than sufficient for all family members having their own health agents, agents they rely on. Most likely the health agent will be a 'virtual' agent. In fact, it will be a knowledge system that will be able to adapt the general knowledge system to a person's particular genetic make-up and lifestyle and communicating with him or her face-to-face using speech recognition. These agents should be completely independent from any governmental institution or insurance company. Adaptation of one's lifestyle according to the recommendations of this agent can then be guided and monitored in such a way that the 'client' will never get the impression that 'big brother is watching me'. The ICT infrastructure will not only allow to transfer the data of (part of) the individual's genome abuse-free, it will also allow non-invasive methods in order to measure the individual's actual health situation and transfer these data to the agent. Without any delay, the agent will analyse the genomic and measured information with newly developed algorithms, and the results of these analyses will be fed back to the individual. The individual will still have the possibility to see a physician for a more thorough analysis, a second opinion or personal contact. In the case of serious health problems, the agent will recommend consulting a team of medical specialists and prepare an electronic patient file for them. However, this file will only contain personal information if approved by the individual whose file it is.

Pharmaceutical companies will have changed their strategy from one or a few 'block busters' to a set of tailor-made pharmaceuticals for all types of diseases. The approval system for new products of the Food and Drug Administration (FDA) and the then existing European equivalent will have changed to make this strategy possible.

3 This discussion paper was used for discussions with various discussion groups during 2004 (see the reports of these meetings in Part II of this book).

4 Single Nucleotide Polymorphisms.

Different perspectives[5]

1 Agents will not replace physicians. The health care system will remain as it is today with a restricted application of ICT and Genomics.
2 The costs of changing from the health care system of today to health agents/personalised prevention and care system is economically unaffordable.
3 The 'FDA' approval system will not be adopted because of liability issues.
4 Several companies will offer home-based systems for monitoring health and analysing data.

C. Tailor-made functional foods

Plants genomics will have resulted in a 'system biological approach' for tailor-made agriculture, providing high quality Functional Foods (FF). Functional Foods are not just characterised by their health promoting properties; they will also be superior in appearance, colour and flavour. This way the two most important wishes of consumers in the Western world will meet in one product. Moreover, the fact that these products will be very good in ways the consumers will instantly see, will help them to accept more speedily that these products will also deliver their health related promises. This way of agriculture will have created a new and prospective future for farmers. The benefits of the tailor-made FF will be secured during the whole supply chain of foods using ICT and precision technology during manufacturing. The analysis of any source of food-borne diseases will have been sped up in such a way that the time required for that analysis will be completely in line with the supply chain for foods products. Both imaging and genomic techniques will have contributed to this improvement of analysis. All raw materials, ingredients and final products and every step in the food supply chain will be tagged, ensuring that in the rare case of a failure of the Quality Assurance System, the tag-based Quality Control System will reduce the size of the food-based outbreak of a disease.

Manufacturing of FF will not be restricted to large factories; on the contrary, the production of many tailor-made products will be finished at retail level or even at home level, where the top notes will be dosed based on the individual's wishes with regard to health and taste. FF will be available at a reasonable price affordable for a large percentage of the population.

This scenario will only be possible when communicated in such a way that benefits for consumers are obvious. Otherwise the mistakes of 30 years ago with the (lack of) communication with regard to recombinant DNA will be repeated.

Note: the term 'tailor-made' is used instead of 'personalised' for two reasons:

– Really personalised is not necessary as considerable groups of consumers will get similar recommendations from their health agents.
– Personalised functional foods will not be affordable for a large part of the population.

5 This discussion paper was used for discussions with various discussion groups during 2004 (see the reports of these meetings in Part II of this book).

Different perspectives[6]

1 Tailor-made FF will be economically impossible.
2 Tailor-made FF will be based on recombinant DNA technology and therefore will not be accepted by consumers.
3 The rewards of using FF will only be visible after many years and most consumers will not have so much patience (see D.).

D. Lifestyle

In 2030, we will receive extensive training (starting at school) using ICT for all aspects related to health and prevention strategies for 'well-known' diseases. This training will have been set up to ensure a smooth and effective change from the old health care system (physicians, hospitals) to the new personalised preventive care system (agents, specialised doctors in hospitals). The costs of this extensive training will only be a fraction of the achieved reduction of health/preventive care costs.

At home, all types of applications of precision technology will be used to ensure that any recommendation made by the agent in relation to changes in lifestyle, in particular in tailor-made functional foods can be implemented. The precision and nanotechnology and all types of imaging techniques will also play a crucial role in marker assistant preventive care. Individuals themselves will be able to take minute amounts of blood without any risk, in fact non-invasively. These blood samples will be analysed on the 'Lab-On-a-Chip' and the results of this analysis can be included in the personal health care record and used whenever the agent advises this, although the final decision will be ours! Precision technology will include the individual's 'non-invasive' monitoring of the health status, and coupled to ICT it should be able to guarantee that over a certain time span (week/month) the individual has followed up the lifestyle recommendations of his agent.

The precision, imaging and information technologies will also be present in the homes of elderly and not too severely disabled individuals. This will ensure that the 'behaviour' of these individuals can be monitored regularly and that information on their health status (using for instance data of the laboratory on chip results) will be available to the health care system.

It will be very important that the ICT infrastructure will also be used to ensure that elderly people have much more social and personalised contact with others (audio-visual contacts).

Human behaviour — just as for any living species — is determined by rewards versus penalties. The reward of adapting the lifestyle is not just a better health even in old age, but the records of the lifestyle monitoring will be important for the prevention of additional 'risk payments' to the insurance companies.

6 This discussion paper was used for discussions with various discussion groups during 2004 (see the reports of these meetings in Part II of this book).

While individualism will be very strong in 2030, the solidarity with the very young and elderly population will not be lost. However, the pensionable age will be 70 years, which will be accepted by the elderly part of the population, because as a result of the preventive care system the number of years of retirement in excellent health conditions will be about the same as at present. The lifespan of individuals will have increased modestly (5-10 years), however the years of mental or physic disability will be substantially reduced (from 10 years for women and 7 years for men at present to only 3 years). This will have reduced the costs of the preventive/health care system considerably. In fact, the percentage of the BNP for health care will have been stabilised around 2015 and due to the implementation of the preventive care system (also from 2015 onwards) it will have decreased from about 2025 onwards, in spite of the fact that more than 30% of the Dutch (Western European) population will be elderly.

Different perspectives[7]

1 Humans will not adapt their lifestyle (from 'cure' to 'prevention'), even if it would be beneficial for them in the long run.
2 Coupling of lifestyle to the insurance system will be ethically unacceptable.
3 The picture that the health care costs — after a rise in the coming 10 years — will dramatically be reduced by genomics, is wishful thinking.

Miscellaneous

1 Therapeutic cloning (human stem cells) will not only be accepted, it will have become an essential element of the preventive care system.
2 Reproductive cloning of humans will still be forbidden.
3 The cloning of cattle will be socially unaccepted.
4 GMO plants will be accepted all over the world. The considerable arrears of Europe in this field will not exist anymore. Due to intensive collaboration between Food Companies (of which the more research-minded ones will be based in Europe) and universities in the area of Functional Foods will have created a climate amongst consumers that Functional Foods, even made via GMO, are of considerable advantage to them.
5 The virtual cell will be 'reality'. The combined application of fully developed genomics, proteomics and metabolomics and X-ray, NMR (Nuclear Magnetic Resonance), Electron Microscopy/Tomography, Atomic Force Microscopy and other physical techniques will have resulted in detailed time/place-dependent knowledge of cellular processes. Moreover, the development of new algorithms will have created the conditions to describe for a considerable number of human cells the influence of external factors on these cells in (time/place) detail. Both have been necessary in order to develop really

7 This discussion paper was used for discussions with various discussion groups during 2004 (see the reports of these meetings in Part II of this book).

preventive care systems. Note that it is assumed that for 70% of the (at present known) diseases this situation will be as described above.

Forecasts and reality

At the turn of the 20th century, Scientific American published the forecast about scientific developments expected by top scientists and futurologists at the turn of the 19th century. Many major developments had not been predicted and many of the predicted developments had either not been made or had been by-passed by more important, unpredicted developments. So there are reasons to expect that many of the above-mentioned developments will also not take place and that others, that have not been mentioned, will influence our daily life to a much greater extent.

Of course, the STT/Beweton study tries to outline possible developments over a much shorter period of time (25-30 years). In general, the rate of successful predictions will be higher for such a period.

In that respect it may be good to go back to the early days of the recombinant DNA technology. Just as for genomics a couple of years ago, the expectations of the benefits of this technology were sky-high. What has been realised?

1 Recombinant DNA pharmaceutical products increased from nought in 1975 to over $ 30 billion/year in 2002 and at present the majority of new drugs in the final stage of the drug development pipeline are either rDNA products or only possible because of the rDNA technology.
2 The determination of the human genome sequence is only possible due to rDNA technology and the benefits of this is already visible in cancer diagnostic, less than 4 years after the elucidation of the sequence of the human genome.
3 Without any doubt, scientists in Europe have been the real pioneers in the area of recombinant plants (GMO). However, due to the lack of obvious benefits to the consumers and due to pressure groups, this technology has disappeared in Europe. However GMO's are cultivated on an enormous scale in the rest of the world (for instance recombinant soy in Argentina is › 90%).

It is well-known that the penetration of new technologies in the Life Sciences is much slower than for instance in the ICT area. Nevertheless, the achievements of rDNA technology in 25 years have been remarkable, in particular taking into account that the approval time of a new drug is 10-12 years.

Many of the aspects mentioned above are a combination of ICT and Life Sciences and although the future will differ from what is expected at present, the influence of Genomics/ICT on our society and our daily life in the coming 25 years will be impressive.

Reference

– Ginsburg, G (2001). *Trends in Biotechnology*, 19. Millennium Pharma Inc. pp 491-496

Pharmacogenomics and Everyday Health Care

Dick Willems[1]

Genomics and regular practice

Genomics is huge, and so is regular practice. I will therefore focus on a specific part of genomics, pharmacogenomics, and on a specific area of regular practice: general practice. I will not address the shift of emphasis for general practitioners as a result of genomics, from treatment to prediction and prevention; this issue has been clearly addressed in Zwart's contribution[2]. I just wish to add that the future role of the general practitioner sketched by him would demand an important re-orientation in the education of students and general practitioners: GP's are now just not prepared for that role. I will not address either the important issue of pharmacogenomics and drug development (especially orphan drugs) that Streng's contribution[3] describes, but I will focus on the impact pharmacogenomics may have on everyday general practice in the next 10-20 years.

1 Prof Dr D.L. Willems, Academic Medical Center/the Universiteit van Amsterdam (UVA), Department of Public Health, Amsterdam, The Netherlands.

2 See article of Zwart 'Genomics: Towards a More Comprehensive View on Human Life' in Part II of this book.

3 See article of Streng 'Living the Future' in Part II of this book.

Lets us turn to pharmacogenomics. Not so very long ago, a paper in the British Medical Journal gave a clear summary of the types of cases in which genomics will become important in the everyday practice of general practitioners:

- "Reproductive risks — for example: haemoglobinopathies, cystic fibrosis, muscular dystrophies, and many rarer autosomal recessive conditions; chromosomal disorders (such as Down's syndrome and Edwards's syndrome).
- Adult onset genetic disorders with a Mendelian inheritance pattern — for example: Huntington's disease, subsets of common diseases such as familial cancers (BRCA1, BRCA2), maturity onset diabetes of the young (MODY).
- Common diseases with a multifactorial aetiology — for example: ischaemic heart disease, asthma, diabetes.
- Normal genetic variations in drug metabolism and immune response." [Emery and Hayflick, 2001].

If the authors are right, pharmacogenomics is one of the important areas of genomics that will become pertinent for general practice and everyday health care. The question, however, remains to what extent this will happen and in what form. In this short contribution we can do no more than discuss the promise pharmacogenomics offers to the GP (as the paradigm of everyday practice) and describe a number of practical and ethical questions associated with it.

The promise

The first results of pharmacogenetic research concern drugs that are used on a large scale and that are being prescribed, at least in the Netherlands, by general practitioners: anti-depressants, anti-hypertension drugs, asthma drugs, and analgesics. In the area of life style advice, the individual susceptibilities to alcohol and smoking are being intensively researched.

The major promise of pharmacogenomics is that the groping and time-consuming approach that physicians actually use and that is usually called 'trial and error' (exemplified in the first consultation in the box), will disappear, because more possibilities will exist for immediately finding the right drug for the right patient. Tailor-made care will get a pharmacological significance. The typical general practice approach (starting slow, increasing if necessary) in the management of diseases like diabetes or hypertension could become outdated: the physician will be able to increase the chance of hitting the target right away by prescribing the drug that fits the patient best.

Two fictional consultations regarding depression

2002

Mr Jansen pays a visit to his general practitioner with complaints that have already made him think that he suffers from depression: he has lost his appetite, does not feel motivated, sleeps less well and is easily upset. After a couple of consultations, the GP confirms the diagnosis of depression without a clear reason or trigger and feels that a treatment with anti-depressants would be appropriate. As advised in the clinical guideline on depression issued by the Dutch College of GPs, he proposes to start using amitriptyline and to see if that is sufficient. He warns Mr Jansen that it mostly takes two to four weeks before the effect of the drug occurs. In the meantime, Mr Jansen is told, side effects may already occur. Should this first anti-depressant have no effects, then there is the possibility of increasing the dosage or of switching to another drug. The patient is a bit disappointed that there is no drug that helps immediately without significant side effects, but he takes his prescription and leaves.

2015

Mr Jansen again visits his GP with complaints that make him think of a recurrence of the depression he had five years ago and for which he had had three different types of drugs, all of them mostly ineffective. Again, his GP diagnoses a depression and explains that times have changed, at least to some extent. Whereas previously finding the right anti-depressant was a matter of trial and error, pharmacogenetic research has increased the possibilities of investigating the chances of both the desired and undesired effects in individual patients. A DNA-test needs to be done that may help to find out whether Mr Jansen belongs to the 'high responders' or, unfortunately, to the 'low responders'. The test also gives information about the chances of really nasty side effects. The DNA-test can be performed that very afternoon by the practice nurse; all it takes is a smear from the inside of the cheek. The prescription will be e-mailed to the pharmacy, where Mr Jansen can collect his medication the next day.

Along the same lines, pharmacogenomics promises to make self-medication more effective and safer, thereby decreasing the role of the doctor in the choice of medications. This might come to mean that more and more 'prescription only' medication will become freely available to those who are genetically 'protected' to side effects, and inversely that freely available drugs (over-the-counter NSAIDs[4], for instance) will become available only to those who have the appropriate SNP[5]-profile. Thus, self-medication may be one of the first areas where, as Van Dam expects in his contribution[6], genomics will become relevant for us not only as citizens but also as consumers. A similar development could be that drugs that, because of safety concerns, were typically prescribed by specialists, could now safely be prescribed by GPs to pharma-

4 Non-Steroidal Anti-Inflammatory Drugs.

5 Single Nucleotide Polymorphisms.

6 See article of Van Dam 'Genomics for consumers?' in Part II of this book.

cogenetically selected patients; for instance, methotrexate in the treatment of rheumatoid arthritis.

However, pharmacogenomics might even begin to question the role of doctors in the prescription of drugs. It is very plausible that the pharmacist will do the actual prescription on the basis of the physician's diagnosis and a pharmacogenetic microarray test. Every pharmacist could then keep a database containing the pharmacogenetic data of his clients. The patient then sees a doctor for a diagnosis and associated prognosis (for instance, whether medication is necessary at all) and then sees his pharmacist who performs a microarray or consults his database in order to find the most appropriate medication.

Thus, the promises of pharmacogenomics are medical and social at the same time: this may lead to better therapies and at the same time to shifting competencies and responsibilities.

Questioning the promise

Proponents of pharmacogenomics say that its core advantage, when compared to current forms of medication treatment, is the wiping-out of what is, somewhat condescendingly, called 'empiricism' in prescribing practices. The first question to ask is: Will 'empiricism' indeed disappear, and should we just be happy about that? My answer would be that 'empiricism' will probably not disappear but will remain the most efficient strategy in many diseases with regard to both desired and undesired effects. Especially for the more mundane drugs with not-too-serious and reversible side effects, it will probably remain quite useless to perform a genetic test which after all predicts such side effects only to a limited extent. Those who take drugs such as normal pain killers, anti-hypertensive medication like ACE-inhibitors, codeine, usually know after one or two tablets whether the drug suits them, and if not, any side effects will disappear when they stop taking the drug. The question then becomes one of balance: at what price will a pharmacogenetic test prevail over the chance of taking a useless drug or a drug with side effects? I expect that in the foreseeable future general practitioners will use pharmacogenetic tests, when these become available, only in treatments where either effects are slow (anti-depressants) or side effects are irreversible or dangerous.

Should we be happy about the disappearance of trial and error? The director of the Dutch branch of GlaxoWellcome, Mr Van Schagen, described in an interview how physicians sometimes have to end their consultations in the pharmacogenomic era: "Unfortunately, we have found a basic deviation in your genes that will make any treatment for your disease medically senseless." [Van Schagen, 1999]. Of course, it can be said that the patient is spared a series of useless treatments, but it also takes away time filled with hope. It may be cost-effective, but it need not be good care. Is it always more desirable to know immediately that no treatment will be available for your disease,

or is it sometimes better that the tough truth crops up after some endeavour, after having at least given it a try? Especially in the case of lethal diseases such as lung cancer, the example Mr Van Schagen uses, for most people the eventual failure of the therapy might be more acceptable if at least something has been tried. There might be a discrepancy here between the logic of cost-effectiveness and that of care: the former will prefer the fastest (and therefore cheapest) way to the eventual result, even if it is incurability, whereas the logic of care may also value the time it takes to get to the result. In treatment rationality, precision and efficiency are paramount, whereas in care rationality, attentiveness, taking time, and mutual trust are central issues. Most often both rationalities can be combined, but sometimes they are in conflict with each other.

Pharmacogenomics may not only lead to conflicts between care logic and cost-effectiveness logic, it may even have an impact on the concept of a diagnosis as made by a general practitioner. In short, the appropriate drug will increasingly be part of the diagnosis — for instance, a diagnosis such as 'depression' will only be complete if it makes clear which anti-depressant (if any!), and in which dosage, is suitable for this patient with regard to both desired and undesired effects. For many diseases, the situation will become comparable to diabetes or breast cancer: insulin-dependent or Herceptin-sensitive, with one difference, however: pharmacogenomics promises to predict not only benefits but also harm.

One of the possible 'side effects' of pharmacogenomics itself could be the following. If a medication treatment, though possible, is not medically necessary, physicians usually discourage such treatment by pointing out possible damage due to side effects. However, if the occurrence of damage would become predictable, at least percentually, then patients would be increasingly right when they would say: 'Even if there's no benefit, there will at least be no harm.' This is comparable to the example Zwart mentions in his contribution[7] of persons who will use their genetic information as a 'licence to smoke'.

Do we need to worry about this? Well, we may: firstly, there will never be more than a relative predictability of side effects. Any prediction will always be in terms of chances. This element of chance tends to disappear into the background during the rhetoric of 'personal pills'.

Secondly, the pharmacogenetic promise could lead to an increase of impatience and activism. It could reinforce the message that there is a pill for every problem, and it could make other ways of dealing with diseases even less popular than they are already. That would make considerate care-giving more difficult. Will the use of pharmacogenomics lead to a more limitless consumption of drugs? This could go two ways. On the one hand, if it can be established in individual cases that a drug will probably be safe and effective, there

7 See article of Zwart 'Genomics: Towards a More Comprehensive View on Human Life' in Part II of this book.

is less reason for prudent use of medication. The typical general practitioner's argument that doubts about effectiveness should lead to the decision not to prescribe the medication (in dubio abstine) would lose force. On the other hand, however, the rise of pharmacogenomics could make the non-necessary use of medication less attractive to patients because many more will or can know beforehand that they run an elevated risk of side effects. In other words: by making the risk of side effects more concrete and personal, pharmacogenomics might limit the clientele of a large number of drugs.
Physicians will increasingly be confronted with the normative questions that surround pharmacogenomics. For example, questions around the right of a patient not to receive certain genetic knowledge, even when such information is needed for the prescription of medication. Especially the situation in which pharmacogenetic information will not only concern the chances that a patient will benefit from a drug, but also the chance that he or she will develop a disease, is likely to give rise to complex ethical problems. The same will be true when pharmacogenetic information would have a negative impact on insurability, for instance in cases in which a patient has a particularly difficult SNP-profile for the treatment of certain common diseases. Since this might lead to higher health care costs, either because no treatment would be available at all, or because possible treatment options would be much more expensive (this is the case, to some extent, in Herceptin), it might also lead to problems with health insurance. New technologies, such as pharmacogenomics, lead to new ethical questions for and — maybe — demands on practitioners; essentially, they require new ways of thinking about what good practice is.

References

- Emery, J, S Hayflick (2001). The Challenge of Integrating Genetic Medicine into Primary Care. *The British Medical Journal*, 322. pp 1027-1030
- Schagen, C. van (1999). New Perspectives in the Drug Industry [in Dutch]. In: M van Zwieten, A Kalden (eds.) *Ons gescreende lichaam*. Balans, Amsterdam

IMPACT ON SOCIETY

Molecular Imaging

Sjaak Deckers[1]

Philips Medical Systems is one of the imaging equipment companies that are very active in research that combines imaging equipment with targeted contrast agents, often together with luminary clinical partners. An example of such a collaboration is the work of Sam Wickline and Greg Lanza of Washington University in St Louis, who have pioneered the research on nano-particles filled with tens of thousands of Gadolinium atoms with an excellent MR visibility. They use MRI to image atherosclerotic plaque by coupling a specific biomarker to their nano-particles that attaches itself to plaque-specific receptors (to be precise, they use an anti-body protein to attach to the $\alpha_v\beta_3$ receptor strongly correlated to angiogenesis). They have even gone one step further by adding a drug to the nano-particle that actively dissolves the plaque. The beauty of this combination is, of course, that this treatment can be monitored in real time using the same MRI imaging procedure subsequent to applying the therapy. This is illustrated in Figure 1, where four images are shown of the aorta of an atherosclerotic rabbit covered with plaque. The two images on the left were taken immediately after injection, the top image using the combined imaging/drug nano-particles, the bottom image without the drug addition. The two figures on the right show the same animals two weeks later. The two images on the left demonstrate clearly that in both cases the targeting principle works nicely with the colourful ring on the inner wall of the aorta clearly showing the plaque. There appears to be no difference between the particles with and without drugs. However, after two weeks, the dissolving

1 Dr S. Deckers, Philips Medical Systems, Corporate Technology Office, Eindhoven, The Netherlands.

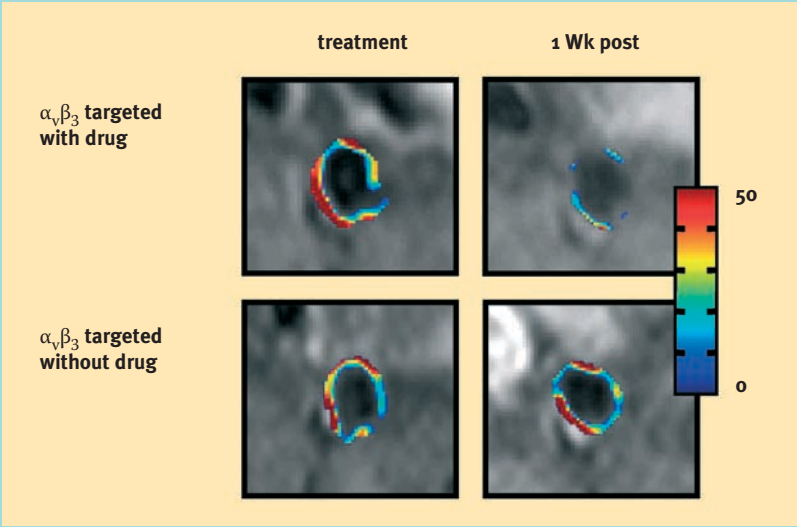


Figure 1
Four images are shown of the aorta of an atherosclerotic rabbit covered with plaque.

of the plaque in the upper image with the drug is obvious, and there is no difference in the bottom image of the contrast agent without the drug.

Of course, much work needs to be done to translate these Molecular Imaging and Molecular Therapy examples into clinical practice, but it clearly indicates the great potential of these targeted agent technologies and their ability to visualize biological processes and functions of the human body.

Living the Future

Peter Streng[1]

It is true for the majority of people suffering from disorders that are the result of a genetic defect that nowadays symptomatic therapies are possible. Many of these therapies are not spectacular. The most successful treatment of neuromuscular diseases (a very heterogeneous group of more than 600 different rare diseases) in the beginning of the 21st century is still home mechanical ventilation (artificial respiration). In order to make this form of treatment available, patients' organisations have had to put up a long-term fight to convince the practitioners of the fact that as a result patients could live long, if not longer, while maintaining a high quality of life.

Still, there is hope for the large group of patients with a rare or common (mono) genetic disease. More and more gene defects are becoming known and this has led to better insights into the pathogeneses of many syndromes. The availability of new technologies, such as the use of microarrays, seems to make the development of causal treatment possibilities real. This is what patients have placed their hope on for many years. There are factors, in particular those based on the ignorance of the general public of new technological possibilities, such as for instance recombinant DNA technology and the use of (embryonic) stem cells, which may hinder or endanger the possible development of new therapies. This situation is unacceptable to the patients.

1 Drs P. Streng, Vereniging Spierziekten Nederland (Dutch Society of Muscular Dystrophy), Baarn, The Netherlands.

Patients' organisations play a continuously more important role in the development of new forms of treatment. In addition to stimulating the wellbeing of their supporters, many patients' organisations make every effort to stimulate scientific research. Fund-raising for research is often seen as the most important activity. However, other matters are in practice more important. Providing both patients and practitioners (the latter in particular in the case of orphan diseases[2]) with information and advice is becoming more and more important. Due to the enormous offer of uncontrolled, and often even false, information on the Internet, it is necessary that patients' organisations themselves screen the available information or solely refer to reliable, checked sources. Patients play an important role in influencing public opinion. But the most important is maybe the patient's role as a matchmaker between scientists, financiers, the government and the industry. For ultimately the patients remain the most important stakeholders.

How do patients see the phenomenon of genomics? What is the importance of genomics for patients and what will the impact of genomics be on the life of patients? These were the questions asked by Verrips with regard to his essay on genomics[3]. Answering these questions is not easy. On the one hand, there is no such thing as 'The Patient' because there are too many different diseases with again a multitude of syndromes, symptoms and problems. The prevalence and seriousness of a disease often play an important role here. But the most important element in answering these questions is formed by a (causal) treatment for chronic illnesses being or becoming available or not.

On the basis of the definition of genomics as phrased by the NWO Programme Genomics (Programme Genomics) in May 2001: "*Genomics is a kind of research that is aimed by way of characterising on a large scale genes and gene products at the elucidation of the way in which genes, RNA, proteins and metabolites work together in the functioning of cells, tissues, organs and the organism as a whole, within a species, within a population or between species and their environment*", the following conclusions can be drawn.
The first conclusion can only be drawn in the case of know-how. Genomics makes it possible to directly study the working of thousands of genes in a living cell. Only by studying many genes in correlation the working of the entire mechanism can be discovered. On the basis of this knowledge, a broad range of treatment strategies can be developed.

Genomics studies the interaction of DNA that encodes the building stones of life, the differences in these building stones between different individuals (in particular between healthy people and people with diseases caused by genetic defects) and external influences on each other and therewith on the

2 Rare diseases are called orphan diseases. A disease is considered rare when its prevalence stays below 5 per 10,000 inhabitants. This means for the Netherlands that a disease is rare when there are less than 8,000 patients. It is estimated that worldwide there are between 5,000 and 8,000 rare diseases.

3 See article of Verrips 'Genomics 2030: Part of Everyday Life' in Part II of this book.

functioning of man, animal or organism.

Apart from developing new drugs, prevention, the use of functional food and adaptation of lifestyle will play important roles in the treatment of diseases and the prevention of (chronic) disorders. That is why genomics seems to be the key to at least a better quality of life for patients. This does not alter the fact that patients ultimately hope to be cured, of course.

On the basis of the definition used, another conclusion can immediately be drawn. If the importance of genomics for both prevention and treatment and possibly curing of many diseases is as large as stated — and why should this not be the case — it is important that there is a social base for investments in these new technologies. In order to create this social base, it is important that both politicians and normal consumers understand what genomics is about. Only by way of a long-term planning with regard to education concerning heredity and genetics the knowledge and therewith the layman's lack of understanding in this field can be improved.

Patients' organisations can be important supporters in this. One thing will certainly be favourable to today's patients. By applying genomics, the number of (possible) patients will increase. More than that, everyone is a patient by nature. With this in mind, the creation of a base for investments in the application possibilities of genomics might be less of a problem.

Currently, the towering costs of development of new drugs are an increasingly growing impediment. The total costs of development for a new drug are currently estimated at 800 to 1,000 million US Dollars. The application of new technology seems to have its price. It is paradoxical that the specific users' group per drug is becoming increasingly smaller as a result of the insights created by genomics. That is why it is more often called 'personalised medicine'. In this respect, the development of the so-called orphan drugs might serve as a model for the development of the individual drugs of the future. The development of orphan drugs depends on surrogate outcome measures and innovative drug development strategies as a result of the high mean costs per patient and due to the lack of sufficient patients for traditional evidence based medicine. Because both in the United States and Europe the development of orphan drugs is stimulated by way of adapted (fiscal) legislation and regulations, the development of orphan drugs offers the possibility to gain experience in the development of drugs for small target groups. Facilities for orphan drugs are provided by EMEA[4] (a 10-year market protection, decrease of certain registration costs, special procedures, i.e. fast track) as well as by the national governments (tax facilitation, promotion and advice (in the Netherlands by the

4 European Agency for the Evaluation of Medicinal Products, London, UK.

institution of the Steering Group Orphan Drugs by the then Health Minister Mrs Borst).[5]

In their turn, the rare diseases will profit from the further differentiation that will occur in the various syndromes; because a genetic profile is unique per definition, practitioners will be forced to an extreme extent to trust and use knowledge systems linked to databases with genetic profiles. As a result, the knowledge with regard to rare diseases will become more broadly and more quickly available. Shortening the so-called diagnostic delay will much influence the treatment possibilities. There where causal treatment is not yet an option, one is often thrown back upon prevention. Heredity counselling is then often very important, certainly in the case of known high-risk groups. Causal and symptomatic therapies, such as treating Pompe's Disease with myozyme® and Duchenne Muscular Dystrophy with corticosteroids, respectively, mainly influence (to a large extent) the progression of the disease. This underlines the importance of early diagnosis by way of prenatal or neonatal screening.

Drugs are not the most important cost items in health care. Prevention of diseases by way of prevention and an active policy in the field of health maintenance can provide much money-saving for the national health budgets. Attention paid to lifestyle and food will be essential here, as mentioned before.

There where the role of first-line health care (GP/MD) is now limited in the diagnostic and treatment stages for rare diseases, the role of the GP/MD will change by linking the (information) technology to the new insights coming from genomics and the possibility of relatively simple and quickly performed diagnostic tests. The possibilities for adjustment by amending the patient's lifestyle, or at least to give counselling in this respect, will become much more concrete.

New possibilities and impossibilities in treatment will lead to new dilemmas. When looking for answers to moral issues, it is very important that interested parties/the patients themselves can also make contributions. The danger of a normative society taking decisions for others, in this case patients, on the basis of ignorance of new technologies is real. That is why interested parties have to be able to make their voices heard.

Counselling and informing patients about the possibilities and impossibilities of the modern medical technology. Managing the expectations patients may have with regard to genomics. Bringing together the parties that are involved in the development of drugs and innovative treatment. Creating awareness

5 For more information, please contact the Dutch Steering Group Orphan Drugs (Stuurgroep Weesgeneesmiddelen, ZonMw, Den Haag, The Netherlands) or Eurordis (European (Patients') Organisation on Orphan Diseases, Paris, France).

and acceptation of genomics with the general public. These are all matters that currently already exist for patients. Professional patients' organisations will have to play an increasingly large role in this. For the matter is becoming more and more complex and the patients' expectations are increasing. Even though it is still the hope of a better quality of life and to be cured in particular that is the drive behind the exertions of many patients' organisations, we are already living the future.

IMPACT ON SOCIETY

Development of a PDMS Spotting Device for Confined Protein Arrays

Bianca Beusink[1], *Richard B.M. Schasfoort*[2]

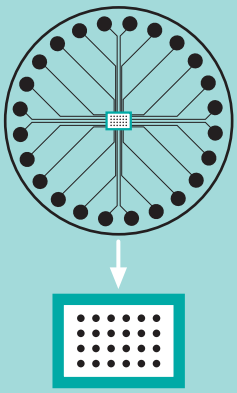
The future of diagnostic tests will acquire as much information as possible and this as fast as possible. Diseases are usually confirmed by testing for several specific biomarkers. These tests are still separately performed, which is very time-consuming. The next step will be to perform these tests simultaneously with the advantage that a better insight of the disease can be obtained. These so-called fingerprints of the disease are needed for accurate treatment of patients with, for instance, drugs. These fingerprints can be acquired with so-called microarrays. Microarrays are build up by many immobilized (bio)markers on a flat surface which only need a small amount of the patient's body fluid (for example blood) in order to perform the test.
The used spotting technique is very important for addressing the proteins properly on the surface, not only for maintaining their biological activity, but also for the availability of their active sites.

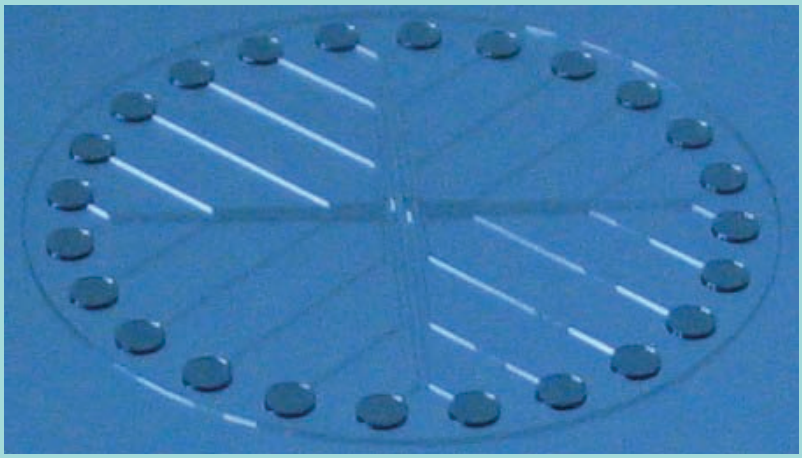
1 Ing B. Beusink, Biochip Group, MESA+ Research Institute, University of Twente, Enschede, The Netherlands.

2 Dr R.B.M. Schasfoort, Biochip Group, MESA+ Research Institute, University of Twente, Enschede, The Netherlands.

In an on-going research project of the Biochip Group entitled 'Proteomics on a chip for monitoring autoimmune diseases', one of the goals is to design a new spotting device made of a polymer (polydimethyl siloxane, PDMS) for monitoring the status of autoimmune diseases by using just a few droplets of a patient's blood in a biochip. The PDMS spotting device is a 2-layer microfluidic system (Figure 1). One layer contains the reservoirs and the channels, while the other layer closes the reservoirs and channels and is provided with nozzles ranging from 80-120 µm in diameter. The array of the immobilized proteins has the same confined size as the nozzles of the PDMS spotting device. The PDMS spotting device should overcome the denaturing effect of evaporation during the fabrication of the protein microarrays because it stays on the surface during the immobilization process.

Figure 1
Schematic view of the PDMS spotting device (left) with the array and or nozzles (insert), and a photograph of the PDMS spotting device (right).





Although several surface treatments have been tried out to fill the intrinsically hydrophobic PDMS spotting device, we have decided to shift to a physically filling technique using a pressure driven flow in order to prevent possible negative influences due to the chemical treatment regarding the ligands. A new device will be designed with wider and considerably shorter channels in order to fill the device more easily.

Consumer Acceptance of Nutrigenomics-Based Food Technology

Amber Ronteltap[1], *Hans van Trijp*[2]

Introduction

In a number of different fields, new technologies have had a major impact and delivered substantial benefits to both individual consumers (for instance, personal computers) and to society as a whole (for instance, preservation technology). Many of these new technologies have been easily accepted and have smoothly found their way into society, while others have met with much more societal resistance (for example, nuclear energy).

In the sphere of food, a similar picture emerges with respect to recently introduced technologies [Cardello, 2003]. However, compared to the in general optimistic view with regard to technology in many other fields, consumer concern dominates much of the literature on consumer acceptance of new food technologies. To a large extent this is due to the problems that accompany most recent food technologies such as food irradiation and food biotechnology. Part also can be explained by the very intimate relationship consumers have with their food as food, contrary to many other goods, is actually ingested into the human system [Rozin, 1999].

1 Ir A. Ronteltap, Marketing and Consumer Behaviour Group, Wageningen University, The Netherlands.

2 Prof Dr Ir J.C.M. van Trijp, Marketing and Consumer Behaviour Group, Wageningen University, The Netherlands.

In this essay we will reflect on key teachings from the literature on consumer acceptance of new (food) technology. We will use these insights to build a case on consumer acceptance of the new opportunities that nutrigenomics may bring. We will argue that a lot can be learned from recent successes and failures (such as irradiation and biotechnology). We anticipate that there will be a bright future for nutrigenomics-based consumer products and services, provided that this field is carefully managed and scientifically substantiated, with a focus on consumer benefits resulting from the technology, and with a proper and pro-active communication towards consumers and society as a whole.

Consumer acceptance of new technology

Both scientific and applied research into consumer acceptance of new food technologies have a long history and can be traced back to an influential study by two American sociologists, Ryan and Gross, in the 1940s on the adoption and diffusion of hybrid corn in Iowa. This study revealed that adoption of agricultural innovation follows an S-shaped curve when measured against time and also that farmers can be significantly classified into five, now widely accepted, adoption categories. Later, this research was extended and popularised by Everett Rogers [Rogers, 1962; Rogers, 2003] who found some of the generics in the process of acceptance of new technology. Since then, Rogers' work has been the foundation for a diversity of applications (see [Tornatzky and Klein, 1982] for a meta-analysis).

Rogers' research has delivered at least five very important insights:

1 The adoption process — the acceptance of an innovation at an individual level — evolves through five consecutive stages: 1. awareness 2. interest 3. evaluation 4. trial and 5. adoption.
2 The diffusion process — the extent to which an innovation finds its way into society from the moment of invention — follows an S-shaped curve. Innovations primarily differ in the slope of the S-shaped curve: the rate at which larger groups of consumers begin to accept the innovation.
3 Users of technology can be classified into five adopter categories: 1. innovators 2. early adopters 3. early majority 4. late majority 5. laggards. These adopter categories considerably differ in terms of their psychological and sociological characteristics.
4 Communication is a crucial process in building up consumer awareness of and interest in innovation. Mass-media communication is particularly appropriate in acquiring awareness, whereas interpersonal communication is much more effective in later stages of the adoption process.
5 There is a particular set of generic characteristics of the innovation that to a large extent explain the differences in the adoption rates of innovations.

These are 1. relative advantage to the user 2. compatibility with existing behavioural practices and values 3. complexity of the innovation 4. small scale trial-ability of the innovation 5. visibility of the application results of the innovation.

Within the marketing literature the basic ideas of Rogers have been applied in several ways, including the Technology Acceptance model [Davis, 1989; Venkatesh et al, 2003] developed for the acceptance of information and communication technology in work situations, as well as consumer acceptance of self-services in the retail environment (see, for example [Dabholkar and Bagozzi, 2002]).

Aspects of consumer behaviour relevant to technology acceptance

From a consumer perspective food technology is a means rather than an end in itself. Consumers primarily evaluate technologies not in terms of the technology itself but rather on the consumer-relevant benefits offered by the technology in comparison with existing choice options. In addition, the uncertainty inherent to what the technology will bring may trigger perceptions of risk. Risks resulting from new technologies are uncertain and difficult to verify by the individual consumer. In consumer behaviour terminology risk-related aspects such as safety, sustainability, health, and naturalness are known as 'credence' qualities [Darby and Kerni, 1973]. The differentiating feature of credence qualities is that consumers themselves are unable to unequivocally verify them, neither upon purchase in the store nor after normal consumption. This contrasts with other product qualities which can either be unequivocally verified when purchased (the so-called 'search' attributes such as price) or at least after normal consumption as in the case of 'experience' attributes, such as taste and convenience.

Although consumers cannot personally and unequivocally verify these, they nevertheless form perceptions with regard to the product and service performance on credence qualities such as safety, naturalness, healthiness and sustainability (see, for instance [Fishbein and Ajzen, 1975]) either by accepting information from relevant others (the process of 'information belief formation') or on the basis of self-developed rules of thumb (the process of 'inferential belief formation').

The fact that consumers have to rely on their own judgement or information from (relevant) other parties when assessing the credence qualities renders them quite susceptible to and dependent on what third parties communicate. This is where the issues of transparency and trust come in. After all, trust is a necessary condition in the consumer assessment of the value and credibility of third party information. In practice, communication about new technology

is far from unequivocal and the consumer will differently weigh arguments advanced by different parties (for instance, NGOs versus government versus industry) in terms of relevance and credibility. For example, research of Lynn Frewer and Brian Salter shows that trust in risk regulators and managers decreased in the case of the BSE crisis [Frewer and Salter, 2002]. Again this shows that trust is hard to acquire and easy to lose.
Moreover, because the relevant information is too complex for consumers to handle, they tend to be more sensitive to superficial but appealing formats of information ('peripheral cues') than to in-depth and detailed information [Petty and Capioppo, 1986]. This lack of knowledge on the part of consumers may lead to consumer scepticism with regard to technological innovation and science in general, also referred to as the 'deficit model' (e.g. [Wynne, 1991]). Accordingly, both Peter Streng[3] and Frans van Dam[4] mention education and knowledge as key issues for progress in the genomics area, as consumers currently lack understanding of the technology. Lack of information is certainly an issue, but more for reasons of trust and confidence than for knowledge reasons. The 'right to be informed' does not equal 'actively search and process all relevant information'. Others (for example [Frewer, 2003]) have also argued that withholding communication on the uncertainty inherent to the scientific process (for instance, out of fear that consumers would be unable to handle this uncertainty) can in itself be a main source of consumer scepticism. In other words, with regard to new technologies not only what is being communicated, but also how and by whom is extremely important.

Acceptance of food innovations

Food holds a special position in the sense that it is actually ingested into the human system and is also quite visible within several layers of society (for instance, primary production, food processing and food marketing). Acceptance of food innovation can best be understood from a perceived cost-benefit perspective, and recent research in food has emphasized the 'cost' side in terms of consumer concerns. Research into consumer acceptance of biotechnology has provided a number of important insights, among other things that the phenomenon of consumer resistance is of a multidimensional nature. Resistance may find its basis in 1. perceived personal risk 2. perceived impact on society at large, but also in 3. the right of information, to be heard, freedom of choice and control on the part of the consumer, as well as 4. moral/ethical issues regarding perceived naturalness. Many of these considerations are subjective, emotional and of a personal nature, quite in contrast to the more objective and rational considerations used in scientific and policy approaches to new technologies.

This may actually lead to quite complicated situations as revealed in the

3 See article of Streng 'Living the Future' in Part II of this book.

4 See article of Van Dam 'Genomics for Consumers?' in Part II of this book.

discussion on biotechnology. Think for example of the very superficial, yet highly effective 'peripheral' communication on the part of Prince Charles when he referred to biotechnology as 'Frankenstein Food'. This communication has probably had far more impact than all detailed scientific information on genetic modification taken together. Similarly, the highly trusted inputs from influential NGOs (such as Greenpeace) into the discussion have probably further contributed to the amplification of consumer concern with regard to biotechnology.

Much of the recent research conducted with regard to consumer acceptance of food innovation has adopted the normative/value model of perceived risk as its dominant paradigm (see, for instance [Cardello, 2003]). From a perceived risk perspective, this research focuses on the evaluation phase of the adoption process and the relative 'advantage/disadvantage' as an innovation characteristic. This research tradition, largely inspired by Slovic and colleagues (see among others [Slovic et al, 1980; Slovic et al, 1981]), has provided a number of important insights. Risk perceptions can be quantified and, to some extent, predicted. Importantly also, risk perceptions differ considerably, yet consistently, between experts and lay people. Consumer perceptions of risk are more strongly related to specific characteristics of the hazard, such as the extent to which they are catastrophic in nature and a threat to future generations, than they are to technical risk assessments. According to this stream of research, the massive destruction of cattle in the UK at the time of the BSE crisis is quite likely to have led to amplification of perceived risk among consumers, even though this policy may have been fully justified on the basis of a rational policy aim to strengthen trust and confidence. Research by Sparks and Shepherd shows that risk perceptions of food technologies are largely determined by the extent of perceived dread and lack of familiarity with the innovation [Sparks and Shepherd, 1994]. The higher the innovation rates on these two dimensions, the higher the perceived risk and the more consumers wish this risk to be managed through regulations apart from other measures [Slovic, 1980].

Specific research into consumer acceptance of nutrigenomics

In the light of the life sciences' progress on nutrigenomics there is a surprising lack of specific scientific and applied research of consumer acceptance of nutrigenomics. Work currently done by the Marketing and Consumer Behaviour Group of Wageningen University on the acceptance of marketing applications of nutrigenomics-based services confirms that trust, and in particular trust established via general practitioners (also argued by Hub Zwart[5]), plays a key role in consumer preference and subsequent acceptance of nutrigenomics.

5 See article of Zwart 'Genomics: Towards a More Comprehensive View on Human Life' in Part II of this book.

Despite the lack of specific research, the present analysis gives food for thought about the anticipated consumer acceptance of nutrigenomics as well as the identification of some of the critical dos and don'ts.

Non-communication is no option

Despite the fact that government and industry have heavily invested in nutrigenomics research, the intensity of the communication to society as a whole is extremely limited. This is a highly undesirable situation, which ironically repeats some of the key mistakes that occurred during the introduction of biotechnology. What is needed is open, transparent and early communication about this technology with consumers. Without such a pro-active approach, the technology will be extremely sensitive to third-party communications, in particular from those parties that are critical towards the technology ('positive news is no news'). Without pro-active communication upon introduction, consumers may feel overwhelmed by the new technology, a feeling of alienation that can easily be further nurtured by critical organisations. Under such circumstances, those committed to nutrigenomics can only communicate from a defensive position, which puts them at a serious disadvantage.

Substantive equivalence is not an option

It seems that many researchers in the genomics field have adopted the opinion that genomics research is 'only' a slightly more advanced variant of the traditional research techniques in plant breeding and nutrition research and that there is therefore hardly any reason to communicate about it in any detail. Even though this viewpoint may be technically correct, it is unlikely that con-

sumers will understand the subtle difference between 'understanding a lot of details on how genes are activated, work and have effect' on the one hand and 'using that understanding to actively manipulate gene structures and activity' on the other. The principle of 'substantive equivalence' should therefore not be used as an argument in the discussion. In order to make this subtle distinction clear to consumers it is important to invest heavily in communication with consumers at an early stage of the development of this new technology. Lack of such early communication may lead to reactive communications later on in the process which would seriously undermine the credibility of and trust in the new technology and its proponents.

Delivery and communication of consumer-relevant benefits is crucial

New technologies, also those on the basis of genomics, hold the potential to deliver a multitude of benefits both to individual consumers and society as a whole. At this stage it is critically important for the acceptance of the technology that personal and directly verifiable benefits are clear to the consumer. Taste and convenience are much more appropriate benefits for this purpose than the exclusive focus on health and sustainability, for example. If the technology has proven its contribution in terms of directly relevant consumer benefits, it will be much easier to also communicate the technology's contribution in terms of unverifiable 'credence' benefits such as health, safety and sustainability.

Build on success in other fields

Trust in and the authority of technology are crucial factors for consumer acceptance. Both can find their basis in success stories in other fields where the technology has provided a relevant advantage. For genomics-based technologies, it seems that the most relevant success stories are to be found in the medical sector. Successful and valuable applications in the medical field should be better and more convincingly communicated as a basis and to facilitate acceptance of these technologies within the areas of food. Dick Willems' essay[6] addresses the improved prediction of undesired side-effects of medication, which may serve as a good example of the advantages of genomics.

Conclusion

Like many other new technologies, genomics-based technologies hold the potential to make a substantial contribution to the quality of life. However, genomics-based technologies have the 'disadvantage' that their core activity is so close to what is the 'essence' of mankind, plants and animals. This proximity to the basic genetics results in a number of specific associations regarding the integrity of nature, privacy and control. Such associations are inevitable and deserve substantial attention and a careful management of expectations.

6 See article of Willems 'Pharmacogenomics and Everyday Health Care' in Part II of this book.

It is very notable that the five essays in Part 2, despite their diversity in topic and considerations, share the view that genomics requires a new way of thinking, a new frame of reference in one way or another. Hub Zwart[7] and Frans van Dam[8] both illustrate this by referring to the new type of ethical questions that arise due to genomics, such as 'What do we expect from life?' All essays emphasise the complex nature of the genomics field, and that it is crucial that all stakeholders are involved at this relatively early stage of its development. However, rather than focus on the differences between genomics and other food technologies (as most of the other essays in this book do) we wish also to consider the similarities. Following Rogers we believe that consumers will evaluate the technology primarily on the benefits (relative to costs) it will provide for them.

To be able to really exploit the private and societal benefits of this new set of technologies in the (near) future, it is of essential importance to start now to pro-actively communicate with consumers and society as a whole about what the technology is and what it is not. This should stimulate societal involvement and commitment at this early stage and also allow society to reflect on what need be the boundary conditions to applications of this new technology. Scientists and policy makers jointly with NGOs should take up this communication challenge pro-actively to prevent themselves from being limited to purely reactive communications in the future.

We are confident that in time these genomics-based technologies will be adopted by society as a whole. However, the rate of adoption will critically depend on 1. credibility obtained from scientific substantiation 2. trust obtained from transparency and public debate and 3. the consumer-relevant benefits provided by the technology.

We appreciate that at the moment it is difficult to scientifically predict the scope of future applications of nutrigenomics. The most important issue at this stage is probably to ensure trust and credibility with which consumer-relevant benefits can be acquired. This can best be achieved in niche markets targeted by innovators and early adopters and by building on success stories in related fields. If we first convincingly show on a smaller scale how these technologies have contributed to medical progress, it will be much easier to leapfrog from these successes to the consumer market as a whole.

References

- Cardello, AV (2003). Consumer Concerns and Expectations about Novel Food Processing Technologies: Effects on Product Liking. *Appetite*, 40 (3). pp 217-233
- Dabholkar, PA, RP Bagozzi (2002). An Attitudinal Model of Technology-Based Self Service: Moderating Effects of Consumer Traits and Situational Factors. *Journal of the Academy of Marketing Science*. pp 184-201

7 See article of Zwart 'Genomics: Towards a More Comprehensive View on Human Life' in Part II of this book.

8 See article of Van Dam 'Genomics for Consumers?' in Part II of this book.

- Darby, M, E Kerni (1973). Free Competition and the Optimal Amount of Fraud. *Journal of Law and Economics*, 16 (1). pp 67-88
- Davis, FD (1989). Perceived Usefulness, Perceived Ease of Use, and User Acceptance of Information Technology. *MIS Quarterly*, 13 (3). pp 319-340
- Fishbein, M, I Ajzen (1975). *Belief, Attitude, Intention, and Behavior. An Introduction to Theory and Research*. Reading, Addison-Wesley, Massachusetts
- Frewer, LJ, B Salter (2002). Public Attitudes, Scientific Advice, and the Politics of Regulatory Policy: the Case of BSE. *Science and Public Policy*, 29 (2). pp 137-145
- Frewer, LJ (2003). Societal Issues and Public Attitudes towards Genetically Modified Foods. *Trends in Food Science and Technology*, 14 (5-8). pp 319-332
- Petty, RE, JT Capioppo (1986). The Elaboration Likelihood Model of Persuasion. *Advances in Experimental Social Psychology*, 19. pp 123-205. Academic Press, New York
- Rogers, EM (1962). *Diffusion of Innovations*. The Free Press of Glencoe, New York
- Rogers, EM (2003). *Diffusion of Innovations* (fifth edition). Free Press, New York
- Rozin, P (1999). Food is Fundamental, Fun, Frightening, and Far-Reaching. *Social Research*, 66 (1). pp 9-30
- Slovic, P, B Fischoff, S Lichtenstein (1980). Facts versus Fears: Understanding Perceived Risk. In: R Schwing and WA Albers (eds.). *Societal Risk Assessment: How Safe is Safe Enough*? Plenum, New York. pp 463-489
- Slovic, P, B Fischoff, S Lichtenstein (1981). Characterizing Perceived Risks. In: RW Kates, C Hohenemser, JX Kasperson (eds.). *Perilous Progress: Managing the Hazards of Technology*. Westview, Boulder, CO. pp 91-125
- Sparks, P, R Shepherd (1994). Public Perceptions of Food Related Hazards, Individual and Social Dimensions. *Food Quality and Preference*, 5. pp 185-194
- Tornatzky, LG, KJ Klein (1982). Innovation Characteristics and Innovation Adoption-Implementation: a Meta-Analysis of Findings. *IEEE Transactions on Engineering Management*, EM-29 (1). pp 28-45
- Venkatesh, V, MG Morris, GB Davis, FD Davis (2003). User Acceptance of Information Technology: Toward a Unified View. *MIS Quarterly*, 27 (3). pp 425-478
- Wynne, B (1991). Knowledge in Context. *Science, Technology and Human Values*, 16 (1). pp 111-121

Genomics for consumers?

Frans van Dam[1]

Is the 'average' consumer interested in genomics? And if not, should he or she be interested? And, if we should decide that consumer involvement is desirable, how are they to be involved, and for what purpose? Associating consumers with genomics immediately will raise many questions and difficulties. But the central question is of a more fundamental nature. Can an individual in his or her capacity as a consumer get an overall view of the field of genomics science and can they make any meaningful choices?

Let us start with an example. As a professional, a senior genomics scientist specialising in yeast molecular biology has an overall view of and understands the meaning of genomics. He reads and writes (scientific) genomics-related articles and he often talks to colleagues in the genomics field. In order to make progress he has to make professional choices every day. When he leaves the lab his world changes. He goes shopping, pays his bills, buys goods and services, and thus becomes an 'ordinary consumer'. He eats as usual and books his yearly holiday at the seaside. Our yeast scientist, as a consumer, behaves like any other consumer, without any interference from his professional knowledge. The same goes for consumers that have little or no knowledge of genomics-related subjects; in their daily lives, they will not be influenced by the present state of the art of genomics science. To them, genomics is meaningless.

1 Drs F. van Dam, Centre for Society and Genomics, Nijmegen, The Netherlands.

Future genomics consumers

Genomics is not very helpful for consumers, as it tends to make things more complex, where simple answers are desirable. That situation can change. If for instance genetic tests are offered on a large scale for fine-tuning individuals' diets, if extensive genetic testing is introduced for applications for life or health insurances, consumers will be confronted with novel goods and services, new choices to be made and, perhaps, new liabilities. In these situations, where the science of genomics has been combined with specific technologies or services, genomics and its consequences become meaningful. Verrips, in his forecast[2], describes this situation. He predicts that "*in 2030 the complete genome of individuals can be determined for € 100-1000*." Based on this information, the individual will be given advice on lifestyle and medication.

Society

Although unnoticed by individual consumers, genomics already has its impacts, but more on society as a whole. Take for instance the use of genomics-derived technology in forensic science. Forensic genomics could increase the percentage of murder and rape cases solved. The question is whether this will result in a decrease of murder cases and an increased feeling of security. In return, innocent individuals whose DNA-sequence is stored in databases may become suspects, when traces of their DNA happen to be present at the crime scene. Another example is the use of genomics as an aid to replace 'old-fashioned' chemical industrial processing with biological processing. Genomics has the potential to deliver industrial processes that spare the environment. For the industry there are multiple incentives for using biological processes, as these save raw materials and are more cost-effective. Moreover, the industry will be able to more easily comply with environmental legislation. The choice between 'chemically produced' and 'biologically produced' materials is not a consumers' choice, it will be made for them.

Not an issue (yet)

Societal issues are usually voiced by public interest groups. In the Netherlands, patients' organisations involved in hereditary diseases are heavily involved in genomics policy. So far, patients' organisations seem to be the exception. If genomics is an issue for consumers, it might be expected that the subject would also be on the consumer organisations' agendas. Up to now, however, genomics has not been an issue in consumer policy, neither in Europe nor probably anywhere else. Also for environmental groups, Third World and animal welfare organisations, genomics has hardly been an issue.[3] As a result of this, these organisations have not (yet) invested in developing expertise on genomics.

Genomics will most probably not become as politicised as genetic modifica-

2 See article of Verrips 'Genomics 2030: Part of Everyday Life' in Part II of this book.

3 The exception is an issue of the pre-genomics era: intellectual property rights on genes and their uses. Starting in the early 1980s, when modern biotechnology set off, this issue raised fierce political and societal disputes.

tion or biotechnology. I agree with Swierstra who recently predicted that genomics will not result in a "*debate between pessimists and optimists*" like the one concerning the monogenetic approach [Swierstra, 2004]. Genomics gives rise to a new type of ethical questions, such as: 'What do we expect from life?' and 'How do we wish to live?'. As these questions are not the type of questions to be found in the newspapers, Swierstra suspects that these questions will be addressed in other media, such as literature, cinema and plays.

Citizens

My point is that if we now wish to confront individuals with genomics in any meaningful way, we need to approach them in their capacity of citizens. It is citizens that cast their votes in elections, discuss societal issues in forums, pay income tax and donate money for the environment or for aiding poor countries. Citizens may be willing to discuss the future of their society as a whole and not just the part which is of direct personal interest. Ronteltap and Van Trijp[4] also warn not to introduce genomics products on the market without consulting consumers beforehand. They stress the need for pro-active communication upon introduction, in order to prevent consumers from feeling overruled or alienated.

The notion of 'let's leave it to the market where consumers decide' without consulting citizens can even be fatal. This was shown by the failed introduction of GM[5] foods in Europe. Tough marketing techniques by multinational companies of GM products that are of no specific use to consumers, combined with bad press and angry NGOs led to a very cold climate for GMOs in Europe. Europeans wish GM foods labelled, not because they like being able to make a choice themselves, but because they feel that labelling can be helpful to others and that it is an instrument of governmental control. This shows that respondents, even if they are addressed as consumers, may respond as citizens.

The GM example shows that there is clearly a need to integrate societal aspects in the design of genomics science and derived products as well as the terms of use of genomics information and products. One way of doing that is to involve citizens. Citizen involvement, however, is not an easy undertaking. One cannot simply ask individuals about their opinions concerning 'genomics'. As I will explain later, the potential of genomics needs to be presented in a fair and meaningful way, and those citizens who are willing to spend some time thinking about genomics need to be empowered. The first pitfall is to present genomics as a tool for everything.

4 See article of Ronteltap and Van Trijp 'Consumer Acceptance of Nutrigenomics-Based Food Technology' in Part II of this book.

5 Genetically modified.

No magic bullet

It is obvious that genomics is not a magic bullet; we can not go further than nature allows us to go. In other words, genomics, just like any other technology or field of science, will not comply with the economist's principle of supply and demand. If we wish to submit genomics to public scrutiny, we need to give a plausible picture of the possible and the impossible, of the pros and cons. If we exaggerate the potential too much, we can expect a critical response which is exaggerated too. For the exact same reason, we should not underestimate the potential of genomics. In this respect Ronteltap and Van Trijp[6] refer to communicating about 'verifiable benefits' of genomics to consumers.

Critics say that genomics is an answer to a question posed by no one; genomics as a solution is looking for a problem to solve. I do agree that it is not wise — and often incorrect — to present genomics as the 'sole solution'. If it is stated that 'genomics feeds the poor', suggesting that genomics can do this job on its own, we do not pay tribute to the enormous complexity of hunger in developing countries and the way in which regions vary in this respect. Genomics is merely one of many technological options that can or should be explored. The same goes for 'nutrigenetics', the fine-tuning of — western — diets based on the individual's personal genetic profile. Nutrition-related problems such as obesity and Type II diabetes are caused by a combination of factors. Genetic predisposition is one of them, but there is an intricate interplay with various life style-related factors.

Fruitful public communication about genomics requires analysis of the major societal issues and problems (such as health, hunger, environment) and the potential of various technologies — including genomics — that may contribute to solutions or assist in dealing with these issues.

Language

When communicating genomics to the public, we need to translate the term into an understandable language. A quantitative (n=1000) and qualitative public survey carried out in 2002 in the Netherlands showed that respondents do not understand the meaning of the word 'genomics' [Stichting Consument en Biotechnologie, 2002]. It is too new and too abstract and should, if possible, be avoided in communication with the public. People do relate to concrete use of genomics technology, such as genetic testing and plant breeding. These uses should preferably be presented in combination with alternative technologies or solutions. Public acceptance of genomics is to a large extent dependent on its specific application. Respondents appeared to have quite strong opinions about the consequences of genomics and the control mechanisms needed.

6 See article of Ronteltap and Van Trijp 'Consumer Acceptance of Nutrigenomics-Based Food Technology' in Part II of this book.

Many respondents from the 2002 survey directly associate plant genomics with GM food, the latter being a known type of application. The authors of the survey suggest that denial of this correlation will result in disbelief. Preferably, the relation between genomics and genetic modification needs to be clarified. A major challenge here is the complexity of genomics. Instead of mentioning 'the gene for disease X or characteristic Y' a more comprehensive view of organisms or health needs to be presented. Genomics in health, as explained by Hub Zwart[7], is not about monogenetic diseases, but rather about multi-factorial health problems.

Citizen empowerment

If we wish citizens or their representatives to actively participate in debates on genomics, it will be advisable to invest them with the necessary information and tools. It is not realistic to expect that a major part of society wishes to be involved; we will have to make do with a small minority. As indicated in various essays written in 2002 about the societal component of genomics, users have to develop competencies in order to be able to articulate their needs [Netherlands Genomics Initiative, 2003]. In his essay on patients and genomics, Streng[8] stresses the need for education to improve the lagging knowledge of laymen in the fields of heredity and genetics. Education is only one of the possibilities for citizen empowerment. Hanssen et al distinguish — in addition to the scientific domain — four domains of debates on genomics: the policy, popular, arts and political-philosophical domains. Every domain has its own arguments, languages, media, etc [Hanssen et al, 2003]. The quality of societal debate increases when all domains interact.

Opportunities?

In western countries, consumption of typical genomics goods and services will become a reality one day. In that respect I agree with Verrips[9]. No doubt, this will provide individuals with new opportunities but it will also give rise to new questions and responsibilities, perhaps even threats. A probability scheme for our future health in combination with preventive advice is one thing. But do we really want to know which nasty diseases are lurking in our dens? Do we want to carry the burden of preventive action every day? Or will the day come that we regard our genetic health card as a list of opportunities instead of a source of constant worry?

Pharmacogenetics — most probably the first type of genomics in medical practice — may result in medical decision-making which may not always be in the patient's personal interest, as pointed out by Willems[10]. One day, the outcomes of an essay may tell a patient that further medical treatment is useless, taking away time filled with hope. Involvement of patients/citizens or

7 See article of Zwart 'Genomics: Towards a More Comprehensive View on Human Life' in Part II of this book.

8 See article of Streng 'Living the Future' in Part II of this book.

9 See article of Verrips 'Genomics 2030: Part of Everyday Life' in Part II of this book.

10 See article of Willems 'Pharmacogenetics and Everyday Health Care' in Part II of this book.

their organisations in designing these tests will be helpful in determining their terms of use.

Conclusion

Summarising it may be said that if our goal is to seek serious involvement from 'society' in genomics policies, we need to look ahead and we need to show how genomics is of influence on society and will be so in the future. Individuals need to be confronted with genomics, primarily in their capacity as citizens. Involvement of public interest groups is difficult as genomics is not yet an issue and there is hardly or no expertise present.

The context in which genomics is to be discussed needs to be one of problems and issues, only then its place becomes clear. It will be best to present genomics unpretentiously, as an instrument for acquiring knowledge and developing tools, to be used in many ways. Those who do wish to participate in debates on genomics need to be empowered. For a fruitful debate, interaction will be required between science and various domains, including policy/politics, art and philosophy.

References

- Hanssen, L et al (2003). Het participatieve gen, participatieve instrumenten in het omgaan met maatschappelijke vraagstukken over ontwikkelingen in voedingsgenomics. In: Netherlands Genomics Initiative. *Genomics, Dreams, Fears and Fantasies*. Den Haag
- Netherlands Genomics Initiative (2003). *Genomics, Dreams, Fears and Fantasies*. Den Haag
- Stichting Consument en Biotechnologie (2002). *Publieksonderzoek Genomics*. Onderzoeksverslag. Den Haag
- Swierstra, T (2004). Van rechtvaardigheid naar het goede leven: genetica en genomics in de dagbladen. In: N Willems, D Willems (eds.). *De genetische ontrafeling van veel voorkomende aandoeningen*. Leschot, Maarssen

IMPACT ON SOCIETY

Microneedles Coupled to a Microanalysis Chip for Lithium Measurement in Blood

Albert van den Berg[1]*, Elwin Vrouwe*[2]

Lithium is one of the most effective medicines for people suffering from mood disorders such as manic depression. One of the major disadvantages is its limited therapeutic window, the space between therapeutic and toxic concentrations, which requires frequent monitoring of the lithium concentration in blood. A Lab-on-a-Chip system comprising a microneedle array for painless blood sampling and a microchannel chip for lithium separation and detection has been developed and enables a rapid (less than one minute) and accurate (R^2=0.94 in comparison with conventional laboratory measurement) measurement, as confirmed by five different samples. The realised microsystem has a potential of being mass-produced in polymer as a disposable system, which would allow a realisation of a consumer price of approximately $ 2-5. Availability of these chips would strongly improve the life quality of patients with lithium medication, since these will allow them to continue to measure and maintain appropriate medication levels when away from home (for instance, on holidays).

1 Prof Dr Ir A. van den Berg, Twente University, Faculty of Electrical Engineering, Mathematics and Computer Science, BIOS chair, MESA+ Institute for Nanotechnology, Enschede, The Netherlands.

2 Dr E.X. Vrouwe, Twente University, Faculty of Electrical Engineering, Mathematics and Computer Science, BIOS chair, MESA+ Institute for Nanotechnology, Enschede, The Netherlands.

Literature

– Gardeniers, JGE, R Luttge, JW Berenschot, MJ de Boer, Y Yeshurun, M Hefetz, R van 't Oever, A van den Berg (2003). *JMEMS*, 12 (6). pp 855-862
– Vrouwe, EX, R Luttge, A van den Berg (2004). *Electrophoresis*, 25. pp 1660-1667

Figure 1
Microneedle array for painless blood sampling.

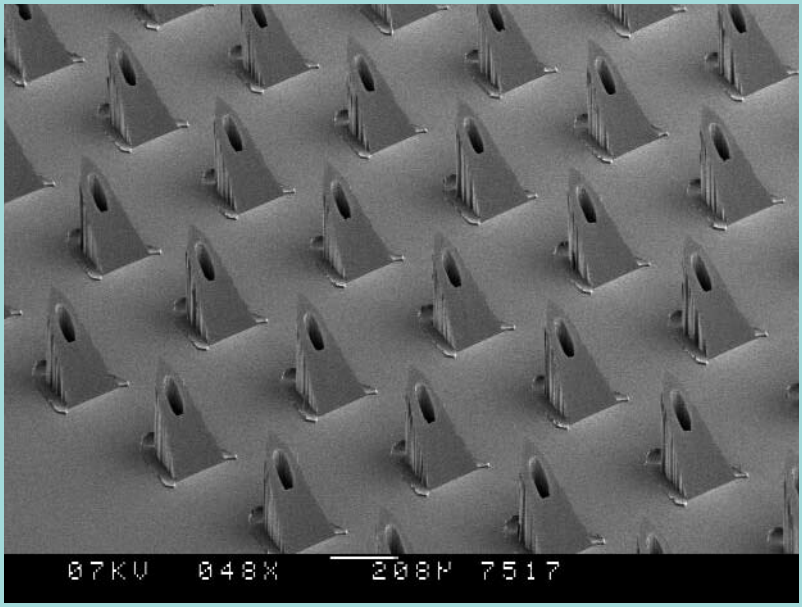


Figure 2
Micrograph of glass chip for lithium separation and detection.

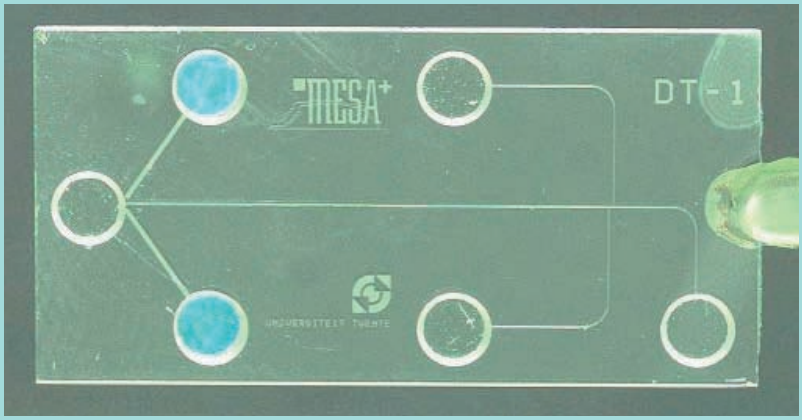
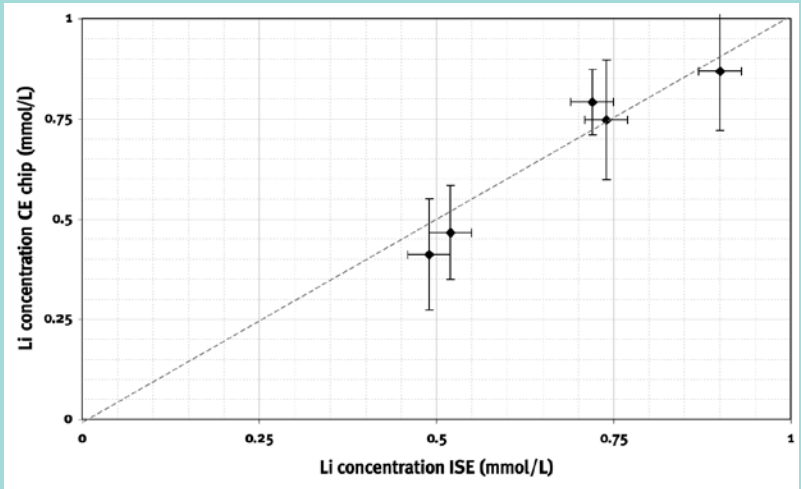


Figure 3
Correlation between chip-based and conventional determination of lithium (R^2=0.94).



Genomics: Towards a More Comprehensive View on Human Life

Hub Zwart[1]

What is genomics?

This is by no means a trivial or academic question but an issue that has serious implications for the way in which the societal debate about genomics has to be defined. Basically, two answers can be given. The first answer stresses the newness of genomics. The neologism genomics is used to emphasise the basic difference between traditional genetics and biotechnology on the one hand, and genomics on the other. Whereas in traditional genetics and biotechnology the focus is on detecting, transferring or deleting single genes, the objective of genomics is to understand complexity, to make visible complex patterns of interaction between large numbers of genetic and environmental factors. Thus, genomics research is said to exemplify a paradigm shift or quantum leap in the history of the life sciences. We have entered a post-reductionistic era.

1 Prof Dr H.A.E. Zwart,
Centre for Society & Genomics,
The Netherlands.

Others, however, stress the continuity between genetics, biotechnology and genomics. Genomics is basically regarded as a set of tools used in the context of research programmes that remain reductionistic and deterministic in orientation. Genomics as a neologism was introduced for strategic reasons in order to open up new avenues of funding and to get away from undesirable connotations associated with biotechnology in the public realm. Up to a certain extent both views are viable, and the difference between genomics and traditional genetics or biotechnology is a fluid one. But if we wish to take genomics and its challenges seriously, the focus should be on its novelty. Or, to put it differently, in this contribution I will discuss genomics in so far as it differs from traditional genetics and biotechnology.

The basic objective of biotechnology as it emerged in the 1980s and 1990s was to change, to modify organisms. In the context of agriculture for example, biotechnology aimed at the introduction of new sets of products, such as crops containing certain additional ingredients. Genomics, however, is basically about knowledge. It generates information about the ways in which genetic and environmental factors interact. How do certain genes respond to certain ingredients, how will certain ingredients affect my health? Rather than producing new sets of products, genomics will basically produce new forms of information. The focus will shift from the question what kind of novel food products consumers will accept to questions such as: 'To what extent will individuals use genomics knowledge in order to adapt their lifestyle and diet?' In a general way we all know, for example, that smoking cigarettes is bad for our health. We also know, however, that smoking is not equally bad for everybody. Some smokers remain healthy until old age. Genomics will probably clarify the genetic basis for these individual differences. For some people, a moderate use of alcohol is part of a happy and productive life. To others, the use of alcohol poses a serious threat. Or, to give yet another example, some people will flourish in a stressful environment, while others will develop serious health problems. Genomics is expected to shed some light on these individual dispositions.

This type of information will not only be of interest to individuals, however. It will have a much broader implication. To begin with, governmental organizations may become increasingly interested in this type of information. In the nineteenth century, national governments became increasingly interested in the physical conditions of the general population and in science-based methods to improve it, such as hygienic living conditions and making available healthy but inexpensive food products (bread, meat, butter, vegetables) for the working classes in the urban centres. It was recognised that the economic and military power of a nation was determined by the general physical condition of its population. Subsequently, during the first decades of the 20th century, governmental organizations developed a growing concern for

the psychic wellbeing of the population. Intelligence tests and other tools for large-scale testing programmes were developed. And now the genomics era can be expected to provide governments with information on the genetic condition of the population. In the near future, contemporary society can expect some challenges. For example, we are confronted with an ageing population. More people will have to stay healthy and active for a longer period of time, notwithstanding the ever-increasing pace of technological innovation. Shall we (will they) be able to cope with that?

In addition to individuals and governments, other stakeholders may well be interested in genomics information, not only insurance companies, but also companies (employers) in a more general sense. The possibility of genetic pre-employment screening is not entirely fictional. A genetic factor has been identified that increases susceptibility to SARS. In the future, a hospital in the vicinity of an international airport may argue that hospital personnel, notably in an emergency room setting, should be subjected to a genetic susceptibility test for SARS and similar infectious diseases, in their own interest as well as that of others. It is not entirely unthinkable that in the near future genomics will provide us with information concerning the likelihood for individuals to develop stress, burn-out, and other life-style related problems. Will it be possible or objectionable to use this kind of information when it comes to selecting candidates for a job? Maybe a new type of expert, the career consultant, will emerge, providing career advice on the basis of a combination of genetic and psychic testing?

Therefore, I agree with Frans van Dam[2] that, in order to confront individuals in a meaningful way with genomics, we must approach them as citizens rather than as consumers. Genomics is not about particular products but rather about new forms of knowledge and information. Who will use this information and how? These are questions to be addressed in the public domain rather than in the supermarket, by citizens rather than by consumers. I do not expect genomics to lead to fierce disputes whether or not a certain product should or should not be developed or introduced. On the contrary, I agree with Swierstra [Swierstra, 2004] that genomics will trigger new sets of ethical questions such as 'What do we expect from life?' and 'How do we wish to live?' Societal debate will shift to other forums, in particular to 'genres of imagination', such as films, novels and plays. This means that genomics issues will not be addressed in the same way as biotechnological issues were in the past. Typically, in the context of a dispute over biotechnology, proponents and opponents of a certain innovation were invited by the media to explain, in two or three sentences, why they were in favour or against a particular innovation (modification). Genomics is a much broader issue. It will have an impact on a much broader scale. The societal and cultural impact of genomics will be addressed in other ways and by other media, such as literature, cinema and

2 See article of Van Dam 'Genomics for consumers?' in Part II of this book.

theatres. The question will be: 'How will genomics information influence our views on health, on personal responsibility, on personal autonomy, on reproduction, on old age?'

Genomics is not about monogenetic diseases, but rather about multi-factorial health problems. Therefore, genomics information is not only interesting for specific risk groups, it is relevant for everybody. In other words, the genomics era will involve a shift from single genes and specific genetic defects to persons as a whole. It will allow them to gear their lifestyles to their genetic profiles. Genomics challenges us to develop a more comprehensive view on human health. This will obviously have consequences for policies as far as screening and prevention are concerned.

Will this stimulate or reduce medicalisation? In order to answer this question, we have to briefly review the history of the medicalisation debate. During the 1950s and 1960s, science and technology dramatically changed medicine as a field. This was exemplified by the sudden emergence of transplantation medicine (the first kidney transplantation took place in 1954, the first heart transplantation in 1967), but also by the fact that more and more people came to die in hospitals instead of at home. This development was both applauded and criticised. There was a general concern among critics that the emergence of a scientific and technological approach to medicine would undermine a more holistic view on man. Rather than seeing the patient as a person, the new, science-based medicine would reduce him or her to a particular condition or disease. Patients would no longer be seen as human being with worlds of their own, but rather as objects, to be talked about in terms of symptoms, treatment options and prognostics. In the 1950s, the Hippocratic ethic was still very much alive. The doctor-patient relationship was seen as a very personal relationship. The physician was something of a friend, someone who knew his patient personally. A patient was to be approached as a human being leading a social and cultural life apart from a physiological one. The new science-based medicine seemed to change that. Attention seemed to shift from people to X-rays and lab results.

Around 1970 the field of bioethics came into existence. The Hippocratic era was definitely over and medicine had finally become a science. How to reaffirm and re-establish the personhood of patients, now that medicine had become a high-tech, science-based field? There was a sense that the triumph of medicine was accompanied by a crisis of medical ethics. How could be made sure that a patient would be more to a physician than his or her X-ray? Those were the typical concerns voiced by bioethicists in the 1970s.

In the genomics era, this is likely to change. The focus will be on a more comprehensive view on individuals and human wellbeing. Genomics is not about specific monogenetic or monocausal health problems. Rather, in the genomics era, we will once again be invited to study the interaction between the

physiological, the social and cultural dimension of human life. I expect, for example, that genomics will be particularly helpful when it comes to furthering our understanding of the so-called new diseases that emerge on the borders between physiology, psychology and sociology, such as burn-out or the chronic fatigue syndrome.

This means that in the future a completely new role will be played by general practitioners. In the high-tech science-based medicine as it emerged in the recent past, the place of the general practitioners in the health system became an increasingly marginal one. But this may well change. In the genomics era the question will be how to interpret genomics information, how to connect it with developments in a person's social or professional life. And the general practitioner may well be the one who is best-fitted to assist individual patients in building a comprehensive view of their health status on the basis of genomics information. How to translate genomics information into concrete every day choices? In other words, general practitioners will play a prominent role in this whole process. In their professional life, a shift of emphasis is likely to occur from intervention towards information management. Are they ready to play this role? On the one hand, health care workers in general will have to be educated in order to be able to deal with the new forms of knowledge and information that will influence both the health domain and our understanding of illness and health. On the other hand, general practitioners are experts in their own right, of course. They are experts of illness and health in daily life and in this position they will no doubt be able to play an important role as intermediaries between genomics science and society, between scientific innovations on the one hand and societal urgencies and developments on the other. Patient organizations will also increasingly function as intermediaries between science and patient (in two directions). They will educate their interests groups, participate in research programmes and stimulate particular lines of genomics research.

Against the background of these developments, I consider the scenario study by Theo Verrips[3] about the virtual health agent quite credible. Such an agent can monitor our health situation. Besides measuring body weight, a health practice many people are already involved in on a daily basis, it can give us information on blood pressure and other parameters, depending on the individual's condition and genetic profile. The focus will be on prevention, on gearing lifestyles to genetic risks and on tailor-made pharmaceuticals and special food products. General practitioners will be called upon to assist their patients in interacting with such a device. A virtual health agent will not replace the physician. On the contrary, patients and physicians will have it at their disposal as a reasonably reliable tool for monitoring the patient's condition (notably for example during periods of drug use), generating input for consultations. The virtual agent can integrate genetic and other types of infor-

3 See article of Verrips 'Genomics 2030: Part of Everyday Life' in Part II of this book.

mation into a comprehensive assessment of the person's physical condition and health options.

For the larger part, genomics is still a laboratory phenomenon. The 1990s are known today as 'the years of controversy', but they also constituted an era of optimism. Life scientists promised their societal audiences that chronic problems of long-standing, such as cancer and global inequality, would finally be addressed. The basic message of genomics, however, is that life is much more complicated than life scientists in the 1990s were willing to realise. More research is needed in order to appreciate and understand nature's extremely complicated and intelligent designs. The trajectory from basic research to applications is complicated and time-consuming. As is indicated by Peter Streng[4], the production of new pharmaceuticals, for example, is a costly process. During the 1990s the 'commercialization' of biotechnology took place. Scientists migrated in large numbers from university laboratories to private companies. In the genomics era, however, we witness a dramatic resurgence of large-scale public forms of funding, for example in the context of the Human Genome Project. It is simply not true that politicians or the public are unwilling to make funding available for basic scientific research. The problem is, rather, that whereas the scientific objectives of research activities are often articulated in a very precise and accurate way, the societal prospects of these programmes tend to be addressed in rather vague and general terms. In order to convince society of the importance of long-term public funding of genomics research, the promises of genomics have to be toned down to realistic proportions and the societal agenda of genomics has to be formulated in a more concrete and, above all, less noncommittal way, in terms of definite milestones. This should be the basis of a new social contract between society and genomics. Genomics research has increasingly to be willing to orient itself towards goals and objectives that really are of substantial societal importance. In other words, the problem is not that the public suffers from a lack of information (a knowledge deficit). The problem is rather how to produce a robust and convincing societal agenda for genomics. This calls for more intimate forms of dialogue between science and society. Genomics researchers can no longer afford to postpone or restrict societal communication to the dissemination phase. The societal arena of genomics research has become a complex setting in its own right.

In short, genomics is not about the modification of organisms or the introduction of specific products. Genomics will rather add a new dimension to our knowledge about ourselves. This will have an impact on the way we interact with our bodies, our general practitioners, our insurance companies, our careers. In a knowledge society, scientific and technological innovations are of essential importance, but we have to move beyond a view that sees the public

4 See article of Streng 'Living the Future' in Part II of this book.

as epistemologically deficient and reduces science communication to 'public relations'. We have to invest in genomics, but we have to invest in developing innovative forms of societal interaction as well.

Reference

– Swierstra, T (2004). Van rechtvaardigheid naar het goede leven: genetica en genomics in de dagbladen. In: N Willems, D Willems (eds.). *De genetische ontrafeling van veel voorkomende aandoeningen*. Leschot, Maarssen

IMPACT ON SOCIETY

DNA Microarrays for Treatment Development in Cancer

Bob Löwenberg[1]

Molecular genetics in cancer

Cancer is considered a multigene disease. This implies that the disease develops following the acquisition of successive genetic events over time. Only when these changes in genes accumulate, the disease will come to its clinical expression. This is the condition in a patient who newly presents diagnosed cancer. It is assumed that these acquired genetic alterations (for instance, mutations) cooperate in a cell, perturb the intracellular machinery of growth and create malignancy. The altered genes (so-called oncogenes) encode for proteins that dismantle normal cell functioning. For instance, oncogenes may thus disturb cell division, cellular maturation, cell death, cell migration.
In 2005 clinical medicine is at a stage where genetic changes in cancer are continuously discovered. The disclosure of these genetic events will be of significant importance for developmental diagnostics and the development of individualized (i.e. better!) therapies.
Nevertheless, nowadays most of the therapeutic practice in clinical oncology still depends on the classical approach of cytotoxic chemotherapy and hormonal therapy, and on the use of surgery and radiotherapy as localized therapies. Therapeutic interventions in critical positions in perturbed cellular pathways in cancer should yield more specific therapies ('targeted therapy').

1 Prof Dr B. Löwenberg, Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands.

The clinical promise of cancer genetics

Diagnosis and treatment of cancer until today is based on half-way technologies that need further development. Results of treatment in lung cancer, prostate cancer, cancer of the bowel, breast cancer, leukaemia and lymphoma are insufficiently satisfactory. This is a consequence of too little efficacy of available therapies and not infrequently also of too much toxicity associated with current therapies. Two examples of the insufficient benefit of current cancer therapies will be given hereafter.

The mortality of localized colon (bowel) cancer, a common form of cancer in man, is approximately 40%. Thus in a significant fraction of patients without detectable metastases (= spreading of cancer to distant sites) at the moment of diagnosis (therefore the cancer is assumed to be localized at a single site), the disease is in fact not localized at all. In those individuals metastases will appear after some time causing these patients to die from their cancer. Better staging and distinction of individual risks will assist in developing more suitable therapies for these heterogeneous groups of patients. In the case of disseminated colon cancer, only 20% of patients will survive current treatment. This underscores the urgent necessity of novel therapies for the latter category of patients.

Breast cancer is the most frequent cancer among women. It has a worldwide frequency of 1 million new cases per year. Half of these women will die from the cancer. It is important to know at the earliest point possible who can be cured by localized therapy only (surgery, radiotherapy) and who requires additional treatment for the prevention of metastases. For patients with disseminated cancer (distant metastases) it is important to be able to predict whether or not the patient will respond to chemotherapy or hormonal therapy. For those predicted with whom current therapies will fail, novel drugs need to be developed with the highest priority.

Acute leukaemia develops in the bone marrow, the production 'factory' of our blood cells. Due to its direct connection with the blood, leukaemia is always a metastatic disease. Leukaemia can be cured in some young and middle-aged patients with highly intensive cytostatic therapies and stem cell transplantations. A proportion of these patients with an a priori high chance of cure are overtreated. It is necessary to spare those patients the highly toxic therapies so that early and late toxic effects are avoided in these individuals. Therefore a predictor of prognosis based on the individual properties of the leukaemia in a given patient is most desirable. It is also desirable to apply specific treatments tailored to the properties of any particular form of leukaemia in any given patient. The ability of applying more specific therapies will automatically extend the use of more effective and less toxic therapies to patients in whom currently available therapies fail and in particular also to elderly patients.

The above mentioned examples for colon, breast and blood cancer (leukaemia)

are representative of the general hurdles and scientific issues in cancer therapy today.

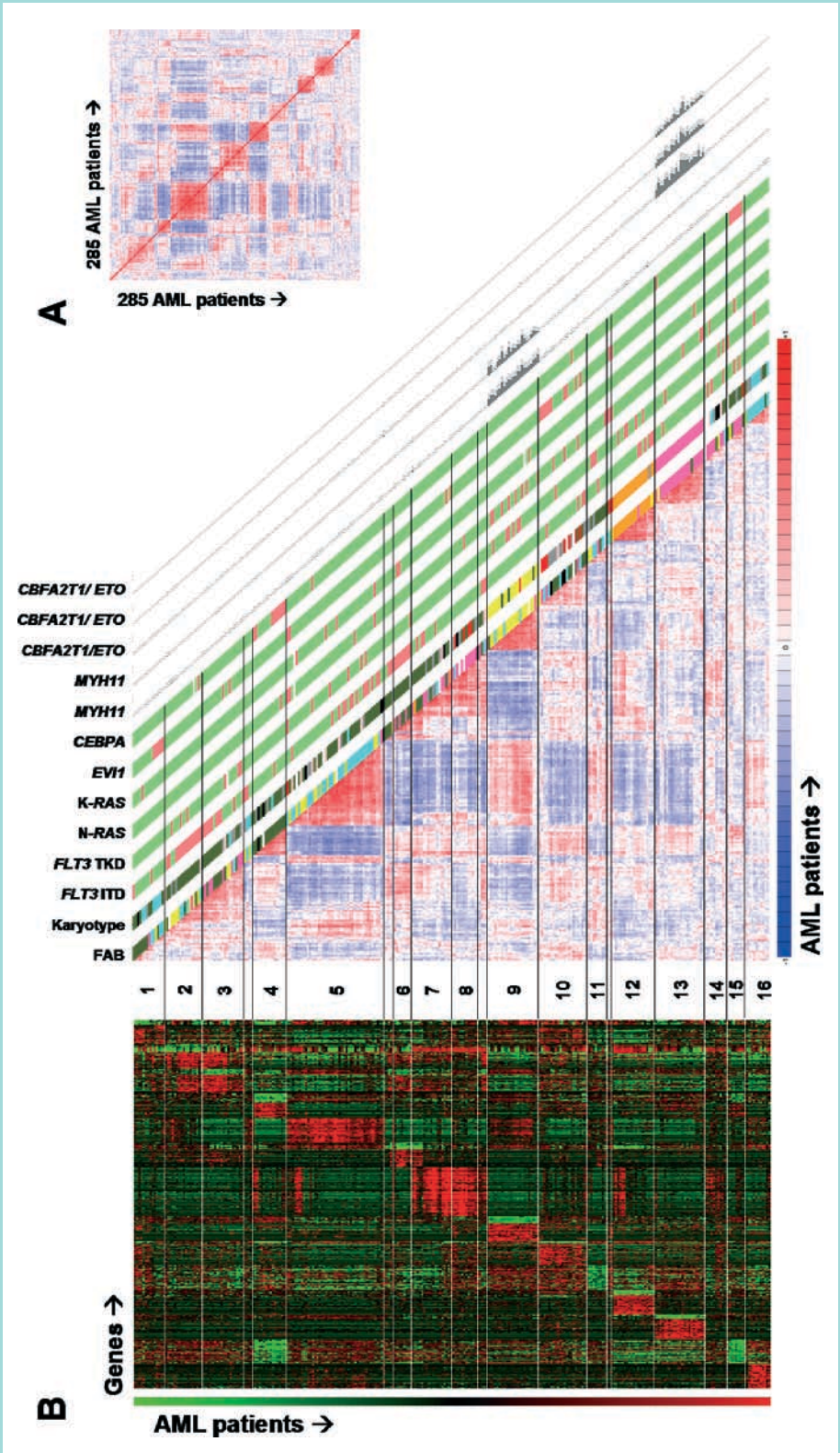
DNA microarrays

DNA microarrays make the simultaneous analysis of the expression of thousands of genes in one and the same tissue sample possible. Fragments of DNA, representative for thousands of genes, are spotted on the gene chip, i.e. at a high density on a tiny surface. When a gene in a cell is active, it will produce a messenger RNA that encodes for a particular protein. The DNA chip measures the presence of the messenger RNA molecules for a wide array of genes in the cell and this furnishes a comprehensive picture of the gene activity of the tumour. The RNA molecules are labelled with a fluorescent marker so that they can be measured. The profile of active (RNA present) or inactive (RNA absent) genes that is measured creates a barcode of the activation state of thousands of genes in the cancer tissue specimen. A variety of technologies of DNA microarrays are being developed that apply different sorts and numbers of DNA molecules, different surfaces, and different reference material. The analysis of the massive amount of information also requires sophisticated mathematical software. A variety of bioinformatics approaches are used to identify patterns in large complex data sets. These techniques are still being developed at full speed and their biologic impact is subjected to intense research. The variations in the gene expression patterns that are apparent will be the consequence of the genetic alterations that have caused the cancer and the genetic profile will therefore provide a direct key to the underlying genetic causes.

Figure 1 (right page)
(A) Gene Chip barcode is shown for 285 patients with acute myeloid leukaemia (using a 2856 gene probe). A comparison is made of the expression patterns for a great number of genes of the patients. Maximal correlation (100%) is indicated by a dark red colour. Inverse correlation by a dark blue colour. 16 Different signatures are distinguished revealing 16 different forms of leukaemia. (B) Adapted Correlation View (2856 probe sets) of 285 AML patients (right panel) and the expression levels of the top40 genes revealing the 16 individual clusters of leukaemia (left panel).
The expression levels of the top40 genes identified for each of the 16 clusters are displayed in the left panel.

The case of acute myeloid leukaemia

Acute myeloid leukaemia is a form of cancer that originates in a so-called stem cell in bone marrow. The production of the abnormal leukaemia cells in the marrow factory results in defective blood cell formation. Leukaemia has traditionally been diagnosed on marrow smears using a microscope. More recently it became evident that cytogenetic abnormalities (for instance the gain of additional chromosomes or the loss of particular chromosomes or fusions between two different chromosomes) and molecular genetic abnormalities (for instance mutations in oncogenes) recognize clinically widely distinct forms of the leukaemia.
In approximately 40% of cases of acute leukaemia no genetic markers have been discovered as yet. Novel techniques, such as molecular gene expression profiling, will be instrumental in disclosing the genetic changes in leukaemia in those instances. Since leukaemia develops subsequently to successive multi-step genetic changes, it may be assumed that many more additional hidden mutations are waiting to be discovered.


A
285 AML patients →
285 AML patients →
CBFA2T1/ ETO
CBFA2T1/ ETO
CBFA2T1/ETO
MYH11
MYH11
CEBPA
EVI1
K-RAS
N-RAS
FLT3 TKD
FLT3 ITD
Karyotype
FAB
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
AML patients →
B
Genes →
AML patients →

The full disclosure of the genetic origin of leukaemia is essential for understanding individual differences in the clinical behaviour of leukaemia among patients, for an exact diagnosis, for predicting the response to a particular treatment (response prediction), for planning and choosing a therapy, for developing new specific drugs targeted at genetic lesions.

DNA microarrays in acute myeloid leukaemia

Gene expression profiling reveals a genome-wide pattern of the differences of gene expression of subtypes of leukaemia. Gene expression bar coding with DNA microarrays will become an essential integrated element in the diagnostic and therapeutic decision process in the foreseeable future. Genetic variations unveiled by DNA microarrays furnish clinically useful insights in the prognosis of acute myeloid leukaemia and will soon be used as guides when selecting the proper treatment for patients.
In the Rotterdam study Valk et al employed a restricted number of differentially expressed probe sets (n=2856), and identified sixteen highly characteristic acute leukaemia signatures among 285 cases (see Figure 1).

Thus, in this study it appeared possible to sharply recognize new forms of leukaemia based on the genetic expression barcode of each individual case of leukaemia. For instance, a new form of leukaemia was identified with a molecular signature that predicts an unfavourable outcome (a high rate of relapse of leukaemia and poor survival rates). Obviously patients with this new type of leukaemia do no benefit from current standard therapy and other therapies have to be developed. The signature has provided clues to developing new therapies specific for this particular type of leukaemia.

The prototype example

Acute promyelocytic leukaemia can in an optimal sense serve as a paradigm for the introduction of genetics in cancer medicine. Two decades ago the form of acute promyelocytic leukaemia was considered the worst type of leukaemia with a notably dismal outcome. At that time patients would die from bleeding early after diagnosis and the overall mortality rate was 90% or more. In the mean time the situation has dramatically changed. Today acute promyelocytic leukaemia is considered a comparatively favourable type of acute leukaemia. The disease is caused and characterized by the fusion of two genes. One of these genes is the gene for a receptor, the receptor for retinoic acid (a vitamin A related compound). The receptor provides the cell with an antenna so that the cell can properly react to the retinoic acid in the environment around the cell. The cell depends on this external signal for its normal life. In the case of acute promyelocytic leukaemia the genetic change in the receptor gene disrupts the function of the antenna. The antenna has become

lazy, and as a result it does not react properly to the external signal. These unique genetic changes have a dramatic impact on the clinical management of patients with this type of leukaemia. For instance, because of the typical genetic alterations, a precise diagnosis of this form of leukaemia has become possible. Furthermore, with sensitive molecular methods the disappearance of the leukaemia can be exactly monitored during the successive phases of treatment. Since the genetic abnormality results in a lazy receptor requiring greater concentrations of retinoic acid, supply of extra retinoic acid as a drug can overcome the laziness of the receptor (antenna) and restore the function of the cell. Introduction of the retinoic acid in treatment protocols together with chemotherapy has resulted in an almost 90% cure rate of this previously uniformly fatal form of leukaemia. This practical example shows that the use of genetic information may be useful for converting a 'bad' disease in a 'good disease. Understanding the effects of the genetic aberrations in malignant cells will set the stage for the development of treatment strategies tailored to the specific condition of the individual patient with cancer.

Future challenges

Currently cytogenetic and molecular analyses provide the most important markers for determining the prognosis and guiding therapy selection in patients with cancer. These techniques provide however far from satisfactory and complete insights into the genetic diversity of cancer. The introduction of DNA microarrays will fill important gaps in the diagnostic approach to the patient with cancer. The application of microarray analysis in leukaemia, for instance, may make it possible to identify distinct subgroups of leukaemia with one comprehensive assay that furnishes a shortcut to a highly precise diagnosis. The unique gene expression signatures will provide insights into the pathobiology of cancer and generate lists of candidate oncogenes. The functional role of these genes will subsequently be examined in mechanistic studies in appropriate cell line and animal models. In addition other genetic technologies, such as comparative genome hybridization, large scale gene mutation analysis, proteomics and various others, will shed light on the genetic alterations in cancer. These technologies will be exploited in combination. It is to be expected that the elucidation of new genes and critical pathways will lead the way to exact predictions of therapy response/failure in individual patients and that it will pave the road to targeted therapies that one day may become the standard of care of patients with cancer.

Reference

– Valk, PJ, RG Verhaak, MA Beijen et al (2004). Prognostically Useful Gene-Expression Profiles in Acute Myeloid Leukemia. *N Engl J Med*., 350. pp 1617-1628

IMPACT ON SOCIETY

Consumers and Manufacturers

The participants were:

Drs Frans van Dam	Stichting Consument en Biotechnologie (Dutch Consumer and Biotechnology Association), Den Haag, The Netherlands
Dr Menno Hulswit	Philosopher of the Natural Science Faculty at Radboud University Nijmegen, The Netherlands
Dr Jan Maat	Molecular Biologist of Unilever Research, Vlaardingen, The Netherlands
Ms Ir Amber Ronteltrap	Marketing and Consumer Behaviour Department of Wageningen University, The Netherlands.

The following persons were present on behalf of STT/Beweton:

Dr Mark de Graef	Project Manager of the STT Study Genomics, STT/Beweton, Den Haag, The Netherlands
Ir Hans van der Veen	Director STT/Beweton, Den Haag, The Netherlands.

Prof Dr Fons Werrij, Wageningen University, President of the programme committee De Maatschappelijke Component van Genomics (The Societal Component of Genomics), The Netherlands, and member of the steering committee of the STT Study Genomics, acted as moderator of the meeting.

1 Ir Frank Biesboer was the reporter of this discussion meeting.

The discussion in this group yielded a mix of conclusions, questions and observations concerning Theo Verrips's view of the future[2].

1 Genomics plays various roles in various stages of life.
2 Mental health should also be taken into account, not only physical health.
3 Food is more than a compulsory medicine.
4 Consumers react very reservedly with regard to gene-specific food.
5 Personalised meals are possible, but are they necessary?
6 Does genomics influence our dietary behaviour?
7 Genomics is more likely to focus on diagnostics than on personalised treatment.
8 More personal responsibility does not have unambiguous results.

1. Genomics plays various roles in various stages of life

At the end of a person's life, he or she is ill for approximately four years and then absorbs 40 to 50 percent of the costs of health care he incurs during his whole life. Is it true that the 'stage of ill health due to age' is inevitable, because man is predestined to age with the accompanying age-related ill health, or are there possibilities to shorten this period of ill health with the aid of genomics and personalised medicines? There may be a difference between diseases that can be tackled with genomics, for instance cancer, and disorders such as worn hips and the like, for which genomics cannot be used. The pursuit of health care is aimed at making the 'stage of ill health due to age' as short and bearable as possible. Verrips's view of the future does not make it very clear which role genomics will play in this instance. In the stage of life prior to this 'stage of ill health due to age', the pursuit of health care aims at making this stage as long as possible with a quality of life that is as good as possible. Verrips's view of the future is aimed in particular at this stage with a focus on prevention and anticipation of ill health.

Because a considerable part of the costs of health care are made in the last stage of life and Verrips's view of the future does not cover this, the claims in Verrips's view of the future concerning the consequences for the costs of health care are unfounded.

2. Mental health should also be taken into account, not only physical health

In Verrips's view of the future, health is in particular defined as physical health, whereas mental health is at least as important. For instance, his view of the future states that we will be able to work longer, because our physical condition will improve, but his view of the future forgets that there are also mental reasons for wishing to stop working. One might even wonder whether an enormous conflict will not occur between what people are physically able

2 See article of Verrips 'Genomics 2030: Part of Everyday Life' in Part II of this book.

to do and therefore what will be expected of them, and their mental state. The role genomics can play in this field will be a limited one. Frustrations in paid labour cannot be solved by genomics. These problems are related to the labour culture with socially dominating beliefs about career and status.
In his view of the future, the role genomics might play in mental health, in human wellbeing, is ignored.

3. Food is more than a compulsory medicine

In Verrips's view of the future, food is depicted all too rationally and in a very medicalised way. And in his view of the future, food is used as a means of coercion: he who does not eat this will no longer be insurable.
This image of food completely clashes with the image of food as a pleasure, as a contribution to the quality of life. The choice of food knows a strong emotional motive that is entirely ignored in his view of the future.

4. Consumers react very reservedly with regard to gene-specific food

Gene-specific food geared to someone's genetic profile is considered by consumers as very drastic, because it is so personal, with consequences for oneself and maybe also one's children. This explains the reserve with which consumers react to it. Consumers argue: I am all right, so why should I change anything? Only when the advantages of gene-specific food can clearly be proven might this attitude change. But it is difficult to prove these advantages, because it is an effect that only occurs at a later age and that is hardly one's priority at 25.
As soon as the positive effects are unclear, 'health food' is seen more as a threat than as an opportunity. Verrips's view of the future does not take this into account. In addition, it places a heavy claim on the younger generation, which has least feeling with the necessity of prevention.

5. Personalised meals are possible, but are they necessary?

It is technically possible to offer personalised meals. Currently, there are already ice and soup dispensers that prepare the product according to personal preferences. It is now already very easy to make a cup of coffee at home for every person as desired. It can therefore also be imagined that each family member may buy their own refrigerated meal. However, it is the question whether food geared to a personal genome will lead to everyone having to eat their own meals with specific ingredients. On the whole, all human beings need the same things, with at the most a few adaptations when someone has a certain genetic deviation.
The image of personalised food invoked by Verrips's view of the future is quite exaggerated, as if food would have to be different for every individual.

6. Does genomics influence our eating behaviour?

On the basis of current experience, it might be stated that the influence of food information on eating behaviour is small if not extremely small. While the Dutch Food Centre tries to enhance its familiarity, at the same time obesity is seen as a worldwide epidemic. Taking this conclusion as a basis, it cannot be expected that dietary behaviour will change much with a technology that tries to gear food to someone's personal constitution. When people cannot resist the urge to overeat now, why should they do so with a genetic passport? Apparently, a complex of factors determines our relation to food.
With smoking, it can be concluded that once certain behaviour is considered socially unacceptable, this does influence people's behaviour. It also works the other way around, there is also a strong social pressure to do things that are not good for one's health, and this pressure will not disappear with the rise of genomics.

This does not mean that circumstances can be imagined in which genomics can play a role in a person's behaviour. Think, for instance, of obesity. It is probable that there are physical factors that create the urge to overeat. Once this need can be triggered in another way, that the feeling of being satisfied can be created in another way, eating can still be a pleasure, but with a different composition of one's food much less calories are ingested. Genomics can play a role in finding out which processes play a role in this feeling of being satisfied.
Another possibility is that genomics is viewed as a reliable diagnostic instrument, the outcome of which is trusted and on the basis of which people adjust their behaviour (see, for instance, the gene diagnostics of the British company Sciona which works the same way as a dietician but couples this to simple gene diagnostics, thus increasing its credibility).

7. Genomics is more likely to focus on diagnostics than on personalised treatment

Genomics is in particular a better tool for understanding what is going on. It is therefore to be expected that with the aid of genomics markers can be indicated, with which it can be determined, for instance, whether someone's metabolism is becoming unbalanced with possible consequences for obesity, diabetes and hypertension. For the advantage of genomics is that it makes it possible to study all aspects within the body.
The arrival of genetic personalised products will take some time. For the sole reason that our human body is not geared to react very specifically, but on the contrary is able to react very flexibly to all stimuli from the environment. It will not be easy to influence/get a grip on this. At best, there are some exceptions regarding a limited number of diseases. For example the PKU[3] test now makes

3 Phenylketonuria (PKU) is a genetic disorder that is characterized by an inability of the body to utilize the essential amino acid, phenylalanine.

it possible to prescribe the patient a special diet.

It is to be expected that genomics will in particular develop as a tool for diagnostics and less as a means for therapy. It appears that Verrips's view of the future, which very much focuses on the prevention of diseases, is based on a much too one-sided view of scientific knowledge and possibilities.

8. More personal responsibility does not have unambiguous results

There is a tendency to be seen in society in which people take more responsibility for their own health. GPs observe this in their surgery; there is a real Internet health circuit, etc. However, it would be a mistake to think that this more extensive responsibility will lead to a larger focus on prevention or a more extensive use of health care. Part of the population will wish to use all the possibilities of modern health techniques (and genomics) and adapt their behaviour and eating habits in order to lead as healthy a life as possible. Another group will entirely ignore this and will only call in health care when they have complaints. A third group will turn against genetisation and medicalisation with conviction and consciously choose a traditional way of life with organic food, natural health care, and the like. This group will call in medical professionals as little as possible. Of course, other variations are possible as well.

Verrips's view of the future is strongly based on one's own responsibility for one's own health, but in doing so it makes two errors in reasoning.

The first is that personal responsibility should in principle be accompanied by the possibility not to wish to know. His view of the future excludes this and is therefore internally contradictory. The other error in reasoning is that personal responsibility will lead to an ambiguous result for one's own health. Even pressure from health insurance companies, if this will ever get public support, does not guarantee such an outcome.

IMPACT ON SOCIETY

General Practitioners (GPs)

The participants were:

Prof Dr Leo ten Kate	Professor of Clinical Genetics, Free University Amsterdam, The Netherlands
Mrs Dr Ingeborg Meijer	Advisory Council on Health Care (RGO), Den Haag, The Netherlands. Member of the steering group of the STT Study Genomics
Mrs Prof Dr Bettie Meyboom-De Jong	Professor of General Medicine, University of Groningen, The Netherlands
Mrs Gerda van der Weele	Dutch Society of General Practitioners, Utrecht, The Netherlands
Dr Arno Wouters	Philosopher, Radboud University Nijmegen, The Netherlands.

The following persons were present on behalf of STT/Beweton:

Dr Mark de Graef	Project Manager of the STT Study Genomics, STT/Beweton, Den Haag, The Netherlands
Ir Hans van der Veen	Director STT/Beweton, Den Haag, The Netherlands.

Prof Dr Ir Theo de Vries, Professor of Future Studies Health Care, Twente University, Enschede, and University for Humanistics Utrecht, The Netherlands, was moderator of the meeting.

1 Ir Frank Biesboer was the reporter of this discussion meeting.

The view of the future is unrealistic

It is not realistic, is how the criticism of the GPs and the public health carers of Theo Verrips's view of the future[2] may be best summed up. In particular they criticise:

1 It is too optimistic about how medical science will be able to use the knowledge of the genome.
2 There is too much focus on preventive medicine.
3 It over-estimates the possibilities to change behaviour.
4 Its view of the future of the insurance system is mistaken.
5 Its expectation of the creation of an elitist health care is mistaken.
6 It does not give a proper view of the role of the GP.

1. Too optimistic about how medical science will be able to use the knowledge of the genome

Verrips's view of the future is based on the premise that in 2030 the genetic background will be known of more than 70 percent of all diseases and that on this basis it will be possible to advise each individual on his lifestyle and on taking (preventive) medicines, for each period of his life.

This will happen in 3020 sooner than in 2030. It takes time to acquire the knowledge necessary to realise what the view of the future predicts. Moreover, it will be necessary to validate that knowledge, also from a clinical point of view: Will the recommended lifestyle and medicines for the detected genetic deviation indeed have a positive effect on the health? The research into this will take decades. Nor will it be easy to prove that certain functional foodstuffs will actually improve the quality of life: such claims are rather based on wishful thinking.

Nor are there any breakthrough developments in the research at present. According to the European Society of Genetics there is hardly any progress at all. The pharmaceutical industry hardly seems to be interested in developing personal targeted medicines. The first applications of genetic technology are to be found in the field of diagnostics rather than in predicting whether somebody runs an increased risk of getting a particular disease.

Furthermore, what is possible in a laboratory environment will not become immediately part of health care. Between laboratory and practice lies at least fifteen years.

Nor are technological possibilities always the deciding factor. It is perfectly possible to screen somebody on a hereditary predisposition for getting a rare monogenetic disease such as cystic fibrosis, but the test is not generally introduced. Other aspects play a role with respect to the implementation of something that is technically possible, e.g. the costs.

2 See article of Verrips 'Genomics 2030: Part of Everyday Life' in Part II of this book.

2. Too much focus on preventive medicine

In Verrips's view of the future the focus of health care is principally on prevention.

The criticism directed against this point is largely the same as the criticism with respect to point 1: The view of the future is entirely unrealistic about what preventive medicine may accomplish.
To be sure, there is a certain shift towards prevention, but it is secondary; if a disorder is already diagnosed, e.g. distinguishing cancer cells genetically, making it possible to apply various specifically designed treatment strategies. A lot of progress can be booked this way and it is a fact that the genetic health care is making this its point of focus.
Reference is sometimes made to self-medication as an instance of preventive medicine, whereby it is possible, for instance, to apply via the Internet for blood sugar level tests. But the results of such tests only say something about the blood sugar level and maybe about what the possible consequences might be. Prevention on the basis of genetic screening is a different thing altogether.

3. Over-estimation of the possibilities to change behaviour

In Verrips's view of the future, people who run an increased risk of getting a particular disease must adapt their lifestyle and must take special functional food.

Warning people about their lifestyle will hardly bring any results, as experiences with smoking and overweight show. Even if people know that their habits are bad for their health, they will continue doing them. This will not be different if you know that a particular deviation in the chromosomes may slightly increase the risk of getting lung cancer. Even if it is known that there is a predisposition within the family of increased blood pressure, people will not stop smoking. You do not need the full technological complex of genetic screening to achieve results in this regard.
Only if medication is possible you might get results, for instance taking a pill against increased blood pressure. People are prepared to take such pills. With respect to smoking it would be helpful if you knew which receptors play a part in the need for a cigarette and if it is possible to satisfy that need by means of a medicine. On the other hand, this would lead to an increased medicalisation of society. Still, manipulating behaviour is very difficult.
It is undeniably a fact that people are health conscious. Take for instance the many slimming products available at the drugstore. People try anything to lose weight, although it is doubtful that they will succeed if they do not tackle the problem at source and eat less and eat more variedly.

4. Mistaken view of the future of the insurance system

In Verrips's view of the future, the health insurance will only pay for medical treatment if the patient has observed a preventive health program, which the insurer will enforce.

This notion of the view of the future introduces a system of 'big insurance is watching you'. People must do what they are told by the computer to do, or the insurer will not pay. People will resist this with all their might.
There is no social or political basis for a drastic selection. Besides, the costs for executing this policy are prohibitive, even when, for instance, a smoker will have to pay higher premiums. How will this be inspected? Recently, it was suggested that people who are actively participating in sports and run a higher risks of getting injuries must pay higher premiums. It turned out to be unfeasible.
There is however, a trend to no longer compensate the costs of certain medicines if a person is demonstrably to blame, for instance cholesterol reducers.

5. Mistaken expectation of the creation of an elitist health care

In Verrips's view of the future, the system of preventive medicine will be linked to higher incomes. The new preventive health care will only be available for them.

There is no way that non-solidarity health care will ever be introduced in the Netherlands; there might be a marginal shift in that direction and it might even increase under pressure from the EU, but the Netherlands will never know a health care system such as the one in Malaysia, where only 2 percent of the population receives adequate care.
Especially now that so many ethicists involve themselves with health care, this egalitarian principle will not be easily given up; its fundaments are too strong.

6. No proper view of the role of the GP

In Verrips's view of the future, there is an 'agent' who advises the individual if, after screening of the genome, a serious genetic defect is found that will increase the risk of getting a particular disease. This 'agent' might be a GP, a team of specialists or a virtual person. The agent's advice about the life style and the functional food to be eaten must be followed, in order to remain insured.

This view of the relationship between an individual and his GP does not correspond with the daily practice experienced by GPs.
People first of all need a GP who will give them the proper answers, who takes away their fears, who shows understanding and with whom they have a

personal relationship. The average helpdesk, which the character of the 'agent' most resembles, will only frustrate people.

Nor do people visit their GP to have themselves generally examined on all kinds of possible disorders. They come with specific questions, for instance because a particular disorder runs in their family.

Still, in the past 30 years there has been a shift in GP practices; they have become more business-like.

More attention is also paid in surgery to the risk of contracting a particular disease. But it remains very difficult to explain what this signifies. People tend to think: Either I have the disease, or I don't. No doubt GPs will learn how to deal with risk factors, also because their training will pay more attention to it.

The notion that the decision of the 'agent' is decisive in order to stay insured runs counter to the current practice, nor are there any developments in that direction.

Of much more importance than the question what the GP will do with genetic information will be the question how many GPs there will still be in 2030.

IMPACT ON SOCIETY

Associations of Patients

The participants were:

Mr Ad van Bellen	Vereniging Samenwerkende Organisaties van Patiënten (Dutch Genetic Alliance) (hereinafter also: 'VSOP'), Soestdijk, The Netherlands
Drs Peter Streng	Vereniging Spierziekten Nederland (Dutch Society of Muscular Dystrophy), Baarn, The Netherlands
Ms Eefje Tjong Joe Wai	Reumafonds, the Dutch Rheumatism Association, Amsterdam, The Netherlands.

The following persons were present on behalf of STT/Beweton:

Dr Mark de Graef	Project Manager of the STT Study Genomics, STT/Beweton, Den Haag, The Netherlands
Prof Dr Ir Theo Verrips	Professor in Applied Molecular Biology at Utrecht University, The Netherlands and chairman of the steering committee of the STT Study Genomics.

Prof Dr Bart van Steenbergen, Professor in Future Studies at Nyenrode Business University, The Netherlands, acted as moderator of the meeting.

1 Ir Frank Biesboer was the reporter of this discussion meeting.

'Theo Verrips's view of the future[2] applies to all of us,' the input of the representatives of the associations of patients can best be summarised.

Their remarks pertained mainly to the following propositions:

1 Great progress has been made in hereditary diagnostics.
2 The cost issue is a great dilemma.
3 Medical science is governed by short-term thinking.
4 Prevention should be given much more focus.
5 Doctors mistakenly deny the value of food supplements.
6 Associations of consumers and patients play an important role of confidence.
7 GPs play a marginal role.
8 More attention should be paid to the education of young people.

1. Great progress has been made in hereditary diagnostics

In the past few years, much attention was paid to diagnostics in muscle diseases in the expectation that a very accurate identification of the disease could lead to tailor-made treatment and medicine. With the development of humane genetics, great progress has been made in this field. Although many of the hereditary causes of the muscle diseases are unknown, the gene defects of 600 different muscle diseases have been established. It is expected that specifically targeted treatments will be developed much further.
In view of the huge progress the knowledge of the human genome has made and the availability of large computing capacity, it will only be a matter of time before a patient is told that with a certain behaviour it will be at least possible to slow down the symptoms of the disease. So much preliminary work has already been done that this will be the case in the near future.

2. The cost issue is a great dilemma

Some figures: the development of a medicine costs approximately € 600 million. The group of patients suffering from Pompe's disease amounts to 5,000 people worldwide. Treatment with an enzyme replacement therapy costs € 300,000 per patient per year. Development of medicines that are specifically intended for muscle diseases with a certain gene deviation, initially appears to be a hopeless task due to the enormously high initial costs.
It cannot be excluded that when more is known about the genetic background of more generally occurring disorders these 'common diseases' will also turn out to fall into a large range of rare diseases. Each disorder will then be a rare disease, and chances are that with the development of the technology the developing costs of medicines will ultimately be much lower.
Should that be the case, current rare diseases might well fill a pioneering role for the more generally occurring diseases; then, medicines will indeed be

2 See article of Verrips 'Genomics 2030: Part of Everyday Life' in Part II of this book.

developed for these rare diseases. In addition, separate fiscal facilities and protective constructions exist for the development of these medicines, so that it is nevertheless attractive for the pharmaceutical industry to invest in it.

3. Medical science is governed by short-term thinking

There is a tendency to look at the future from a dogmatic perspective, for instance when considering affordability. But the first car and the first mobile phone were also very expensive and look at these now!

The same applies to medical developments. 25 Years ago, the Louise Brown case, the first IVF baby, was highly controversial, but now more than half of the world population considers IVF is an entirely accepted way of treating infertility.

Medical science is also governed/affected by short-term thinking. That is why the control of costs for medicines has an absolute top priority, whereas these form only ten per cent of the total health care budget. In the meantime, 20 per cent of the chronically ill absorb 80 per cent of health care costs. Part of this group will always need health care due to genetic diseases, but the largest group may be fragile, but will not require much care if properly referred and helped in time. Three-quarters of the patients with type II diabetes have no problems provided they watch their weight. It is therefore also very smart from a financial point of view to invest in prevention. However, oddly enough the Ministry of Health and the health insurance companies fail to do so.

4. Prevention should be given much more focus

The chronically ill are only treated in the final days of their lives, whereas earlier intervention is very well possible, see before under 3. All social parties in health care, but also, for instance, the food industry, should make a joint effort to develop programmes aimed at prevention in an as early a phase as possible. They should start when the options to take proper action are still open. They should not bury their heads in the sand but use the opportunities to prevent worse from happening.

In the case of hereditary muscle diseases, prevention means screening embryos on possible hereditary defects, i.e. pre-implantation diagnostics, checking of the in vitro fertilised ovum before placing it back in the uterus.

This method encounters natural resistance in many people and causes enormous fear of the unknown. It calls for a drastic change in thinking for people to accept this method, see also sub 8 below. But in the end it will be just as ordinary a part of health care as a vaccination programme.

5. Doctors mistakenly deny the value of food supplements

Half of the population use food supplements in one way or another, including dietary and light products. In rheumatics and most cardiovascular diseases,

inflammation is the underlying process, and it is well-known that fish products and olive oil have a positive effect on this. Therefore it can indeed make a difference if you have used products that have a positive or negative effect on the inflammation over a period of twenty years. This knowledge should be made much more specific. But doctors object to this, because there is no conclusive link between the use of food supplements and their effects on one's health. This view is much too one-sided. The organisations of patients and consumers, on the other hand, undertake to play a role in this field; the VSOP has also started studies/research into this matter.

6. Associations of consumers and patients play an important role of confidence

Since the advent of the Internet, there has been an enormous reinforcement of patient associations. They are very keen on using technology whilst putting great focus on prevention, often much more than the medical circles themselves do.

It is also observed that people who are confronted with a diagnosis for the first time are very fragile and have much faith in patients' groups because of the sympathy they encounter and because they know that the patients' groups are well-informed and reliable.

Due to the enormous increase in research and knowledge and the ongoing differentiation of separate types of diseases it is far from simple for patients' groups to fill this role of confidence. Following the main developments is all they can do.

7. GPs play a marginal role

For the chronically ill, GPs play no role of importance; they go to their own association of patients. Just think about it. There are 7,000 physicians and the largest group of patients with muscle diseases has 1200 patients. Therefore you cannot expect the GPs to be conversant with all the specific information concerning these rare diseases. In practice, this means that when visiting the GP, patients themselves bring the information validated by the association of patients with them.

It is also often the case that GPs tell the patients that nothing can be done about the disease, whereas this is not true. GPs often know nothing about chronic diseases.

It would be better to empty the pipeline to the GP in this respect and give them a role they are able to play.

8. More attention should be paid to the education of young people

Genetics and their application raise many questions and much uncertainty. If no attention is paid to genetics in education at an early stage, it will be hard

to have genetics accepted by society. Only when genetics and their application have become common knowledge, much of the fear can be taken away.
The Internet is a wonderful source of information, but at the same time this information is overwhelming and often poor, in any case not validated. It would be wise to start to teach young people how to sift the wheat from the chaff and how to select proper information at an early age.
All this means that children have to be taught the possibilities of information technology and genetics at an early age and at the same time what the limitations are. Only then will we be able to reap the harvest of both new technological developments. The new knowledge has to be brought to the generation that is able to work with it in a fast manner.

IMPACT ON SOCIETY

Technologists

The participants were:

Prof Dr Ir Albert van den Berg	Professor of Nanotechnology (Lab-On-a-Chip), MESA+ Twente University, Enschede, The Netherlands
Dr Sjaak Deckers	Technology officer Molecular Imaging and Diagnostics, Philips Medical Systems, Eindhoven, The Netherlands
Drs Juriën Taams	Business Consulting Services, IBM, Amsterdam, The Netherlands
Prof Dr Arjen van Tunen	Director of Swammerdam Institute for Life Sciences, University of Amsterdam, The Netherlands.

The following persons were present on behalf of STT/Beweton:

Dr Mark de Graef	Project Manager of the STT Study Genomics, STT/Beweton, Den Haag, The Netherlands
Ir Hans van der Veen	Director STT/Beweton, Den Haag, The Netherlands.

Prof Dr Ir Theo Verrips, Professor in Applied Molecular Biology at Utrecht University, The Netherlands and chairman of the steering committee of the STT Study Genomics, was moderator of the meeting.

1 Ir Frank Biesboer was the reporter of this discussion meeting.

The two sides to the argument might best be summed up as: 'The future view goes much further than the one given by Verrips'[2], versus 'The future view is a doom scenario that will do no favours for genetics'. Both sides were presented, followed by a discussion about the part played by validation in the development of medical genomics applications and about the possibility to change behaviour.

Great expectations regarding genomics research

Arjen van Tunen mentions as most important addition to Verrips's view of the future: "*Gaining insight in the genetic and molecular basis of behaviour, the way memory works and of neurological diseases such as stress and depression*." In this regard, which sets man fundamentally apart from animals, genomics research will result in a considerable increase of knowledge within the next 25 years.

As example he mentions an experiment carried out on rats, whereby a particular stimulus is followed by a reward or punishment. The experiment shows that certain brain cells are active during the entire cycle, whereas some are only active when the reward or punishment is given, and yet others immediately after the stimulus only. This means that there is a cellular basis of expectation.

Van Tunen also expects an increase in knowledge about the molecular basis for race/group distinctions, or: what makes a Japanese a Japanese, or someone from Edam[3] an Edammer and not a Volendammer[4].

The result of all this is that hybrids will be created of biological and non-biological (synthetic) life forms, based on a mix of life sciences and material sciences. Bionic man will soon become a reality; the distinction between living and inorganic material will be abolished. In addition, new life forms will be created.

What worries Van Tunen especially is the socio-economic embedding of genomics research. If investments are not increased, if we lack the culture of knowledge, "*we will lose out to the US and Asia*." This is even more important because institutions which think that genomics does not concern them, for instance banks and insurance companies, will also be forced to pay attention to it in the future. "*Just as ICT has done, genomics will become part of society*." Van Tunen thinks that this also stresses the importance of paying attention to genomics in (primary) education.

Albert van den Berg supports Van Tunen's argument; he notes a number of encouraging developments. In five years' time it will be possible to quickly sequence the entire DNA of a cell. This means that it will become possible to quickly detect new infectious diseases, to understand the way they work and to make anti-bodies. "*This is possible provided system biology continues to develop at the current speed*", Van Tunen adds.

2 See article of Verrips 'Genomics 2030: Part of Everyday Life' in Part II of this book.

3 A small town near Amsterdam in the Netherlands.

4 An inhabitant of the small town Volendam in the Netherlands.

Another development in the field of diagnostics is the Lab-On-a-Chip. Van den Berg thinks that this will allow many things, for instance determining the level of insulin of the blood at home, by simply placing your finger on it.
He expects a high degree of social acceptance. "*If it is necessary and it offers advantages, society will quickly accept this new form of diagnostics*." Still, this will depend on clear guarantees about what will happen with the results and on who will be entitled to use the resulting data.

A completely unrealistic view of the future

Sjaak Deckers holds that this view of the future is unrealistic and far too simplified. It is entirely based on technological optimism and ignores numerous aspects. As an example he brings up the blockbuster dilemma of the pharmaceutical industry: "*It is only possible to earn back the enormous investments, up to 800 million per drug, if the drugs are intended for general use; therefore, the costs of designing customized drugs will be prohibitive. There is an incredible bottleneck in the financing*."
According to Deckers, the future view is unrealistic when it comes to expectations about the consumers' behaviour: "*If it is already so hard to get people to stop smoking, how do you ever expect them to react to advice about diseases they run the risk of getting*?"
Furthermore, the future view does not take the complexity regarding regulation into account. "*I am afraid that there will be a Chernobyl-like mutation in the next 25 years, or a bio-911. This will throw the entire development back 30 years*." He emphasizes the importance of reliability. "*It is not unlikely that due to the reliability, everybody will become too afraid to move*."
Deckers also thinks that the future view is too naively optimistic about the possibilities of system biology. "*System biologists believe that as long as the model is right, everything will be known.*" He compares this optimism with the optimism of physicists at the end of the 19th century, who believed that they more or less knew everything there was to know. He thinks that system biologists underestimate the complexity of feedback in biological systems, "*as a result of which they show rather a chaotic and therefore by definition unpredictable behaviour, which is impossible to influence effectively*."
The future view is also too optimistic about infectious diseases. "*Increasingly, we are confronted with diseases that jump from animals to people, for instance fowl pest, which also spread rapidly due to globalization*."
The future view overestimates the possibilities of predictive medicine. "*There are hundreds of different types of cancer, which will not simply disappear; there are too many sudden diseases that cannot be predicted and that have nested themselves in the body as a time bomb*." And even if it is possible to 'predict' hereditary diseases, the costs of treating them with gene therapy will be prohibitive.

The statement that in the future there will be people who will be excluded from health care is not supported by reality, according to Deckers. "*Society will never accept health insurance based on a gene passport or behaviour*." He thinks it inconceivable that medical assistance will be denied in the event of a cardiac arrest because the patient's fingers are nicotine-stained. And how about people who practice extreme sports, such as mountaineering? Sunbathing on the beach is much more risky. Meaningfully, Deckers quotes the adagio: "*Tomatoes will give you spots, and life causes death*."
In summary, Deckers states: "*I do see progress, but seeing how slowly it goes, it will take at least another 300 years before we even get close to what the future view holds for health practice. Implementing it in health practice in particular will require a lot of effort*."
For this reason, he proposes the development of several scenarios, and to compare these in order to find out the possible consequences and whether society is ready to deal with these consequences. For instance: a scenario that sets forth everything that is possible from a technological point of view and where financing is no problem, a scenario that includes a biodisaster, and a scenario in which validation presents the biggest bottleneck.

Juriën Taams agrees with Deckers' criticism. He foresees that in 2030 genomics will be joined up with information technology, in the shape of biobanks or epidemiological databases, "*when the biggest challenge will be to sift information from a gigantic amount of unstructured data and to draw conclusions from that information*."
He is very doubtful about the possibilities to change behaviour: "*Without obligations imposed by insurance, it will be very difficult*." Linking the gene passport to the possibility of becoming insured is very undesirable in his opinion. "*In that case, insurance will no longer be insurance*."
The future view pays insufficient attention, in his view, to the role of the GP as psycho-social expert. "*Together with the results from genomics research, the importance of this will only increase*."

Further to both views, a number of specific discussions ensued.

The role played by validation

It is to be expected that with continuing genomics research, it will become possible to develop drugs more rapidly. However, in order to be admitted to the clinical practice, new drugs must be tested on quality and effect.
Van Tunen expects an acceleration in this regard as well. "*Already there are small companies who specialize in this field, for instance by conducting toxicity tests in cultivated liver cells*." He believes that the emergence of biomarkers will also result in a quicker understanding of the effectiveness of drugs.

"*The question is whether regulators will be prepared to accept new technology — for instance biomarkers — as indication of the reliability of a drug*."
Van den Berg points out the possibility to skip part of the current testing on animals by using chips.
Verrips and Deckers are rather doubtful about the acceleration of the admittance procedures. Verrips: "*In the past 40 years, I have seen hardly any change in this respect*." Deckers: "*On the contrary, it seems to take longer nowadays*." He is worried that the question of reliability will result in "*everybody becoming too scared too move*", and he fears that a biodisaster on Chernobyl-scale, for example, will lead to even stricter regulation.

Changes in behaviour

Verrips is optimistic about the possibilities to change behaviour. He mentions as example the successful introduction of Becel. "*It has prevented more heart diseases than anything else*." Another example is two French villages where a successful program against overweight is carried out. And in addition he points out the popularity of jogging and fitness.
Deckers is very doubtful about the possibilities to change behaviour. Reducing or compensating certain stimuli by means of pills is very complicated in his opinion and although it may be true that there are positive developments, such as the popularity of jogging or the introduction of lettuce at McDonald's, it "*still is just as entropy, the major movement is heading in the opposite direction because we lack the self-discipline to resist every temptation*."
Van der Veen points out that change in behaviour is not so much money-related — no matter how expensive cigarettes are, people continue to smoke — as related to social acceptance: "*When as a smoker perceives that he has become a social pariah, he will be inclined to change*." To which Taams reacts "*that if money is not a factor that induces change in behaviour, the notion put forward in the future view, of linking change of behaviour to health insurance, will no longer have any foundation*."

Molecular Medicine — A Revolution in Health Care

Hans Hofstraat[1]

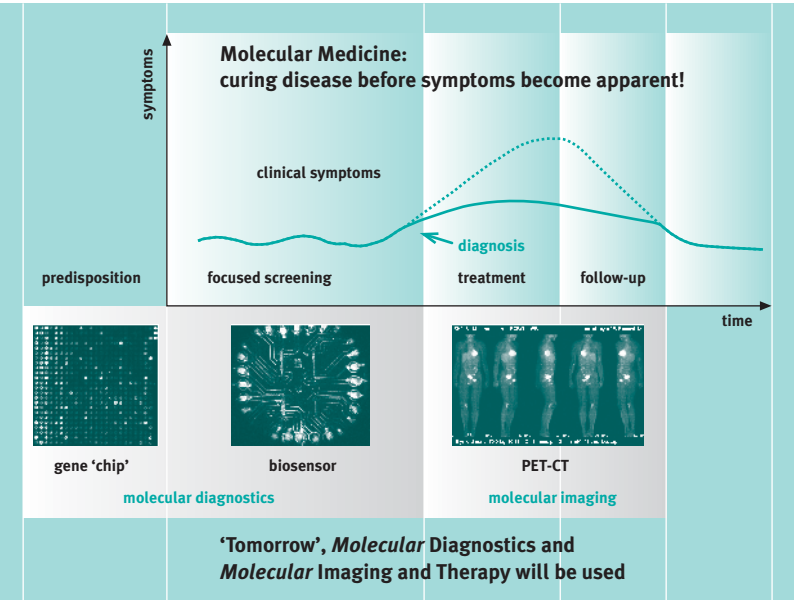
Introduction

Advances in human genome research are opening the door to a new paradigm for practicing medicine that promises to transform health care. Personalised, Molecular Medicine, the use of marker-assisted diagnosis, based on both *in vitro* testing and *in vivo* targeted imaging, and therapy planning, and targeted therapies adapted to an individual's molecular profile, will influence the way drugs are developed and medicine is practiced. In addition, patient care will be revolutionised through the use of novel approaches like the determination of molecular predisposition, the screening of individuals with an elevated risk profile, and by the exploitation of diagnostic, prognostic, pharmacogenomic and monitoring biomarkers. Although numerous challenges need to be met in order to make personalised medicine a reality, this approach will replace the traditional trial-and-error practice of medicine in due time by evidence-based medicine (see Figure 1).

1 Prof Dr J.W. Hofstraat, Vice-President Philips Research, Department Head Biomolecular Engineering, Eindhoven, The Netherlands.

Characteristics of Molecular Medicine are early and faster diagnoses, better prognoses, and tailored therapies with higher efficacy and reduced side effects as compared to the present. The basis for this revolution is the explosive growth in knowledge of the structure of the human genome and its translation into its functional elements, the proteins. The key to the introduction of evidence-based medicine is the availability of advanced medical instrumentation, in particular for *in vitro* and *in vivo* diagnostics, and to support therapies, and advanced information technology to integrate the multiple and complex data streams generated, in support of clinical decision taking.

Figure 1



System Biology and Biomarkers

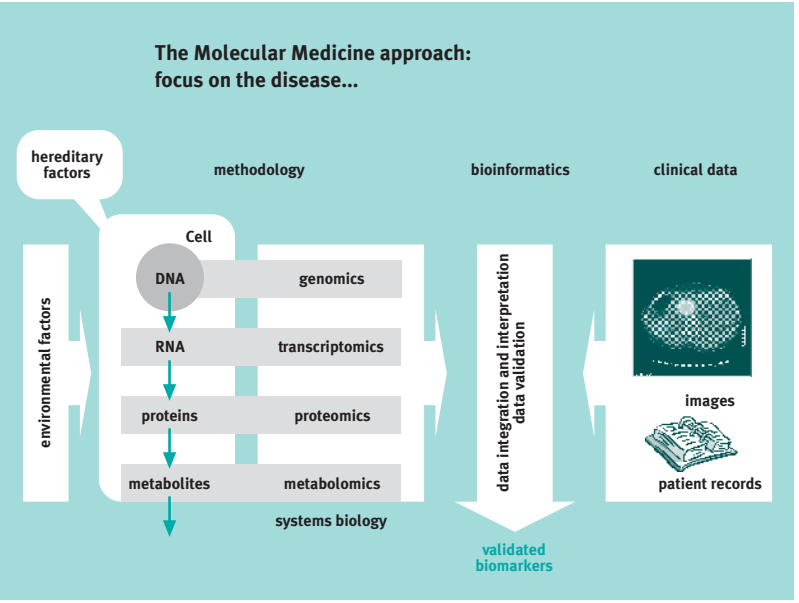
The next step, namely relating the knowledge of the molecular translation cycle to the onset, development and ultimately treatment of diseases, is still extremely complex. It is based on insight in the genetic make-up of the individual, primarily given by hereditary factors, and laid down in the DNA and subsequently transcribed by RNA into the proteins, the molecules which are instrumental in all major biological processes taking place in human cells, tissues and organs. Advances in technology have led to elucidation of the genetic make-up of, by now many, species, including humans, fuelled by the ambitious Human Genome Project. Similarly, efforts will continue to establish RNA patterns (the 'transcriptome') and — extremely challenging still — get insight in the range of proteins present (the 'proteome'). Knowledge of the genome, transcriptome and proteome by itself is not sufficient. Gaining insight in the functioning of protein signalling, and its influence on cell multiplication, interaction and transformation (stem cells) forms the main challenge

of ‘systems biology’. In systems biology or ‘integrative’ biology efforts are made to integrate all information available from genomics, transcriptomics, proteomics, the metabolic processes in our cells and organs (‘metabolomics’) in an effort to understand the intricate processes governing the human body — and to provide the basis for understanding the origins of diseases. So as to establish the link to a disease it is not sufficient to identify the primary genetic structures. In addition, we have to gain knowledge on the influence of ‘environmental’ factors, such as the effects of nutrition, lifestyle, environment, stress, etc. These external factors may have profound effects on the structure of the genome (for example the modification of DNA due to methylation, ‘epigenetics’), and will be translated into the proteome. In particular understanding of these environmental factors is required to really get an insight in the origin of most diseases and to be able to devise effective cures.

In an effort to reach this goal it is endeavoured to relate the wealth of information, which is provided by patient samples (information derived from healthy and diseased tissue generally comprising DNA, RNA, proteins and metabolites), to clinical information with the aim to identify biomarkers — observables that are characteristic for a particular disease and can be used for an early diagnosis. Such biomarkers can be discovered in bodily fluids, for example in blood or serum, so that they may be determined by *in vitro* diagnostic approaches, but also in tissue or organs, providing leads for targeted contrast agents that can be visualised *in vivo* by making use of advanced imaging equipment. Specific biomarkers can be applied for early diagnoses and for the monitoring of diseases, but they can also be used to accelerate the process of drug discovery and development: by using biomarkers as ‘surrogate endpoints’ in clinical trials, drug effectiveness (and toxicity or other side effects) can be determined much earlier than in the conventional practice based on survival rates. The key to these data interpretation and analysis challenge lies in linking the rich ‘molecular’ information to the relatively scarce patient data, which is furthermore complicated by the inherent biological variability. Bioinformatics here plays a central role. A diagrammatic representation of this complex process is presented in Figure 2. The main aims of the process are:

- To identify characteristic and clinically validated biomarkers for diseases.
- To gain insight in the effects of external factors, like food or pharmaceuticals on the individual human health status.
- Defining the fields of nutrigenomics and pharmacogenomics.
- The effective implementation of personalised medicine.

Figure 2



Opportunities of Molecular Medicine

The insight in the molecular origin of disease is growing. It becomes increasingly clear that the majority of life-threatening diseases has its origin, or at least is significantly influenced by, genetic effects. The susceptibility to all diseases that are the main causes of death — cardiovascular disease, cancer, diabetes, and infectious diseases (TBC, malaria, AIDS, ...) — is to some extent genetically determined. The same is true for the major debilitating diseases, which strongly influence the quality of life: neuro-degenerative diseases (for example, Alzheimer's, Parkinson's) and autoimmune diseases (like rheumatoid arthritis). Early detection of these diseases greatly improves the therapeutic success rate, leading to a prolongation of the healthy and productive lifespan of the individual, and a treatment with fewer side effects. In addition, it has a potential cost-containment effect as well: particularly a shift in the onset of debilitating diseases results in a significant reduction of the very high personnel costs in connection with the care of the patients.

Molecular Medicine may completely change the health care 'industry'. Traditional medicine practice based on trial-and-error results both in under-treatment and over-treatment, multiple consultations, the need for drug monitoring and frequent changes in the regimen. More than 100,000 deaths per year (USA alone) are attributed to adverse drug reactions. A personalised approach of tailored care for every individual based on his or her specific, molecular disease will become standard. The introduction of targeted drugs that block receptors in the membrane of tumour cells, for instance, may result in slowing down their proliferation or even lead to their elimination.

Apart from a more effective treatment, it may well be that some cancer types may be contained, thereby effectively turning cancer into a manageable, 'chronic' disease. The first successful targeted drugs have already been introduced, of which the Herceptin (Genentech/Roche, indication: metastatic breast cancer), Gleevec (Novartis, indication: chronic myeloid leukaemia), Bexxar (GlaxoSmithKline, indication: non-Hodgkin's lymphoma), and Zevalin (BiogenIdec, indication: non-Hodgkin's lymphoma) drugs are the best-known. All these drugs are based on monoclonal antibodies that bind selectively to the tumour cells and may be equipped with toxic substances so as to enhance their efficiency (for example, in Bexxar radioactive ^{131}I is present in order to provide radioimmunotherapy). The targeted or 'smart' drugs are extremely expensive; for instance, for treatments with Zevalin and Bexxar the cost of medication amounts to 25-30 k$ per patient. It is therefore also very important from a financial point of view to identify those patients who respond well to the medication before the treatment is started.

Technology is the key

Molecular Medicine is made possible by medical technologies, particularly by Molecular Diagnostics, that are applied for screening and monitoring so as to effect early detection, and by Molecular Imaging, relying on the joint application of advanced imaging equipment and targeted and or functional contrast agents. Molecular Imaging offers unique opportunities for a combination with Molecular (targeted) Therapy, which can be much better planned and monitored with the aid of advanced hardware and especially developed software tools, which make pharmacodynamic modeling possible. Typically, Molecular Diagnostics and Molecular Imaging will be applied in tandem with the aim to provide tailored solutions for a wide range of diseases. A secondary possibility may be the application of imaging techniques in order to advance and simplify the drug discovery and drug development process stimulated by the collaboration between pharmaceutical and biotech companies on the one hand, and medical technology companies on the other. The important and increasing role of medical technologies in Molecular Medicine offers opportunities to new players in this area, particularly to technology-rich companies.

Below, some brief observations will be made on the two main technology areas.

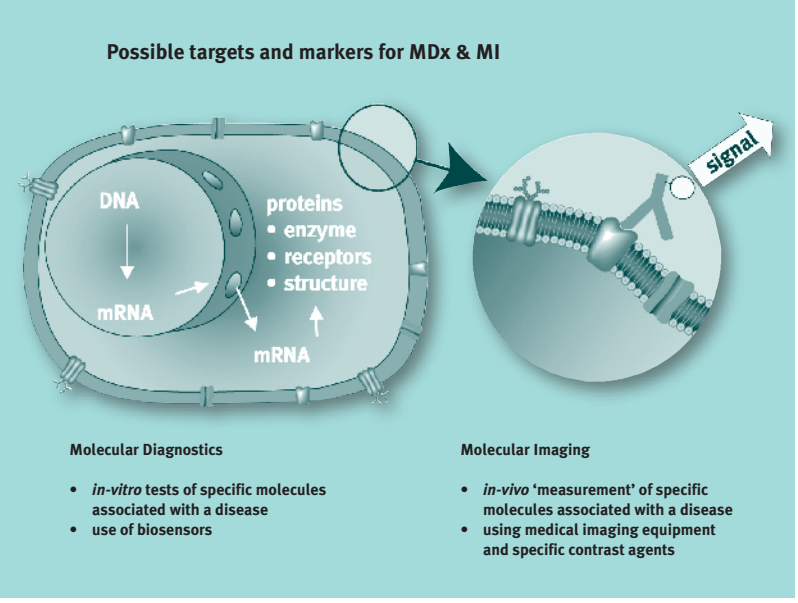
Molecular Diagnostics and Biosensors

In vitro diagnostic approaches will become indispensable for early diagnosis, for the selection of personalised therapy, and for effective follow-up, after completion of the treatment or to support maintenance of a chronic condition. A distinction should be made between techniques that are applied for the

identification of genomic fingerprints and methods that are suitable for the identification of particular biomarkers.
Genomic fingerprints can be used to phenotype individuals and therefore to identify their predisposition to particular diseases or to tailor individual therapeutic interventions (for example, selection of the appropriate dose of medication on the basis of metabolic characteristics). The genomic fingerprints depend on the application of high-density arrays (for example, the GeneChips provided by the American company Affymetrix, or the DNA Microarrays sold by, also US-based, Agilent). Typically, these high-density arrays contain many thousands of different oligonucleotide strings located at different, well-known locations. The presence of complementary oligonucleotides in the sample can be measured optically through the sensitive detection of fluorescent labels; even single mismatches, so-called single nucleotide polymorphisms, can be identified. By careful executing the measurement protocol, genetic expression profiles, highlighting upregulation or downregulation of certain parts of DNA or RNA can be made visible as well. In Figure 1 an image of (part of) a DNA chip is shown.

Alternatively, the measurement can be focused on the identification of a (generally more limited) set of biomarkers. Biomarkers in general are proteins, which are triggered by the presence of a disease, such as membrane proteins, synthesised in response to a disease (for example, proteins that signal apoptosis, or programmed cell death, or enzymes that are released following a stroke or a myocardial infarction). Another example is the detection of pathogens, which can be realised by way of the measurement of selected nucleotide

Figure 3



sequences that are characteristic for the different species, so that the cause of the infection and the optimal cure can be established at once.

For the massive introduction of Molecular Diagnostics the availability of cheaper and more accessible technologies is essential. For applications in which rapid turnaround times are important, in particular at the point-of-care (for instance, for diagnosing a cardiovascular problem in the ambulance), rapid, simple and 'stand-alone' approaches are needed. Miniaturised, integrated, 'Lab-On-a-Chip' tools, based on microfluidic solutions and made possible by improvements in microtechnology and nanotechnology may meet this need. In Figure 1 a detail of Philips' very sensitive and integrated magnetic biosensor chip is shown, a true product of advanced microsystems technology. Elsewhere in this book, a more detailed discussion of the developments in the area of micro- and nanotechnology, and their possible applications in the genomics era, can be found in Andersson and Van den Berg[2], mainly focusing on devices for the detection of DNA while utilising the Lab-On-a-Chip technology.

Molecular Imaging and Therapy

The possibilities offered by Molecular Imaging are impressive as well. Developments in medical imaging systems, increasingly integrating advanced, high-resolution instruments with sophisticated data and image processing to provide ever increasing quality of information to the medical professional, go hand in hand with developments of sophisticated functional and targeted contrast agents. In particular, the advances in nuclear imaging technologies, such as Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET), extremely low concentrations of targets can be localised and quantified. These techniques can be utilised in order to visualise nanomolar or even picomolar concentrations of (radioactive) molecules and can not only be applied for measurement of targeted contrast agents, but also for functional monitoring (for example, measuring increased metabolic rates in relation to tumour growth). Combining the sensitive, but not very highly resolved nuclear imaging techniques with other imaging modalities, which do provide high-resolution morphological data, such as Computed Tomography (CT), leads to very powerful Molecular Imaging tools. In Magnetic Resonance Imaging (MRI) impressive improvements in sensitivity have been realised as well. By applying targeted nanoparticles, sub-micromolar concentrations of suitable contrasting agents can be measured. An interesting opportunity of MRI is the direct use of the imaging instrument without the application of contrasting agents, for example, in order to measure brain activity. This so-called 'functional MRI' technique obviously has the advantage that truly non-invasive characterisation can be effected.

2 See article of Anderson and Van den Berg 'Micro- and Nanotechnology for Genomics' in Part I of this book.

The chapter on Molecular Imaging of Sjaak Deckers[3] provides a detailed account of the potential of *in vivo* Medical Imaging for tomorrow's health care.

Implementation: the 'Care Cycle'

The full-fledged introduction of Molecular Medicine is the basis for an integrated approach of tomorrow's health care, with the following characteristics:

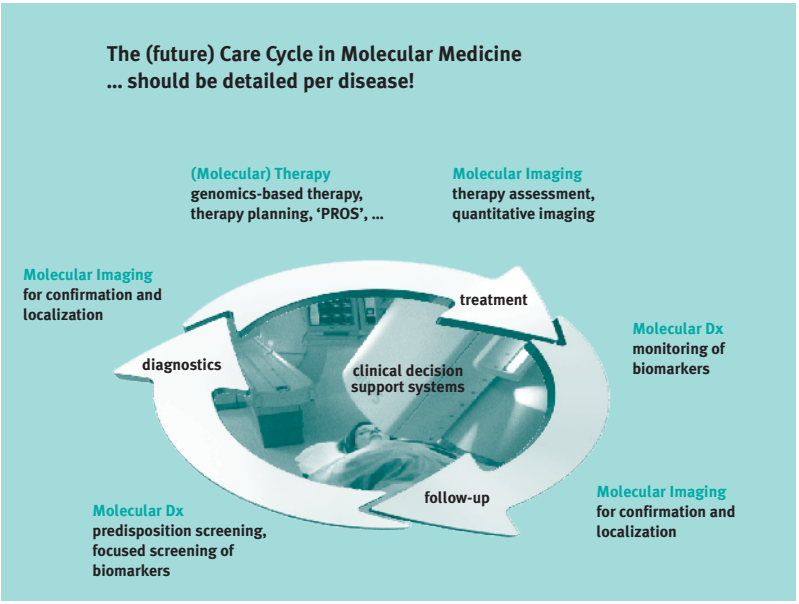
- An earlier detection of diseases by careful screening persons with elevated genetically inherited and or lifestyle-related risks by using highly specific biomarkers.
- A better diagnosis for a more suitable treatment based on the individual patient's own biochemistry.
- A targeted and minimally invasive treatment with more efficacy and less side effects.

This picture of the future is based on technological advancements but depends on important and challenging advancements in the biomedical sciences and in information technology as well.
It is Philips' ambition to address health care in an integrated fashion, addressing all aspects of the 'Care Cycle' as schematically depicted in Figure 4. The Care Cycle approach starts with determining the individual's predisposition so as to identify genetically inherited or to lifestyle related risks by using Molecular Diagnostics. It then moves on to the focused screening of persons at risk, initially by employing Molecular Diagnostic technologies, but in combination with Molecular Imaging for confirmation, localisation and quantification, aiming at an early detection of the onset of the disease. Subsequently, if necessary, the individualised therapy is started, guided by treatment planning and monitoring the therapeutic results with the aid of (Molecular) Imaging.
In addition, imaging techniques can be provided for minimally invasive treatment, ensuring better directed surgery and treatment. Finally, post-treatment Molecular Diagnostics and Molecular Imaging can be utilised to monitor any recurrence or an active containment of the disease. The proposed approaches, which of course need to be combined with established clinical procedures, lead to an explosive increase of data, both qualitative and quantitative (enabling more objective, evidence-based medicine), which makes taking the right decisions more and more complex. Therefore, attention has to be paid in order to derive transparent information from the extensive data sets and to help the physician to come to the right diagnosis and therapy. Philips has responded to this challenge and is developing 'Clinical Decision Support Systems' to meet this need.

The first elements of Molecular Medicine have already been introduced into clinical practice. Examples are the screening for a predisposition to breast

3 See article of Deckers 'Myths and Miracles of Medical Imaging' in Part I of this book.

Figure 4



cancer, which is offered by the company Myriad Genetics. Focused screening of women at risk may result in the detection of breast cancer at an early stage when it is still localised with a chance of successful treatment of almost 100%. The Dutch starting up company Agendia has developed a tool for the stratification of patients based on 70 marker genes and allowing for the administration of the best treatment to the individual patient. Philips Radiation Oncology Systems (PROS) provides innovative solutions to manage patient treatment, which include the imaging, localisation, simulation and planning of minimally invasive, image-guided procedures and the planning of conformal external beams for a more effective radiation treatment. Finally, Genentech has developed a targeted, antibody-based drug that can be used to cure women with metastasised breast cancer, provided they show an over-expression of the Her2/Neu membrane receptor. The company Vysis has developed a molecular diagnostic test to screen for this receptor, so that those patients can be identified who will benefit from the treatment.

Even though individual tests are available, it will take time to introduce Molecular Medicine throughout the whole Care Cycle. No comprehensive insight is available in the origin of many diseases and no unambiguous biomarkers have as yet been identified. So as to counter this challenge, a tremendous effort is required, involving advanced academic research together with contributions from pharmaceutical and biotech companies, and from medical technology companies, which should join forces to realise breakthroughs. At the same time, it is crucial to link the increasing insights in the fundamental biochemistry of diseases to clinical observations. In particular Molecular

Imaging can play a crucial role in this translational challenge. Finally, the medical profession is (justifiably) conservative; therefore, convincing evidence for the efficacy of the Molecular Medicine approaches needs to be provided, before these will be accepted. The expectation is, however, that within the next decades an increasing number of Molecular Diagnostic and Molecular Imaging approaches will be introduced, providing Molecular Medicine Care Cycles for many important diseases.

Final Thoughts and Recommendations

Theo Verrips[1], *Mark de Graef*[2]

If the history of mankind is looked at from a helicopter view it is amazing how often the application of technology has enabled mankind to leap forward in their development. Quite often, the scientific basis behind the technological development is understood only after centuries.
It is only since the 19th century that a parallel development of sciences and technology has taken place, sometimes the one leading the other and vice versa. A good example is pasteurisation. For reasons of simplicity and as an introduction to an other important issue later on, we will consider it as an invention of Louis Pasteur. Ever since Antonie van Leeuwenhoek we have had knowledge of small creatures in watery substances, but only after discoveries by Pasteur and others the connection was made between these creatures and certain diseases, and how technology could help to eliminate these sources of diseases on the one hand, and how to use these creatures to produce delicious products like cheeses and wines on the other. Hardly ever a more important contribution of science and technology has been delivered to mankind. Another great discovery is that of antibiotics. Without understanding the basic principles of antibiotics, Fleming applied his invention to human beings; and more than a century later both the principle and the knowledge to produce antibiotics on a large scale save the lives of millions of wounded soldiers and citizens.

1 Prof Dr Ir C.T. Verrips, Utrecht University, Utrecht/IOP Genomics, The Hague, The Netherlands.

2 Dr M.R. de Graef, STT/Beweton, The Hague, The Netherlands.

Although it is not always realised it are technological developments (like the production and application of restriction enzymes for cutting the carrier of information for all living species DNA in pieces, clever precision technology for labeling and separating the building blocks of DNA (nucleotides), and information technology and new algorithms for coping with the for biologists extremely large data sets) that enabled an enormous progress in Life Sciences.
In 1973, we called this technology rDNA[3] technology, it has provided mankind with quite a number of molecules that have found their way to the health care market. However, the elucidation of sequences of the billions of nucleotides of the human genome discovered around the turn of the 20th to 21st century (now often called Genomics) will become much more important to mankind than any scientific or technological development before. Although it will take a considerable amount of time, it will enable us to understand the processes in living cells in great detail. Knowing these details will enable us to design complete new routes to improve all aspects of human life.

In this study, we have collected the views of a number of players in these developments. Players such as scientists and technologists, but also players who are concerned with societal and ethical aspects related to these developments and those that have to communicate these developments to the public and to policy makers. Pasteur demonstrated better than any other scientist how important it is to work on issues of direct relevance to the public, and how to communicate science to them and policy makers.
Such a study will always be no more than a snapshot and we do not pretend at all to have painted a complete picture of present and future developments. However, by formulating recommendations we hope to contribute to the discussions and finally to the decisions to impart that the Netherlands utilise at least some of the opportunities of these developments.

Our recommendations are:

a The education of Physics and Life Sciences has to be based on knowledge of the human genome/genomes, the effect of genes and external factors on human behaviour and the probability to get a certain (genetically or externally) determined disease. Only if such education is really anchored in our school and university systems, the Netherlands will be able to collect the fruits of Genomics.

b Even more important than training of elderly people in the area of ICT will be their training in Life Sciences (in particular Genomics). On the one hand because elderly people will have to face the results of Genomics sooner rather than in the future, on the other hand they should be able to play an important role in the discussion how results of Genomics will be used in the last third part of their lives.

3 r stands for recombinant.

c The first two recommendations deal with communication. Without any doubt the Netherlands Genomics Initiative (NGI) has spent considerable effort on communication. However, it is well known that communications are only effective if done in a consistent way in which the frequency and positioning of the messages are very well organized. The communication on the advantages and potential dangers of Genomics should be effected by an independent body with sufficient financial support of government, health care insurance companies, and food and pharmaceutical companies, and even electronic and ICT companies.

d A very significant part of physicians does not have sufficient knowledge of Genomics. Moreover, they underestimate the importance of Genomics, new diagnostic tools, ICT and algorithms in order to come to the right diagnosis. At present, more than 100,000 EU patients are incorrectly diagnosed, often with fatal consequences and resulting in enormous social and economical 'costs'. In fact, it can be questioned whether it is possible for the human mind to make the right diagnosis when having to cope with the enormous complexity of living systems on the one hand, and the enormous man-to-man variation in genetic make-up and lifestyle on the other. Therefore, a smooth evolution in health care is necessary to change physicians from medical doctors to 'health counsellors' for citizens (not only patients) and to develop knowledge systems that are coupled to all the new technologies described in previous chapters of this study. In this new first-line health care approach the knowledge system will determine with a high probability the cause of the 'problem', and the counsellors will discuss the consequences with the citizens. The consequences can be adapting their lifestyle or taking preventive medicines or consulting a medical doctor at the hospital so as to treat the 'problem' in a personalised way.

e Simultaneously with this development, health care should change from cure to prevention. Before, this could hardly be done on a large scale (although one of the exceptions, vaccination, has provided enormous benefits). However, with the knowledge and technologies that will become available in the coming decade, and the follow-up of the recommendations made under 'd', this switch can be made. The CBS (Dutch Central Statistical Office) should be able — in close collaboration with scientists and technologists in this field — to make good prognoses on the development of costs in health care systems while taking these recommendations into account.

f Communication techniques are not only a blessing, but also an enormous threat to preventive health care. Billions are being spent at present for all sorts of products of which the functionality is at least questionable and often even potentially dangerous. The same is true for the large number of websites dealing with health, but in fact providing misleading or insufficient information. Health care authorities, together with patients' organi-

zations should receive financial aid in order to develop search engines that will help the (educated) consumer/patient to select the real fruits in many fields of weeds (the present seal of approval is not sufficient).

g At present, electronic patient files are being introduced in the Netherlands. These files should be compatible with present and future genomics data of patients. At the same time, ways should be developed so that these files, with sensitive information remain private. Such systems are indispensable for the realisation of recommendation sub 'd'.

h The valorisation of Genomics has quite different time axes for the various applications. The time axis to come to better diagnostic tools based on DNA currently (2005) lies in the S-phase of development (Figure 1). For proteomics, a much better diagnostic marker, the S-curve is in its initial phase, while for cellular diagnostics (coupled to non-invasive diagnostics), the ultimate diagnostic tool, the development will require about 5 to 10 years. For food products based on using the results of human and plant genomics, the S-curve has not yet started and a total time frame of 10-15 years is realistic, because at least 5 years will be required for the clearance of really new food components. For pharmaceutical products, the time frame is about the same as for foods. Although they have started earlier, the clearance is even more time-consuming. All these time axes are quite long, but history has made clear that for companies and governments the return on these long turn investments is profitable.

i The EU (and Dutch) legislation for orphan drugs should be adapted so as to cope with all personalised foods and drugs. This is the only way in which the costs for clearance can be reduced and 'time to market' can be sped up.

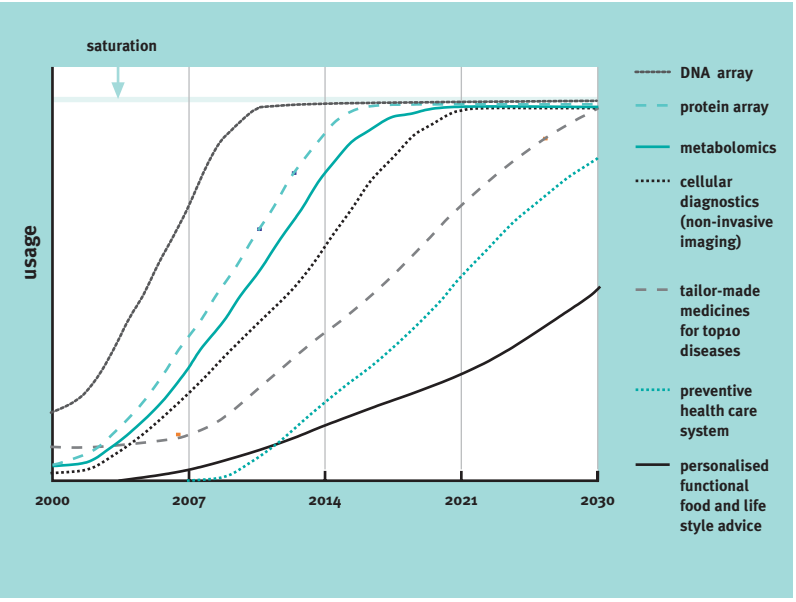


Figure 1
Forecasts for development of genomics techniques and uptake of genomics-driven breakthrough in health care. There can be considerable deviations in the projected time scales.

Survey Organization

Acknowledgements

This publication has been effected by the active cooperation of a multidisciplinary group of experts and persons involved. STT/Beweton owes many thanks to all those who have unselfishly put much time and energy into this project.
We would expressly like to thank the Advisory Committee for determining the direction of the survey and the valuable discussions with regard to content. We would also in particular like to thank Theo Verrips, who has co-designed the whole process of the survey and in particular the discussions with regard to the view of the future written by him, and who has also largely contributed to this publication.

Advisory Committee

Dr H.J. Huizing	InnovatieNetwerk Groene Ruimte en Agrocluster, The Hague
Dr J. Lanphen	Forum Biotechnologie en Gezondheid, The Hague
Dr I. Meijer	RGO, The Hague
Ir J.H. van der Veen	STT/Beweton, The Hague
Prof Dr Ir C.T. Verrips (chairman)	University of Utrecht/IOP Genomics, The Hague
Prof Dr P.A.Th.J. Werrij	Wageningen UR/NWO Programme 'Maatschappelijke aspecten van Genomics', The Hague
Prof Dr H.A.E. Zwart	Centre for Society and Genomics, Nijmegen.

Project Management

This survey has been managed by Mark de Graef, project manager STT/Beweton. Rosemarijke Otten, project secretary at STT/Beweton, has assisted him in the organization of the survey. Theo Verrips's valuable discussions and advice have also contributed to the survey. Rosemarijke Otten has participated in the editing of the publication.

Project Cooperation

The Dutch Advisory Council on Health Research (Raad voor Gezondheidsonderzoek, RGO) has cooperated with this survey. This cooperation has been formalised in the context of the Dutch Consultative Committee of Sector Councils for research and development (Commissie van Overleg Sectorraden COS), of which both RGO and STT/Beweton are members.
In addition, COS and the Netherlands Genomics Initiative (Regie-orgaan Genomics, NGI) have given their financial support to the survey.

RGO

The Dutch Advisory Council on Health Research (Raad voor Gezondheids-onderzoek, RGO), established in 1987, advises the government, especially the ministry of Health, the ministry of Education and Science, and the ministry of Economic Affairs, on matters relating to health research, health services research and the infrastructure of such research.

Health research is defined as research on epidemiologic and etiologic aspects of disease, diagnosis, prevention, cure and care, and the development of relevant technology. Health services research concerns aspects of health services such as structure and organisation, its function, and the demand for health services. The RGO's main task is to set priorities for research aimed at the solution of problems in health and health services and to give recommendations on financial and infrastructural matters.

The RGO is one of four Sector Councils working together in a platform (COS). Their task is to gear scientific research to social needs by means of a close interaction between government, scientific investigators, and end-users of the results of research.
The following sectors are covered by the Sector Councils and the COS member STT/Beweton: Health (RGO), Environmental issues, spatial planning (RMNO), Research for Development (RAWOO), Agricultural Research (NRLO) and Technology (STT/Beweton).

The recommendations by the RGO are given after a comprehensive investigation of the field of interest. Each report is based on a careful balance of the scientific requirements and the social needs for health (care) research.

For more information on the RGO please visit rgo.nl/en/index.html

COS

The Consultative Committee of Sector Councils for research and development (COS) in the Netherlands is the collaborative platform for sector councils and other members specialised in foresight studies. Legal basis is the Sector Councils Framework Act on research and development (1989, as amended in 1997):
A sector council is a foresight body, comprising representatives from the scientific community, civil society (including trade and industry) and the

government (as an advisory member). They present an independent view of societal demands for knowledge and the consequent priorities for strategic research in their respective sectors. Their views are based on thorough studies, such as foresight activities, necessary to obtain a long-term perspective on societal and scientific trends. In order to acquire mass for a necessary comprehensive approach sector councils collaborate as to consider one domain in coherence with another. Sector councils also map developments in science and technology and interpret the implications for society.
The domain of the sector councils involves: Spatial Planning; Nature and Environment; Rural Areas and Agriculture; Health; Technology; Development Cooperation.
The possibility of a sector council or a sector council-style approach for Education; Public Administration, Justice and Security; Traffic, Transport and Infrastructure and for labour is presently investigated.
Functions of the COS as a collaborative platform are e.g. promoting a joint approach in foresight- and programming studies as well as studies on the development of methodology, funded by the COS Coordination Fund. Furthermore the COS sees to joint input in administrative consultations with ministries and other organisations. The COS is a member of the European Research Area (ERA) Network For Society in which 15 EU member states are working together on joint foresight activities en benchmarking.

For more information please visit www.minocw.nl/cos

STT/Beweton Publications

All publications with an ISBN number can be ordered from STT/Beweton or from the bookshop.

The remaining publications are only available from:
STT/Beweton
P.O. Box 30424
2500 GK The Hague
The Netherlands
Telephone +31 70 302 98 30
Fax +31 70 361 61 85
E-mail info@stt.nl
Website www.stt.nl

70 Genomics 2030: part of everyday life
Edited by Mark de Graef, 2005 (ISBN-10: 90 809613 2 9 / ISBN-13: 978 90 809613 2 6)

69* Techniek als menselijk ontwerp; nieuwe opleidings- en loopbaanroutes voor jongeren
Redactie: dr.ir. Remke M. Bras-Klapwijk, 2005 (ISBN 90 809613 1 0)

68* Beter bouwen en bewonen. Een praktijkgerichte toekomstverkenning
Redactie: drs. Michiel D.J. van Well, 2004 (ISBN 90 804496 9 5)

67 Zee in zicht, zilte waarden duurzaam benut
Redactie: dr. Esther Luiten, 2004 (ISBN 90 804496 8 7)

66 Zorgtechnologie, kansen voor innovatie en gebruik
Redactie: dr.ir. Jessika van Kammen, 2002 (ISBN 90 804496 7 9)

65 Dealing with the data flood, mining data, text and multimedia
Edited by Jeroen Meij, 2002 (ISBN 90 804496 6 0)

64 Betrouwbaarheid van technische systemen, anticiperen op trends
Redactie: dr. M.R. de Graef, 2001 (ISBN 9084496 5 2)

63 Toekomst@werk.nl, reflecties op economie, technologie en arbeid
Redactie: drs. Rifka M. Weehuizen, 2000 (ISBN 9084496 4 4)

62 Vernieuwing in productontwikkeling, strategie voor de toekomst
Redactie: ir. Arie Korbijn, 1999

61* Stroomversnelling, de volgende elektrische innovatiegolf
Redactie: ir. J.M. Meij, 1999 (ISBN 90 804496 2 8)

60 Nanotechnology, towards a molecular construction kit
Edited by Arthur ten Wolde, 1998

59* Bouwwijs, materialen en methoden voor toekomstige gebouwen
Redactie: ir. Annemieke Venemans, 1997 (ISBN 90 6155 816 6)

58* Gezonde productiviteit, innoveren voor betere arbeidsomstandigheden
Redactie: ir. Arie Korbijn, 1996 (ISBN 90 6155 744 5)

57* Digitale leermiddelen in beroepsopleidingen (incl. cd-i en samenvatting)
Redactie: dr. A. ten Wolde, 1996

56 Microsystem technology: exploring opportunities
Edited by Gerben Klein Lebbink, 1994 (ISBN 90 14 05088 7)

55* Schone kansen, denkbeelden over ondernemerschap en milieumanagement
Redactie: ir. E.W.L. van Engelen, J. van Goor, 1994 (ISBN 90 14 04929 3)

54* Goederenvervoer over korte afstand
Redactie: ir. M.J. Venemans, 1994 (ISBN 90 14 04928 5)

53* Elektriciteit in perspectief, 'energie en milieu'
Redactie: ir. E.W.L. van Engelen, 1992

52* Inspelen op complexiteit
Redactie: drs. M.J.A. Alkemade, 1992 (ISBN 90 14 03883 6)

* English summary available.

51* Plantaardige grondstoffen voor de industrie
Redactie: drs. W.G.J. Brouwer, 1991 (ISBN 9014 03882 8)

50 Opleiden voor de toekomst: onderdeel van bedrijfsbeleid
ir. H.B. van Terwisga en drs. E. van Sluijs, 1990

49 Grenzen aan techniek
Redactie: ir. A.J. van Griethuysen, 1989 (ISBN 90 14 03880 1)

48 Kennissystemen in de industrie
Redactie: ir. J.J.S.C. de Witte en drs. A.Y.L. Kwee, 1988

47 Kennissystemen in de dienstensector
Redactie: drs. A.Y.L. Kwee en ir. J.J.S.C. de Witte, 1987

46 Kennissystemen en medische besluitvorming
Redactie: ir. J.J.S.C. de Witte en drs. A.Y.L. Kwee, 1987

45 Kennissystemen in het onderwijs
Redactie: ir. J.J.S.C. de Witte en drs. A.Y.L. Kwee, 1987

44 Onderhoudsbewust ontwerpen nu en in de toekomst
Redactie: ir. G. Laurentius, 1987

43 Nieuwe toepassingen van materialen
Redactie: ir. A.J. van Griethuysen, 1986

42 Techniek voor ouderen
Redactie: ir. M.H. Blom Fuhri Snethlage, 1986 (ISBN 90 14 03822 4)

41 De toekomst van onze voedingsmiddelenindustrie
Redactie: drs. J.C.M. Schogt en prof.dr.ir. W.J. Beek, 1985

40 Bedrijf, kennis en innovatie
Redactie: ir. H. Timmerman, 1985

39 De kwetsbaarheid van de stad; verstoringen in water, gas, elektriciteit en telefonie
Samensteller: ir. G. Laurentius, 1984

38 Man and information technology: towards friendlier systems
Edited by J.H.F. van Apeldoorn, 1983

37 Nederland en de rijkdommen van de zee: industrieel perspectief en het nieuwe zeerecht
Redactie: ir. J.F.P. Schönfeld en mr.drs. Ph.J. de Koning Gans, 1983

36 Informatietechniek in het kantoor; ervaringen in zeven organisaties
Samensteller: drs. F.J.G. Fransen, 1983

35 Automatisering in de fabriek; vertrekpunten voor beleid
Redactie: ir. H. Timmerman, 1983

34 Flexibele automatisering in Nederland; ervaringen en opinies
Redactie: ir. G. Laurentius, ir. H. Timmerman en ir. A.A.M. Vermeulen, 1982

33 Toekomstige verwarming van woningen en gebouwen
Eindredactie: ir. A.C. Sjoerdsma, 1982

* English summary available.

32 Micro-elektronica voor onze toekomst; een kritische beschouwing
Samenstellers: burggraaf E. Davignon e.a., 1982

31-9 Micro-elektronica: de belastingdienst
Samensteller: ir. H.K. Boswijk, 1981

31-8 Micro-elektronica: het reiswezen
Samensteller: ir. H.K. Boswijk, 1981

31-7 Micro-elektronica: het kantoor
Samensteller: ir. H.K. Boswijk, 1981

31-6 Micro-elektronica: het bankwezen
Samensteller: ir. H.K. Boswijk, 1981

31-5 Micro-elektronica: het ontwerpproces
Samensteller: ir. H.K. Boswijk, 1981

31-4 Micro-elektronica: productinnovatie van consumentenprodukten en diensten voor gebruik in huis
Samensteller: ir. H.K. Boswijk, 1981

31-3 Micro-elektronica: procesinnovatie in de sector elektrometaal
Samensteller: ir. H.K. Boswijk, 1981

31-2 Micro-elektronica: de grafische industrie en uitgeverijen
Samensteller: ir. H.K. Boswijk, 1981

31-1 Micro-elektronica: de rundveehouderij
Samensteller: ir. H.K. Boswijk, 1981

31 Micro-elektronica in beroep en bedrijf; balans en verwachting
Samensteller: ir. H.K. Boswijk, 1981

30 Biotechnology; a Dutch perspective
Edited by J.H.F. van Apeldoorn, 1981

29 Wonen en techniek; ervaringen van gisteren, ideeën voor morgen
Redactie: ir. J. Overeem en dr. G.H. Jansen, 1981

28 Distributie van consumentengoederen; informatie en communicatie in perspectief
Redactie: ir. R.G.F. de Groot, 1980

27 Steenkool voor onze toekomst
Eindredactie: ir. A.C. Sjoerdsma, 1980

26 Bos en hout voor onze toekomst
Redactie: ir. T.K. de Haas, ir. J.H.F. van Apeldoorn, ir. A.C. Sjoerdsma, 1979

25 Arts en gegevensverwerking
Redactie: ir. R.G.F. de Groot, 1979

24 Toekomstbeeld der industrie
prof.dr. P. de Wolff e.a., 1978

23 De industrie in Nederland: verkenning van knelpunten en mogelijkheden
Redactie: ir. H.K. Boswijk en ir. R.G.F. de Groot, 1978

22 Materialen voor onze samenleving
Redactie: ir. J.A. Over, 1976

21 Stedelijk verkeer en vervoer langs nieuwe banen?
Redactie: ir. J. Overeem, 1976

20 Voedsel voor allen, plaats en rol van de EEG
prof.dr. J. Tinbergen e.a., 1976

19 Energy conservation: ways and means
edited by J.A. Over and A.C. Sjoerdsma, 1974

18 Mens en milieu: kringlopen van materie
Stuurgroep en Werkgroepen voor Milieuzorg, 1973

17 Mens en milieu: zorg voor zuivere lucht
Stuurgroep en Werkgroepen voor Milieuzorg, 1973

16 Mens en milieu: beheerste groei
Stuurgroep en Werkgroepen voor Milieuzorg, 1973

15 Technologisch verkennen: methoden en mogelijkheden
ir. A. van der Lee e.a., 1973

14 Techniek en preventief gezondheidsonderzoek
dr. M.J. Hartgerink e.a., 1973

13 Communicatiestad 1985: elektronische communicatie met huis en bedrijf
prof.dr.ir. J.L. Bordewijk e.a., 1973

12 Elektriciteit in onze toekomstige energievoorziening: mogelijkheden en consequenties
dr.ir. H. Hoog e.a., 1972

11 Transmissiesystemen voor elektrische energie in Nederland
prof.dr. J.J. Went e.a., 1972

10 Barge carriers: some technical, economic and legal aspects
drs. W. Cordia e.a., 1972

9 Het voeden van Nederland nu en in de toekomst
prof.dr.ir. M.J.L. Dols e.a., 1971

8 Mens en milieu: prioriteiten en keuze
ir. L. Schepers e.a., 1971

7 Electrical energy needs and environmental problems, now and in the future
ir. J.H. Bakker e.a., 1971

6 De invloed van goedkope elektrische energie op de technische ontwikkeling in Nederland
dr. P.J. van Duin, 1971

5 De overgangsprocedures in het verkeer
prof.ir. J.L.A. Cuperus e.a., 1969

4 Hoe komt een beleidsvisie tot stand?
Ir. P.H. Bosboom, 1969

3 Verkeersmiddelen
prof.ir. J.L.A. Cuperus e.a., 1968

2 Techniek en toekomstbeeld; telecommunicatie in telescopisch beeld
prof.dr.ir. R.M.M. Oberman, 1968

1 Toekomstbeeld der techniek
ir. J. Smit, 1968

Other publications

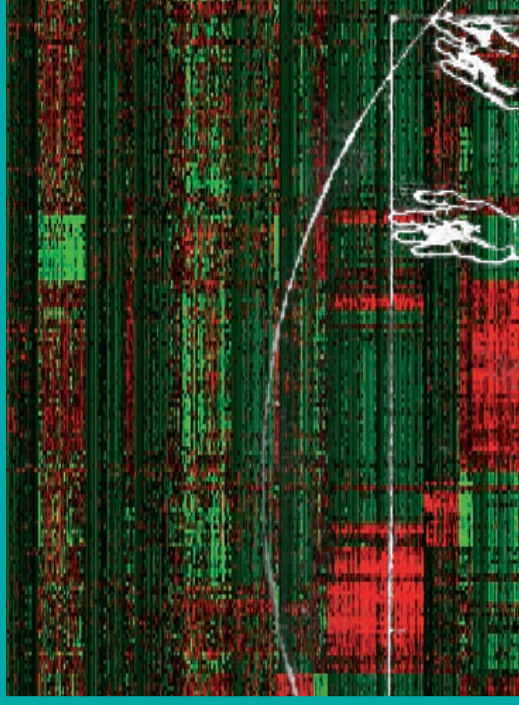
- New applications of materials;
  edited by A.J. van Griethuysen, 1988 (ISBN 0 95 13623 0 5)
- Mariene ontwikkelingen in de Verenigde Staten, Japan, Frankrijk, West-Duitsland, het Verenigd Koninkrijk en Nederland: organisatie, aandachtsgebieden en budgets
  Redactie: ir. J.F.P. Schönfeld en mr.drs. Ph.J. de Koning Gans, 1984
- Het belang van STT (toespraak bij het 15-jarig bestaan van STT)
  door prof.ir. Th. Quené, 1983
- De innovatienota; een aanvulling;
  H.K. Boswijk, J.G. Wissema, en W.C.L. Zegveld, 1980

Financial support STT/Beweton

This study came about thanks to the financial support from companies, government and the Royal Institution of Engineers (KIVI NIRIA).

Aalberts Industries
Akzo Nobel
Arcadis
Atos Origin Nederland
Commissie van Overleg Sectorraden
Corus Group
DAF Trucks
DSM
Eldim
Fugro
ING Bank
KEMA
KIVI NIRIA
Koninklijke BAM Groep
McKinsey & Company
Ministerie van Economische Zaken
Ministerie van Landbouw, Natuur en Voedselkwaliteit
Ministerie van Onderwijs, Cultuur en Wetenschap
Nederlandse Gasunie
Nederlandse Unilever Bedrijven
Océ-Technologies
Philips Electronics
PinkRoccade
Rabobank Nederland
Sdu
Shell Nederland
Siemens Nederland
Sogeti Nederland
Solvay Nederland
TNO
Vopak Oil Logistics Europe & Middle East

STT Netherlands
Study Centre for
Technology Trends



The 21st century is often referred to as the century of Life Sciences. The large number of developments in the field of genetic technology in the late 20th century are one of the reasons for this name. Determining the complete sequence of the human genome has given a new impulse to research in this field and thus a whole range of new research techniques has become within reach, which are referred to as genomics. What role will genomics play in our lives several years from now? This book tries to shed light on several social perspectives on these technological developments from various points of view in the fields of health care and nutrition. In addition, the book gives a picture of how developments in Life Sciences — jointly with developments in nanotechnology, imaging and information technology — offer new possibilities in health care.

This book is the concrete result of a joint effort made by many experts from the business community, universities, knowledge institutions and welfare organisations. It is intended for policymakers and managers in the business community, educational and knowledge institutions, government and health care professionals.

ISBN 90-809613-2-9

Laser Proof

9 789080 961326 >