SUMMARY

INTRODUCTION

Genomics occupies a very wide research territory within medical science that ranges from the detection of genetically determined risk factors for certain disorders to the development of medicines. The ministers of Health, Welfare and Sport (VWS), and Education, Culture and Science (OCenW) have asked the Advisory Council on Health Research (RGO) which developments in knowledge are needed to socially integrate, in a responsible way, those products, remedies and care practices that come out of genomics research. The RGO has given special attention to areas where research could have relatively short term (in the coming 5 years) consequences for medical care. These areas are *diagnostics, pharmacogenetics* and some *genetic diseases of adulthood.* The Council also focussed on a short survey on the subject of genetic screening. The central question was which research is needed so that current genetic knowledge and available techniques can be efficiently adopted into medical practice. Recommendations for research were formulated on the basis of data from the literature, conversations with experts and developments occurring during the preparation of the advice.

DIAGNOSTICS AT THE DNA-LEVEL: MEDICAL MICROBIOLOGY AND PATHOLOGY

As far as diagnostics are concerned, the advise is restricted to the specialisations of medical microbiology and pathology, fields in which diagnostics at the DNA-level have already found clinical applications. Among the many DNA-techniques being used, the microarray appears to have achieved the greatest influence. DNA-microarrays are still too expensive to be used in routine diagnostics, but they have become indispensable in genomics. Stimulation of bio-informatics is vital for the processing of the huge amount of data generated by microarrays.

DNA-techniques in (medical) microbiology can be employed for various purposes: characterization of difficult-to-grow micro-organisms, diagnosis of antibiotic resistance, quantification of the number of micro-organisms (in order to follow the clinical course of an infection and the success of a therapy) and surveillance (in order to, among other things, obtain an insight into infections, infection routes and resistance patterns). Applications in pathology are mainly in the area of oncology (tumour classification and assessment of prognoses).

Conventional diagnostic techniques are developing at an equal pace. The Council holds that it is therefore necessary for comparative research to be conducted regarding DNA- and conventional techniques. This research needs to focus, in particular, upon the impact on public health, patient safety and the quality of care, and not only upon specificity, sensitivity, speed and the costs of these assays. This applies to the use of DNA-techniques in pathology as well as in medical microbiology. Even though there are countless new possibilities for diagnosis with the help of DNA-assays, the Council recommends that research first be aimed at assays where the outcome will have practical consequences, such as with, for example, the determination of a prognosis or the choice of a certain treatment.

PHARMACOGENETICS

Under the rubric of pharmacogenetics, attention is focussed upon research into the metabolism of medicines, insensitivity or over-sensitivity for certain medicines and the development of medicines. It is expected that the results of research in the area of the metabolism of medicines will come the closest to application in clinical practice. This should make it possible to provide reliable predictions of optimal individual dosing. Research with larger groups of patients than have been used so far will be required before adjustments of dose in general practice can be made upon the basis of genotyping. More research is also needed in order to make predictions, based on genotype, for individual patients' metabolism of certain medicines. There must also be an assessment of the cost-effectiveness of genotyping for dose-adjustment.

The prediction of insensitivity or over-sensitivity to certain medications is probably far from practical application. Nonetheless, it would be useful if people had a simple assay to distinguish responders from non-responders, especially in the case of an expensive medicine with a substantial percentage of non-responders. It would also be worthwhile to investigate the differences in the effect of certain medicines in various ethnic groups. The Council recommends that this line of research concentrates upon polymorphisms that are of interest to regular practice.

Bio-informatics appears to be essential to the development of medicine on the basis of genomics. The RGO expects that the already-existing intensification of genome research (including proteomics) will be adequate to provide the stimulation needed, now and in the future, to identify new points of treatment application.

The Council calls attention to the rapid development of new possibilities for treatment. The clinical application of gene therapies with non-viral vectors

appears to be possible within the observable future. Clinical research is needed to determine the value of gene therapy in practice. The Council recommends the creation of sufficient (financial) opportunities for research that is necessary to bring gene therapy out of the laboratory and into the clinical situation. Investment into these developments by companies should, likewise, be made more attractive. This research could be funded out of the fundamentally strategic Innovation-Oriented Genomics Research Programme (IOP Genomics) or the ICES-KIS program. There is, though, also a possibility of financing via a new (sub)programme with the Netherlands Organisation for Health Research and Development (ZonMw).
It is expected that genome research will also lead to innovations in the development of vaccines. The RGO holds that research in this direction deserves support, possibly from the National Steering Committee for Genomics, within the research theme of Infectious Diseases.

GENETIC DISEASES OF ADULTHOOD

With the phrase "genetic diseases of adulthood", the RGO points to disorders with a known genetic (monogenetic) component where there are possible preventive and/or therapeutic interventions. Disorders in which there are weak associations with genes and where environmental factors play a great role have not received explicit attention in this advice. The Council intends to provide separate advice about multifactorial disorders and gene-environment interactions.
Four examples of genetic diseases of adulthood (hemochromatosis, familial hypercholesterolaemia, familial Mediterranean fever and Factor V Leiden) illustrate the importance of knowledge about the relation between phenotype and genotype in certain chronic disorders. This knowledge is essential for making responsible decisions about interventions, such as screening, at the population level. A nationwide screening of healthy persons is not appropriate for any of the above-mentioned examples. It is either clear that it is not useful for the detection of the sick person and their family members, or it is clear that more knowledge is needed before a decision about this can be made.
A general recommendation is that research should, initially, concentrate upon a solid description of the relationship between phenotype and genotype in chronic disorders that lend themselves to preventive or therapeutic guidelines. Along with the relationship between phenotype and genotype, the causal relationships each also illustrate another aspect of the application of genetic knowledge: incidental problems and the research that can contribute to the solution of these problems.

Using the example of familial Mediterranean fever, the Council recommends that genomic research provide adequate attention to the Dutch population's various ethnic groups. Consideration should be given to cultural aspects that are relevant to genetics, such as consanguinity (marriage between cousins) in certain population subgroups.
A corollary of large-scale genome research is the possibility of screening for genetic predispositions towards certain disorders. The RGO concluded that there is a need for research into the possibilities for the realisation of genetic screening. Research is needed regarding the social acceptability of selecting limited target groups for genetic screening. Questions about whether there should be more or less directive approaches to screening also deserve further research.
This fits well into the Programme for the Social Component of Genomics of the Netherlands Organization for Scientific Research (NWO). In any case, the programming of research into the above-named questions should involve the Association of Co-operating Organizations for Patients and Parents who are involved with hereditary or congenital disorders (VSOP).

The Council recognizes that knowledge about an individual's genetic make-up can have undesirable side effects, arising from the awareness that, for example, the risk of a serious disorder is increased. Research into the psychological consequences of knowledge of this increased risk is necessary. This sort of knowledge can also have an unfavourable impact upon insurability or access to work. The Council finds that instructions (at the European context, if necessary) should be issued to resist these unfavourable influences. The adequacy of the current instructions can be seen within the context of ZonMw's Programme Evaluation of Health Care Acts. The ZonMw sub-programme "Using genetics in health care: juridical aspects" deserves continuation. Given the rapid developments in the area of genomics, legislation should be reviewed at regular intervals.

Thanks to data banks (such as the national pathologic-anatomic archive [PALGA] and various biobanks), unique opportunities are available in The Netherlands (which are not available elsewhere) for the study the relationship between genotype and phenotype. The Council also finds that a search must be made for possibilities for the Netherlands' data to be used for research that will, in the end, have a positive effect upon health care. The Council has observed an area of tension between legislation (including the Medical Treatment

Contracts Act [WGBO] and Personal Data Protection Act [WBP]) and the use of personal data and bodily material for research. The need for a high degree of privacy protection is first on the list. A good balance is needed between self-determination and the social interest in scientific investigations. The observed bottleneck deserves attention in the national strategy put forward by the National Steering Committee for Genomics. One solution could be contributed by the continuation of the above-named ZonMw's Programme Evaluation of Health Care Acts. Such a program should provide an answer to the question of how people can make possible, within the context of European legislation, a socially responsible use of patient data and bodily material.