Annual report on screening for disease 2007

Medical self-test kits

Gezondheidsraad **President**
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : Presentation of advisory report *Annual report on screening for disease 2007*
Your reference : -
Our reference : U-1528/WvV/ts/757-J8
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Date : December 17, 2007

Dear Minister,

I am pleased to present you with the 2007 Annual Report on Population Screening. In the second issue of this report the Health Council of the Netherlands would like to inform you of the most recent scientific developments in a fast-changing field, namely that of self-testing. As you know, today's citizens have more opportunities than ever before to test themselves or have themselves tested at their own initiative, outside the regular health service, in order to detect diseases and risk factors at an early stage. Two questions arise here. To what extent do these tests contribute to better public health? And are citizens sufficiently protected against unfounded claims and pointless or even harmful tests?

To provide answers to these questions, the Committee that prepared this annual report has evaluated 20 tests ranging across the field of self-testing. The conclusion is that most tests lack a scientific basis. Only three of the evaluated tests provided added value. It also emerges that the existing regulations are not sufficient to guarantee an adequate assessment of self-tests, even though there are many similarities with population screening organised at the national level. The Committee therefore recommends a tightening of the Dutch and European regulations on self-testing. Progress can also be made by improving information for consumers. This seems a particularly opportune moment to consider these isues, because the European Commission is now contemplating a revision of the IVD Directive.

The recommendations have been considered by the Standing Committee on Genetics and the Standing Committee on Medical Ethics and Health Law, two advisory groups within the Health Council of the Netherlands, and were also were submitted to external experts for comment.

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I wholeheartedly endorse the conclusions contained within this annual report, and trust that it will contribute to evidence-based policy making in the field of self-testing.

Yours sincerely,

(signed)
Professor J.A. Knottnerus

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‘The revolution in human genomics, though barely understood by professionals, is about to hit the street, at least for those able to pay about $ 1,000 for a glance at their entire genome.’

N. Wade. The New York Times. November 16, 2007.

to:

the Minister of Health, Welfare and Sport

No. 2007/26E, The Hague, December 17, 2007 *(Revised version, April 24, 2008)*

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

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This report can be downloaded from www.healthcouncil.nl. The original Dutch language report can be downloaded from www.gr.nl.

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Executive summary

The value of medical self-test kits

The market for so-called medical self-tests is expanding. An increasing number of products and services have become available which enable people to test or have tests done on their blood, urine, faeces or saliva to detect the presence of specific markers. The manufacturers claim that this will enable users to detect the presence of a disease or an increased risk of disease, and that this early detection will be beneficial to their health.

The question is whether this is true. This 2007 Annual Report on Population Screening focuses on the value of self-testing of body samples. Using the available research in this subject area, we have investigated the extent to which self-tests actually live up to their claim of high test accuracy and providing a health benefit through early detection. To this end, we have examined 20 self-tests which, as a group, provide a good overview of what is currently on offer.

This review is preceded by a discussion of the relevant legislation. There is an effective authorisation system in place in the Netherlands for population screening. This protects citizens against tests which may be detrimental to their health. The question now is whether the current legislation and regulations are also sufficient to protect the population in cases where early detection is undertaken on the initiative of the people themselves or individuals, or whether there are gaps in the legislation.

Regulations are not yet adequate to regulate self-tests

In terms of legislation, the Decree on In-Vitro Diagnostic Devices (*Besluit in-vitrodiagnostica* (IVD)) covers self-tests on body samples. This decree is based on the European Directive 98/79/EC and covers recent regulations which will soon be evaluated. The European Commission is expected to make a proposal for this evaluation in 2009. The evaluation should focus on a number of gaps in the legislation.

Firstly, the 'essential requirements' of the IVD Directive are open to interpretation, making it difficult to clearly and consistently assess the tests in terms of diagnostic validity or clinical benefit.

Secondly, there is a lack of clarity about what actions manufacturers and notified bodies should undertake for the Conformity assessment required in order to affix the CE marking for a test. A CE marking should guarantee that a self-test fulfils the essential requirements listed in the IVD Directive. The files are not public, however, and can only be requested for viewing by the Netherlands Health Care Inspectorate. Furthermore, the assessment is generally left to the manufacturer, even for genetic tests or those which detect cancer. This calls into question the credibility of the CE marking system.

Thirdly, for the conformity assessment procedure of self-test kits manufacturers are only required in exceptional cases to provide results of studies with lay persons, even though this could have important implications in terms of reliability of test results. The main exception relates to HIV tests. Thus, for most other tests any available study results are usually based on use by experienced professionals.

Finally, the importance of the Population Screening Act (*Wet op het bevolkingsonderzoek* (WBO)) as an assessment framework may diminish through the increase in self-tests, even though self-tests and screening do share many similarities. As more people start using cancer self-test kits, the similarity to population screening (*e.g.* for colorectal cancer for which a permit is required) will become greater. Legally, however, the self-tests are products which fall in the free market category and therefore cannot be made subject to the WBO permit requirement as this would be considered an obstacle to trade. However, testing services (home-collecting and street-corner testing) which seek to detect cancer or a serious untreatable condition are subject to WBO evaluation.

Scientific evidence is an important requirement in the evaluation procedure

To evaluate the self-tests, four general criteria have been applied in this Annual Report: diagnostic validity, clinical utility, favourable risk-benefit ratio, and favourable cost-benefit ratio. If no peer-reviewed publications are available for these points, the requirements of objective evaluation of the test's quality and of publicised and verifiable results are not considered to have been fulfilled.

How do these criteria relate to the legislative and regulatory requirements? They correspond to the essential requirements in the IVD Directive. These should ensure that the purpose of the test is clear, that the test actually works as it is supposed to (and that it therefore performs well in evaluations) and that the risks to the user's health are acceptable when weighed up against the benefit.

In addition, the assessment in this Annual Report focuses on a number of criteria specific to self-test kits: whether the test can be used responsibly by lay persons, the availability of adequate information/recommendations and whether the test meets the legal requirements.

A handful of tests do have added value, but for many the value is unproven

Twenty tests, chosen to provide an adequate reflection of the growing field of self-tests, were evaluated. They range from self-tests to measure the glucose level in blood or urine to tests for cancer and genetic tests. The findings are summarised in table 1.

The conclusion is that self-test kits and services could have added value but, based on the present available evidence, only a small number of the evaluated tests currently represent a welcome addition. Of those tests discussed in the Annual Report, the HPV home-test for cervical cancer and tests which monitor blood glucose concentration and clotting time received a positive evaluation. The faecal occult blood test (FOBT) was also positively assessed. This has been used in a number of trial regions in the Netherlands as a home collecting test for colorectal cancer screening.

The remaining seventeen self-tests cannot be recommended due to a lack of scientific basis. It should be noted that this not only applies to new tests, but also to some which have been routinely used for decades.

Table 1 Quality of self-tests.

	Diagnostic validity	Clinical utility	Favourable benefit / risk ratio	Efficiency	Tested with lay persons	Adequate information	Mention of CE marking of conformity	Risk category for conformity assessment procedure	Fulfils the 'essential requirements' of the IVD Directive	Sales channelling	WBO permit required	Comments
Self-test kits												
Blood glucose: self diagnosis	N	N	N	N	N	N	?	L	N	N	N	
Blood glucose: monitoring	Y	Y	Y	?	Y	Y	Y	M	Y	N	N	A
Prothrombin time test	Y	Y	Y	?	-	Y	Y	L	Y	N	N	A
AMH test for bladder cancer	N	N	N	N	N	N	?	L	N	N	N	
Albuminuria test for renal damage	N	N	?	?	N	N	Y	L	N	N	N	
PSA test for prostate cancer	Y	?	?	?	N		?	M	N	Y	N	
FOBT for colorectal cancer:	Y	Y	?	?	N	N	Y	L	N	N	N	
Coeliac disease self-test	N	N	N	N	N	N	Y	L	N	N	N	
Tumour markers												
AMAS test for (breast) cancer:	N	N	N	N	N/A	N					Y	
HPV self sampling cervical cancer:	Y	Y	Y	Y	Y	Y	Y	L	Y	N/A	Y	A
CA 15-3 test for breast cancer:	N	N	N	N	N/A	N	?	L	N	N/A	Y	
CEA test for colorectal cancer:	N	N	N	N	N/A	N	?	L	N	N/A	Y	
PreGen-Plus for colorectal cancer:	N	N	N	N	N/A	N	N	L	N	N/A	Y	
Genetic self-tests												
Genetic predisp. to coeliac disease	N	N	N	N	N	N	N	L		N/A	N	
Gen. predisp. to lactose intolerance	N	N	N	N	N	N	N	L	N	N/A	N	
Hereditary risk of thrombosis	N	N	N	N	N	N	N	L	N	N/A	N	
Gen. predisp. to osteoporosis	N	N	N	N	N	N	N	L	N	N/A	N	
Gen. predisp. to hypertension	N	N	N	N	N	N	N/A	L	N	N/A	N	

A = added-value; N = no; Y = yes; N/A = not applicable; ? = research into this is currently underway, or unknown; L = low-risk; M = moderate; H = high

The conformity assessment procedure before coming onto the market is unsatisfactory

Seventeen tests did not pass the evaluation in this Annual Report, and therefore also fail to fulfil the essential requirements of the IVD Directive. In some cases it was not possible to properly investigate whether they met these criteria, since there is considerable scope for questioning current interpretations.

This strongly suggests that self-tests are not properly evaluated according to the essential criteria before being put on the market. Either the required evaluation is not carried out, or the requirements are interpreted in a minimal manner. It is also questionable whether the 'notified bodies' are adequately equipped to carry out this type of assessment, as their primary skills do not lie in the field of medicine and epidemiology.

Provision of information to the consumer is inadequate

A further conclusion is that the information provided through the Internet by the manufacturer or supplier regarding a self-test kit is generally inadequate. This makes it difficult for the consumer to reach a well-considered decision about the value of a particular self-test. A description of the precise aim, the anticipated gain and health risk and the diagnostic value are often missing. Furthermore, it is often not possible to find out whether the self-test has the CE marking before purchasing it over the Internet.

A further problem is that the IVD decree often leaves it up to the manufacturer to describe the aim of a self-test. This leaves scope for claims of outstanding test performance, using terms such as 'reliability index' or 'agreement' with an unspecified reference test, which have little to do with the diagnostic validity and the actual aim of the test. Consequently, sound information on the diagnostic value of the test is lacking and the risk of false-positive and false-negative results is masked. In addition, there are no guarantees that consumers will be able to properly interpret the results of a self-test.

Recommendations

The Annual Report contains a set of recommendations to deal with the identified problems. Some of these recommendations relate to regulatory issues. For example, it is necessary to define the current IVD essential requirements more clearly,

and to improve the quality of the conformity assessment. Furthermore, an investigation is necessary into how CE marking is assigned.

Even if a product is allowed to be introduced onto the market, the necessary changes can still be made. For example, product information requirements should be put in place to enable consumers to make a well-considered choice. An investigation into the most appropriate channel of sales is recommended, and advertising claims should only be permitted if backed up by scientific evidence.

Chapter 1

Introduction

1.1 Purpose of this annual report

The first Annual Report on Population Screening was published in June 2006. It included an overview of new developments in existing population screening programmes and of conditions for which population screening was being considered.[1] This second annual report does not include an update of this overview, as that seemed somewhat premature. It instead focuses on a single issue: the quality of the range of available diagnostic self-tests of body samples and the regulations that apply to them.

Self-testing as a choice for individual citizens

The market for self-testing is rapidly expanding. A community survey in the United Kingdom showed that 104 different self-test kits can now be bought on the Internet.[2] These kits can apparently detect or diagnose 24 conditions, including bowel cancer and HIV-infection, or control the course of a condition or therapy (with a monitoring test) as in the case of diabetes and anti-coagulation therapy. The Netherlands can match the United Kingdom in this respect.[3,4] Besides being available on the Internet, self-test kits can also be obtained from community pharmacies and chemist chains. At the same time, we are witnessing the growth of direct-access testing (DAT) and organisations promoting periodic health examinations (PHEs). Stichting ServiceLabs, launched in late 2004, has

been offering consumers a very wide range of clinical chemicals tests ranging from alpha-1antitrypsin to zinc and pregnancy tests. These can be performed in a hospital laboratory without the need for referral, after a blood test at one of the affiliated testing centres.

The growth of self-testing evokes mixed emotions. 'The Netherlands is suffering from collective hypochondria', suggested one commentator. 'Measuring without knowing', concluded the Consumers Association (Consumentenbond) after visiting 15 clinics (www.consumentenbond.nl). However, another commentator takes the view that 'the time is ripe for self-diagnosis, because consumers are now better able to decide whether they should consult a physician'.

The tone in the media is chiefly critical, particularly with regard to the diagnostic value of self-testing. But the public is more enthusiastic about self-testing. Thus, one in eleven Dutch adults took up an offer for a free 'kidney check' by the Dutch Kidney Foundation (Nierstichting Nederland) in the autumn of 2006.[5] Of course, pregnancy tests have been popular for many years. In fact, the number of pregnancy tests taken in the Netherlands exceeds the number of childbirths by a factor of more than four.

Several values clash in the debate on self-testing. People are entitled to decide for themselves what they want to do or have done. The rush of self-tests coming on the market fits in with the healthcare development in which patients play a full role in their treatment and in which the right to self-determination is a fundamental principle.[6,7] This is, of course, on condition that people can make considered choices and can grasp the consequences of their choices.6 This is why it is essential for consumers to have access to reliable information.[6]

However, do we know enough about the test characteristics, the users and the consequences of use to meet this condition? Is the advertising objective and balanced? Do charities, chemists, insurance companies, mail order companies, manufacturers, occupational health departments, pharmaceutical firms, pharmacists, sports shops, suppliers and other market parties always put health interest at the top of the agenda?[8] Is there not a potential for a conflict of interests in the case of initiatives such as the Cholesterol Treatment in Pharmacies for Diabetes Patients (CADS) project, which has been launched by a drug manufacturer, or Internet-based pharmacies that sell self-test kits as well as drugs and food supplements? It is precisely because conflicts of interest may arise that it is important that objective safeguards are in place.

Protective role of the government

The government plays a pivotal role in this context. When the exercise of the right of self-determination is detrimental to health, the question arises as to whether the government should protect citizens.[6] Is this the case here?

Self-testing may benefit consumers, and may even benefit personal and public health to some extent. In the case of emotionally charged conditions (such as HIV infection), for instance, people may be more likely to take a test when they can do so not only anonymously but also at home. The blood coagulation test is another example. Oral anticoagulation therapy works well, but setting the dose is precision work. Too high a dose can lead to haemorrhaging, and too low a dose to thrombosis. If patients can measure the blood coagulation time and adjust the dose at home, this will be at least as safe as the standard treatment and it will also yield a major improvement in the patient's mobility.[9-11]

So self-tests may have advantages, but they always have disadvantages. After all, virtually every test will produce false-positive and false-negative outcomes, each with their own implications. Moreover, the reliability and diagnostic value of a test may be significantly reduced when it is not conducted by an experienced professional.[12-14] Even when the instructions in the patient information leaflet are very clear, inexperienced users can easily make crucial mistakes, for example in timing the reading of the result. Furthermore, the predictive value of a test is by definition lower when it is conducted outside a hospital, an Outpatients' Department or general practitioner's surgery (see also section 3.1).

However, the problems need not be restricted to taking the test and interpreting the result. How strong are the supplier's claims of clinical utility and diagnostic value? For example, lay people do not expect a pregnancy test to be less sensitive than the manufacturer claims. Nonetheless, that is often the case, even though these products have been on the market for more than 35 years.[15] A US study showed that only 8 out of 18 different pregnancy tests could demonstrate a hCG value of 100 IE per litre.[16,17] Such a test can identify around 16% of pregnancies on the day of the missed menses.[16,17] That is far less than the claim of 99% certainty from the first day that a woman's period is overdue.

The more severe the condition being tested for, the greater the consequences of false-positive and false-negative results. This is also true if the screening outcome affects not only the person being tested, but also his or her relatives. Hence it is important to investigate whether the government can effectively execute its protective role with regard to self-testing, and whether the current range of available products does not cause damage to public health. The Committee on the

Annual Report on Population Screening (*Commissie Jaarbericht Bevolkingsonderzoek*) will be considering these matters in this report.

1.2 Scope of the report and questions

In principle, there are a number of instruments for evaluating the quality and utility of screening methods, such as the Decree on In Vitro Diagnostic Medical Devices (*Besluit in-vitrodiagnostica*) and the Population Screening Act (*Wet op het bevolkingsonderzoek*, WBO). In this annual report, we will examine which laws and regulations are relevant in terms of self-testing, and we will be evaluating a number of tests.

Selection of the discussed self-tests

The selection of self-tests was made as follows. This annual report is concerned with in vitro tests, that is, tests that involve taking body samples. This means that self-measurement of blood pressure, breast or testicular self-examination, and other forms of self-diagnosis have not been considered, because the regulations governing these are different or not relevant. Nor have pregnancy tests, ovulation tests and paternity tests been considered, because these do not involve diseases and comprehensiveness was not an aim. Point-of-care tests (performed, for example, at general practitioners' surgeries) and direct-access testing (DAT) are also outside the scope of this report. Strictly speaking, monitoring tests fall outside the domain of self-diagnosis. However, because they can be used for self-diagnosis they have been included in this report.

Within these parameters, the Committee primarily wanted to investigate the kinds of problems that may arise with self-testing. Incidentally, the concept of 'self-testing' is not entirely unambiguous. In the wake of a report on self-testing[6] published by the Council for Public Health and Health Care (*Raad voor de Volksgezondheid en Zorg*, RVZ), three types of self-tests are often distinguished: 1. do-it-yourself tests, intended for home use; 2. home-collecting tests, in which a commercial or non-commercial laboratory tests body samples that a person has taken or collected from himself or herself; and 3. street-corner tests, in which a commercial or non-commercial laboratory tests body samples taken by a third party.

This annual report considers all three types of self-testing. The Committee based its selections within these domains on two criteria: the severity of the condition being tested, and (with a view to differences in regulatory regimes) the distribution across 'products', 'services' and 'risk categories' under the IVD Decree. We have therefore chosen examples of do-it-yourself tests (Chapter 4),

tests for a tumour marker (Chapter 5) and genetic self-tests (Chapter 6). The supplier or manufacturer was not a factor in choosing the brand of self-test kit.

Research questions

On the basis of the above selection criteria, the Committee formulated the following questions:

1 What are the current laws and regulations governing self-testing?
2 Are these sufficient to protect the population or are there gaps?
3 What criteria should self-tests fulfil?
4 What is the verdict on a number of widely used do-it-yourself tests?
5 What is the verdict on home-collecting or street-corner tests for tumour markers?
6 What is the verdict on home-collecting tests for genetic disorders?
7 What improvements can be recommended to encourage an appropriate and sensible use of self-tests?

1.3 Relationship with other reports on population screening

Relationship with two forthcoming advisory reports

This annual report restricts itself to the current range of available self-tests. It differs in that sense from two more wide-ranging reports which are to be published in April 2008; one by the Health Council of the Netherlands and one by the RVZ. These two bodies will make recommendations from their own perspectives (scientific advice and policy advice, respectively) on medium-term developments in population screening. The growing availability of screening tests and public information will be considered in more general terms in these reports, as well as the role of government and the human rights at issue. In this report we will be concentrating on self-tests.

Relationship with previous recommendations and reports

As early as 1988 and 1989 the Health Council of the Netherlands observed that self-test kits were being marketed – especially abroad – for cancer, neural tube defects and hereditary conditions.[18-20] Because of the many false-positive and false-negative results, and the likely improper use associated with these tests, the Council recommended changes in the relevant regulations and a ban on the general sale of self-test kits for hereditary conditions. In 1998 the Council expressed

its preference for the Dutch approach to DNA-based diagnostics within the regular health service, with its careful referral, genetic counselling and recommendations on the basis of the test result.[21]

The European Directive on In Vitro Diagnostic Medical Devices (98/79/EC, hereafter 'IVD Directive') came into force in 1998. This was enshrined in Dutch law in the Decree on In Vitro Diagnostic Medical Devices *(Besluit in-vitrodiagnostica*, hereafter 'IVD Decree') issued in 2001. In 1999 the RVZ saw no reason to further regulate the use of self-tests. The government, the Council argued, should only intervene if self-diagnosis was harmful.[6]

These developments seemed to have largely resolved the problems identified by the Health Council of the Netherlands. However, self-testing subsequently started to again attract considerable attention. In the 2006 Annual Report on Population Screening (*Jaarbericht bevolkingsonderzoek 2006*) the Council pointed to the growing availability of screening tests of unproven value.[1] Following the publication of this report, the Minister of Health, Welfare and Sport also expressed his concern about the 'proliferation of easily available health tests' (*NRC Handelsblad*, 20 June 2006).

According to the Netherlands Society for Clinical Chemistry and Laboratory Medicine (*Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde*, NVKC), the quality of self-tests is unclear. In October 2006 the NVKC called for an independent quality mark for self-tests. In November 2007 the NVKC, the Royal Netherlands Pharmacists Association (*Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie*, KNMP) and the Netherlands Association of Hospital Dispensaries (*Nederlandse Vereniging voor Ziekenhuisapothekers*, NVZA) published a declaration of intent on cooperation on a number of issues. Specifically, the three organisations committed themselves to formulating joint recommendations to consumers about the quality and use of self-tests, including blood glucose meters.

In March 2007 the Dutch Cancer Society (*KWF Kankerbestrijding*) published a report on the use of biomarkers in screening, genetic testing, diagnosis and treatment.[22,23] This report warned about the proliferation of self-tests for which the quality and diagnostic value could not be verified by the user. The Society takes the view that the government should impose similarly strict rules on self-tests as exist for medical drugs.[2]

In April 2007 the Care and Public Heath Research Institute (CAPHRI) of Maastricht University published a report on self-testing commissioned by the Health Care Insurance Board (*College voor zorgverzekeringen*, CVZ) (www.cvz.nl/zorgpakket/preventie/diagnostischezelftests).[4] This report chiefly concentrated on the perceptions and backgrounds of users of self-tests. It showed

that Dutch consumers have access to self-tests for 28 conditions or symptoms, roughly the same as identified in the British study mentioned above.[2] It also emerged that 16% of Internet users had used one or more self-tests. The view that it is mainly the 'worried well' who use self-tests was confirmed. Self-testers often reported poorer health, overweight and a higher consumption of food supplements and homeopathic remedies than non-self-testers. The CAPHRI researchers did not expect a further spectacular growth in the use of self-tests, but they did want to further study this. It proved more difficult than anticipated to obtain information on test characteristics from suppliers. One of the report's recommendations was for further study into the diagnostic value of self-tests. CAPHRI is using a follow-up study to investigate why people use self-tests, whether they subsequently take the appropriate steps, and what additional information they would like.

A report by two advisory committees and the Health Council of the Netherlands on trends in biotechnology published in May 2007 indicated that the growing opportunities for genetic testing are raising great expectations among the public.[24] Internet-based businesses are responding to this by selling self-tests of dubious quality and reliability. The careful embedding of genetic tests in heredity-related advice is coming under pressure, according to this report.[24]

1.4 Structure of the report, responses to questions

The Committee outlines the current laws and regulations on self-testing in Chapter 2. The first two questions are answered at the end of this chapter. Chapter 3 discusses the criteria by which self-tests can be evaluated. The selected tests are then evaluated in Chapters 4, 5 and 6. Taken together, these evaluations give an indication of the problems that may occur in this field, thus providing answers to questions 3 to 6. Conclusions and recommendations are outlined in Chapters 7 and 8, respectively.

A list of concepts and their definitions is provided in Annex C.

Chapter 2

Laws and regulations on self-testing

This chapter sets out the laws and regulations which apply to self-tests. The weak points in the regulatory regime are also considered.

2.1 Different regulations for products and services

Difference between self-tests as products and as services

The difference between do-it-yourself tests on the one hand and home-collecting and street-corner tests on the other hand is significant in legal terms. The latter two test forms comprise not only a product, but also a service rendered by a third party (*e.g.* a laboratory) to the person in question. This chapter first looks at the regulations for self-tests as products (section 2.2), then the regulations for services (section 2.3), and finally the regulations relevant for products and services (section 2.4).

Key concepts in the regulatory regime

The statutory basis for the in vitro diagnostic test as a product in the Netherlands is the Decree on In Vitro Diagnostic Medical Devices (*Besluit in-vitrodiagnostica*, hereafter 'IVD Decree'). The IVD Decree (Bulletin of Acts and Decrees 2001, 385) is based on an EU directive (see section 2.2.1), and on such concepts as 'in vitro diagnostic medical device', 'high-risk diagnostic medical device',

and device for self-testing'. Article 1.1a of the IVD Decree defines an 'in vitro diagnostic medical device' as "a medical device intended for diagnosis with body samples". Article 1.lf defines the concept of 'in vitro diagnostic medical device intended for self-testing' as "an in vitro diagnostic medical device intended by the manufacturer to be able to be used by lay persons in a home environment". In the IVD Decree, then, the key element of the definition of self-testing is "intended for use by lay persons in a home environment". This is the definition of the do-it-yourself test.

The 'high-risk diagnostic medical devices' within the meaning of Article 1.1b of the IVD Decree include tests for HIV infection and tumour markers, tests for the diagnosis of hereditary diseases, and predictive genetic tests (see Table 2). 'High-risk' thus clearly refers to the severity of the disease and the risk of a false-negative or false-positive test result, and should not be confused with a high *a priori* probability of a particular disease. The products mentioned here may not be supplied directly to the user without the intervention of a doctor or pharmacist (under the sales channel regulation). A do-it-yourself test may also be a high-risk diagnostic medical device, which therefore can only be supplied by a doctor or pharmacist.

The IVD Decree divides in vitro diagnostic medical devices into categories, namely 'high risk' ('List A'), 'medium risk' ('List B') and 'low risk' (other tests) (see Table 2). This classification determines which 'conformity assessment procedure' (hereafter 'CE assessment; 'CE' stands for '*Conformité Européenne*') will have to be undergone before the test can be placed on the market. A do-it-yourself test may belong to any one of the risk categories (i.e. high, medium or low). The classification in risk categories is taken from European Directive 98/79/EC of the European Parliament and the Council of 27 October 1998 on in vitro diagnostic medical devices (hereafter 'IVD Directive').

2.2 Regulations for self-tests as products

2.2.1 Content of the IVD Directive

The IVD Directive is important for self-tests as products. The definitions of 'in vitro diagnostic medical device' and 'self-testing' in Articles 1.2b and 1.2d of the IVD Directive correspond to those of the IVD Decree (see section 2.1). The IVD Directive does not apply to what are called 'homebrew tests'.*

* 'Homebrew tests' are tests that are used only within the same health institution without having been transferred to another legal entity (Article 1.5 of the IVD Directive). These tests are thus not commercial products.

Table 2 Tests by risk category for CE assessment procedure, and do-it-yourself tests which fall under the sales channel regulation.

CE assessment		Sales channel regulation
'High risk'	list A: - tests for the blood groups ABO system, rhesus (C, c, D, E, e), anti-Kell - tests for HIV 1 and 2, HTLV I and II, hepatitis B, C and D	do-it-yourself tests for HIV, HTLV I and II, hepatitis B, C and D, for tumour markers, for the diagnosis of hereditary diseases, and predictive genetic tests
'Medium risk'	list B: - tests for the blood groups anti-Duffy and anti-Kidd, and for irregular anti-erythrocyte antibodies - tests for rubella, toxoplasmosis, phenylketonuria, cytomegalovirus, chlamydia, HLA tissue groups DR, A, B, PSA, trisomy 21 and blood glucose meters	
'Low risk'	tests not mentioned in list A or B	

European directives are particularly concerned with guaranteeing the free movement of goods, people, services and capital on the internal market. Their aim is to harmonise regulations in the EU member states and to remove trade barriers. Another primary main objective of the IVD Directive (preamble 5) is to maintain or improve the level of health protection attained in the member states.

Essential requirements in the IVD Directive

The 'essential requirements' that in vitro diagnostic medical devices must meet (Annex I of the Directive) are at the core of the IVD Directive. These are divided into 'general requirements' and 'design and manufacturing requirements'. The general requirements seek to ensure that the intended purpose of the device isclear, that it works as intended, and that it will not compromise the safety or health of patients and users. They comprise five points, of which the first and the third are particularly important:

> The devices must be designed and manufactured in such a way that ... they will not compromise, directly or indirectly, the clinical condition or the safety of the patients, the safety or health of users ... Any risks which may be associated with their use must be acceptable when weighed against the benefits to the patient and be compatible with a high level of protection of health and safety.

> The devices must be designed and manufactured in such a way that they are suitable for the purposes referred to ... , taking account of the generally acknowledged state of the art. They must achieve the

performances, in particular, where appropriate, in terms of analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, ..., stated by the manufacturer.

A crucial question is whether the essential requirements refer only to the analytical validity of in vitro diagnostic medical devices, or also to their diagnostic validity and clinical utility. The former is the most common interpretation[243], although the Committee believes that there are convincing arguments for using the latter.

First, a manufacturer cannot comply with requirement (1) solely with laboratory data (on the analytical validity).[25,243] After all, (1) can only be complied with on the basis of clinical data on the 'benefit for the patient' weighed up against the risks for the user. The risks of false-positive and false-negative results are among the direct and indirect risks for the user that relate directly to the diagnostic validity of the test. Comprehensive assessment must evaluate the diagnostic validity and clinical utility of the test.

Second, a manufacturer cannot comply with requirement (3) without performance data on the diagnostic validity of the test in its intended clinical purpose.

Third, the Committee argues that the regulations in the IVD Directive revolve around the risks for the user. After all, the division into categories for the purpose of the 'conformity assessment procedure' (see below) is closely linked to the risks of use. That is evident from the criteria for placing a diagnostic medical device in a particular category (Article 14.2b of the IVD Directive). The application of these criteria presupposes the availability of data on a test's diagnostic validity and clinical utility.[25] It is worth noting that, under Articles 1.1 and 1.2a, the IVD Directive applies to in vitro medical devices which are intended to be used for the diagnosis of diseases. This is pre-eminently a clinical matter.

Supplementary requirements in the IVD Directive for do-it-yourself tests

Devices for self-testing must be designed and manufactured in such a way that they perform appropriately for their intended purpose taking into account the skills and the means available to users and the influence resulting from variation that can reasonably be anticipated in users' technique and environment. The information and instructions provided by the manufacturer should be easily understood and applied by the user(Annex I B, point 7).

Supplementary requirements have also been made for the instructions for use. The results need to be expressed and presented in a way that is readily understood by a lay person; information needs to be provided with advice to the user on action to be taken (in case of positive, negative or indeterminate result)

and on the possibility of false positive or false negative result. The information supplied by the manufacturer should be sufficient to enable the user to use the device and to understand the result(s). The information provided must include a statement clearly directing that the user should not take any decision of medical relevance without first consulting his or her medical practitioner (Annex I B, point 8 sub t).

Demand for conformity with essential requirements prior to market launch

Before a product is allowed to be placed on the market, the manufacturer shall follow a conformity assessment procedure (CE assessment) to prove that the product meets the essential requirements of the IVD Directive and to have permission to affix the CE marking (see below).

Determining the risk category

The IVD Directive distinguishes different risk categories. This distinction is related to the severity of the disease or condition to be detected and to the risk associated with a false-negative or false-positive test result (Table 2). In Annex II, the IVD Directive distinguishes:

- high-risk devices, including tests for determining certain blood groups and tests for HIV-infection (Annex II, List A)
- medium-risk devices, including tests for Chlamydia, the tumoral marker PSA and devices for the measurement of blood sugar (List B)
- low-risk devices: all tests not named in List A or List B
- devices to be used by lay persons in a home environment. These devices for self-testing can belong to the high-, medium- or low-risk category.

A major problem is a lack of consistency. For instance, PSA is on List B, but no other cancer tests, such as do-it-yourself tests for bowel cancer (see table 2 and section 4.6).

This risk classification is specific to the extent that it limitatively summarises the markers or conditions to be detected within a particular risk category. The disadvantage of this approach is that all new products have to be regarded as low-risk for the simple reason that they are not named in List A or List B. For instance, PCA3 has not been added to List B, although it has the same function as PSA. This creates further inconsistency.

Assessment dependent on risk category

The assessment procedure to be followeddepends on the risk category. The more severe the disease or condition and the higher the risk associated with a particular test, the more onerous the assessment procedure.

The most onerous procedures apply for the tests on List A, while tests named in List B are slightly less onerous. Products from List A and List B are assessed by a 'notified body'. In the Netherlands this is KEMA Quality.

Low-risk diagnostic medical devices are assessed by the manufacturer itself, without intervention from a notified body. In the case of a do-it-yourself test, the manufacturer has to let the notified body assess its conformity with the supplementary requirements for do-it-yourself tests (regarding, for example the information on the label and in the instructions for use)*. Whether a do-it-yourself test needs any further assessment depends on the risk category into which the device in question falls (i.e. high, medium or low).

The Dutch notified body that carries out an assessment is an 'administrative body' for these activities. Its findings are 'decisions' within the meaning of the General Administrative Law Act (*Algemene wet bestuursrecht*). Under Article 10e of the Medical Devices Act (*Wet op de medische hulpmiddelen*), an interested party can appeal against such a decision to the Minister.

The way manufacturers and notified bodies go about a CE assessment procedure takes place behind closed doors. The files in question are currently kept secret, and can only be requested for viewing by the Health Care Inspectorate if concerns arise. For that reason the Committee has not been able to ascertain the role played by the general 'essential requirements' in the assessment procedure.

For the products named in List A, Common Technical Specifications (CTSs) have been drawn up on the basis of Article 5.3 of the IVD Directive (Commission Decision of 7 May 2002, 2002/364/EC, OJ EC L 131/17). These are binding specifications with which the products in question and the performance evaluations must comply. Do-it-yourself tests referred to in List A must meet the same requirements for sensitivity and specificity as the respective devices for professional use. It is confusing, however, that diagnostic sensitivity, for instance, is defined in terms of analytical sensitivity, namely as 'the probability that the device gives a positive result in the presence of the target marker'. The perfor-

* On the basis of the IVD Directive, the notified body need only consider the label and the instructions when assessing the information on do-it-yourself tests, not the information that consumers need to be able to decide whether or not to buy the product. As evident from the formulation in Annex III concerning the EC Declaration of Conformity, under point 6.1, first dash, 'where appropriate' indicates that as part of its application the manufacturer is not obliged to provide results from studies with lay persons.

mance evaluation must be carried out or repeated by inexperienced users* in order to validate the operation of the device and the instructions for use. A new version of the Annex to the CTS Decision that lists the specifications will probably be published in 2008. Furthermore, Article 5.3 of the IVD Directive also provides for the possibility of drawing up CTSs for List B devices, but this option has not yet been taken up.

Affixing the CE marking

CE marking is not a quality mark, but it should guarantee that the product meets the essential requirements of the IVD Directive. If the manufacturer has followed the prescribed CE assessment procedure, then it may affix the CE marking to its product.

An in vitro diagnostic medical device may not be placed on the EU market without a CE marking. If the product bears the CE marking, it is assured of access to the European market: Member States shall not create any obstacle to the placing on the market of devices bearing the CE marking (Article 4(1) of the IVD Directive). If a manufacturer based outside Europe wants to sell products in Europe (on the Internet or otherwise), it must appoint an 'authorised representative' that will fulfil all the manufacturer's rights and obligations, including those for CE marking.

Scope in the IVD Directive for EU member states

Article 4(1) shows that the IVD Directive's stipulations applying to the 'essential requirements' are not minimum standards but absolute standards. Tightening the requirements in national legislation is therefore not allowed. If a member state takes the view that the 'essential requirements' should be tightened, it will have to argue for this at EU level. The procedure to effect a change can take years. However, the Directive does give member states some freedom to regulate the commercial practices surrounding the products (*e.g.* sale, advertising). The Netherlands has used this freedom to introduce the 'sales channel regulation' (see section 2.2.2).

Article 13 of the IVD Directive gives member states the right to intervene and take transitional measures in the interests of public health. This Article has the character of an exception clause. It says:

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* The requirement for performance evaluation with inexperienced users applies only to do-it-yourself tests on List A and to self-tests for which performance evaluations have been conducted.

Where a Member State considers, in relation to a given product , that, in order to ensure protection of health and safety and/or to ensure that public health requirements are observed pursuant toArticle 36 of the Treaty, the availability of such products should be prohibited, restricted or made subject to particular requirements, it maytake any necessary and justified transitional measures. It shall then inform the Commission and all the Member States, giving the reasons fot its decision. The Commission shall consult the interested parties and the Member States and, where the national measures are justified, adopt necessary Community measures.

2.2.2 *Implementation of the IVD Directive in the Netherlands: IVD Decree*

The IVD Directive was enshrined in Dutch law in 2001 with the Decree on In Vitro Diagnostic Medical Devices (*Besluit in-vitrodiagnostica*, hereafter 'IVD Decree'). This incorporates the stipulations of the IVD Directive. Article 5(2) of the IVD Decree names the common technical specifications (CTSs) that apply for the devices in List A to be designated by the Minister. The technical specifications set out in the Annex to the Commission Decision of 7 May 2002 (OJ EC L 131/17) were accordingly designated in the Ministerial Regulation of 4 September 2002 (GMT/MT23 11237).

The IVD Decree is an Order in Council (*Algemene Maatregel van Bestuur*), based on the Medical Devices Act. Article 3(1) of this law provides for the designation by Order in Council of specific types of medical devices whose importation, storage and sale is prohibited unless certain conditions or requirements have been met. This has been done in the IVD Decree for in vitro diagnostic medical devices. The Health Care Inspectorate supervises compliance with the IVD Decree.

Language requirement, sales channel regulation

The EU member states' freedom to regulate the commercial practices surrounding the products in question has been used by the Netherlands in two ways: the language requirement and the restricted sale of do-it-yourself tests. Under Article 6.1 of the IVD Decree, the information for the user must be in the Dutch language. Furthermore, it has been decided on the basis of Article 4 of the Medical Devices Act that certain do-it-yourself tests cannot be sold to users without the intervention of a healthcare professional. Article 3.4 of the IVD Decree stipulates that only physicians and pharmacists are allowed to supply users with the high-risk diagnostic medical devices named in Article 1.1b (including tests for the detection of HIV infection and tumour markers, tests for the diagnosis of hereditary diseases, and predictive genetic tests). Hence this regulation concerns only

products, not services. It is known as the ‘sales channel regulation’ because it channels the sale of in vitro diagnostic medical devices.

Article 13a forms part of the sales channel regulation. This Article sets the requirements for the sale of high-risk diagnostic medical devices by pharmacists. These requirements concern the content of the patient information leaflet (Article 13a.2) and the information provided prior to the sale (Article 13a.3). The patient information leaflet should include the following additional details:

- adequate information on the severity of the condition and the importance of medical supervision in the use of the high-risk diagnostic medical device
- instructions, sufficiently understandable for non-professional users, on how to correctly use the high-risk diagnostic medical device and to correctly interpret the test results
- presentation, in an easily understood form, of the test results
- information on the possibility of a false-positive or false-negative result
- a recommendation on appropriate measures in case of a positive, negative or unclear result
- a recommendation not to take a medical decision without consulting a physician, with references to relevant professional healthcare institutions.

The information provided prior to the sale of the product (Article 13a.3) should include the following points:

- the availability of anonymous tests under medical supervision
- the importance of medical supervision in case of a positive test result
- the correct use of the high-risk diagnostic medical device
- the correct interpretation of the test results.

The sale of do-it-yourself tests (for example, for HIV or PSA) without the intervention of a physician or pharmacist is therefore prohibited in the Netherlands. However, the sales channel regulation does not, for example, apply to a do-it-yourself test for bowel cancer (the FOBT) because blood is not a tumour marker. This means that FOBTs can indeed be sold without the intervention of a physician or pharmacist. Another weakness in the regulation is that users obtain most of the information (through the patient information leaflet) only after they have bought the test.

Several other EU member states have imposed a Netherlands-like sale restriction on, for example, HIV self-tests. However, many member states have no such restrictions. As a result, manufacturers from EU countries without sales channel regulation can, in practice, sell high-risk tests with the CE marking to Dutch consumers on the Internet without the intervention of a physician or phar-

macist, even though this conflicts with the IVD Decree. The growing availability of tests for sale on the Internet, including by companies outside Netherlands, limits the application of the sales channel regulation and makes it difficult to enforce. The Minister of Health, Welfare and Sport has, in response to parliamentary questions on Internet sales of biomarker tests, announced that he will ask the RVZ whether there are grounds for reviewing the risk classification concerning the sale of diagnostic tests as set out in the IVD Decree now that ever more self-tests for cancer are offerred.[22] However, such a review will not solve the fundamental problems with the maintenance and enforceability of the sales channel regulation.

It is possible for a manufacturer based outside Europe to sell in vitro diagnostic medical devices to Dutch consumers on the Internet without the required CE marking, although Article 3.1 of the IVD Decree forbids the sale of such a product. Article 3.3 likewise forbids the use such an in vitro diagnostic medical device. This means that a Dutch consumer who uses such a test at home is, strictly speaking, guilty of an offence, although such an offence will not be easy to establish.

2.2.3 Analysis after admission to the market

Once the manufacturer has placed the in vitro diagnostic medical device on the market, the IVD Directive (and the IVD Decree) (Annex part 3, paragraph 5) oblige it to institute, within the framework of 'post-marketing surveillance' (PMS), a system and procedure for the collection and analysis of experiences with the product. The aim of this is to determine whether the product designs, including the instructions and application, require adjustment. The Health Care Inspectorate expects manufacturers to both passively and actively conduct PMS. Manufacturers usually passively (reactively) conduct PMS by waiting for incidents and user complaints (through a complaint procedure). The Inspectorate is urging manufacturers to proactively conduct PMS (for example, through customer satisfaction surveys, purchase satisfaction forms and meetings with users).

'Vigilance' is one element of PMS. The Annex mentioned above requires the manufacturer to notify the Health Care Inspectorate of the following:

1 any malfunction, failure or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use that, directly or indirectly, might lead to, or might have led to, the death of a patient or user or other persons or to a severe deterioration in his or their state of health;

2 any technical or medical reason connected with the characteristics or the performance of a device for the reasons referred to in subparagraph 1 leading to systematic recall of devices of the same type by the manufacturer.

Agreements between the industry and governments on the specific aspects of these notifications are set out in the EU's Guidelines on Medical Devices (MEDDEV) (2.12-1 [rev 5] April 2007). The Health Care Inspectorate has asked manufacturers to use the standard forms included with the MEDDEV when submitting notifications. However, in practice users tend not to complain about self-tests and the Inspectorate has received virtually no notifications of incidents or recalls (although it certainly does not follow from this that the products are of high quality). Where the lay public is concerned, the registration of notified incidents probably has only limited value.

2.2.4 *Other regulations*

In addition to the IVD Directive and the IVD Decree, the supply and sale of do-it-your-self tests is also governed by general law in the Netherlands, in particular the rules in Book 7 of the Dutch Civil Code (*Burgerlijk Wetboek*, BW) covering consumer purchases and distance selling (whereby the contact with the seller is via telephone, post, fax or Internet).

In a consumer purchase, the seller has to provide goods of high quality. The product must live up to the claims the seller makes for it, the seller must indicate whether the product is suitable for whatever purpose the buyer wants to use it, and the seller is bound by the product expectations created by the manufacturer. Before a distance contract can be concluded, the consumer must have timely access to sufficient, clear and understandable information that sets out, among others, the key features of the product or service.

The Civil Code also includes rules on the illegality of misleading advertising (Articles 6:194-196) and rules on product liability (Articles 6:185-193). The latter does not deal with the general quality of the product, but with its safety. A consumer who feels misled or cheated can use these rules to claim damages from the seller or manufacturer.

These civil law rules have only limited relevance for do-it-yourself tests. It is consumers who have to activate these rules by calling upon them when they feel they have been misled or cheated. A claim against a manufacturer or seller only has a chance of success if the consumer can show that he or she has been harmed.

2.3 Regulations for self-tests as a service

Home-collecting tests and street-corner tests are not only products, to which the IVD Decree applies, but also services. These services are certainly of a medical nature, namely the assessment of a person's state of health. The question thus arises as to what extent this type of service is covered by the regimes enshrined in the Population Screening Act (WBO), the Individual Health Care Professions Act (*Wet op de beroepen in de individuele gezondheidszorg*, BIG) and the Medical Treatment Contracts Act (*Wet op de geneeskundige behandelingsovereenkomst*, WGBO). The Health Care Institutions Quality Act (hereafter 'Quality Act') may also apply, although this law certainly does not apply to single individuals acting on their own. We consider the relevant statutory regulations below.

2.3.1 Population Screening Act

In this Act screening is defined as: "medical examination of persons performed for the purpose of implementing an offer made to the whole population or a section thereof and aimed at detecting specific diseases or risk factors for the benefit, or in part for the benefit, of the persons to be examined."

Home-collecting testing or street-corner testing fall under this definition. Examinations of this nature require a permit if ionising radiation is used, if they concern cancer, or if they concern severe diseases, defects or anomalies for which there is no treatment or prevention (Article 2.1). For instance, if the home-collecting test or street-corner test concerns the detection of cancer (PSA test, FOBT or AMAS test) or a predisposition to cancer, then this examination requires a permit under this law and is thus prohibited without the required permit (Article 3.1). Compliance with the WBO is supervised by the Health Care Inspectorate (Articles 10 and 11). Contraventions of the WBO are punishable (Article 13).

The WBO does not apply to do-it-yourself tests. Such tests are commercial products and they do not amount to population screening within the meaning of the WBO. This also applies to do-it-yourself tests for prostate cancer or bowel cancer. Products with the CE marking are commercial products. If the WBO also required a permit for market placement, this would constitute an obstacle to trade and would thus contravene the IVD Decree.

However, if a FOBT or PSA test is offered or sold in the form of a service, then the WBO does apply to this service and this examination requires a permit under the WBO. The IVD Decree applies to the *product* with which a home-col-

lecting test or street-corner test is performed (unless it is what is called a 'home-brew test', that is, a test used within the same health institution without having been transferred to another legal entity: Article 2.2 of the IVD Decree, see also section 2.2.1).

2.3.2 *Individual Health Care Professions (BIG) Act*

The BIG Act allows anyone to perform procedures in the area of individual healthcare, unless the procedure is a 'reserved procedure', such as an injection, puncture or catheterisation (Articles 35 and 36). Reserved procedures can only be performed by or on behalf of a physician or obstetrician. As far as the BIG is concerned, the ban on the independent performance of reserved procedures only applies to healthcare professionals.

With a home-collecting test, a person collects or takes body samples from himself or herself for the purpose of analysis. This is not a reserved procedure within the meaning of a healthcare professional's work. Street-corner tests do not usually involve a medical professional, but they do involve professional procedures in the health service. That is why it is usually not allowed to obtain body samples for this type of test by means of a reserved procedure, such as a puncture. It should be noted here that finger pricking is not a puncture within the meaning of the law and is thus not a reserved procedure.

The BIG is also relevant in terms of title protection. Only those people who are entered on a BIG register are entitled to use the title of physician, dentist, pharmacist, clinical psychologist, psychotherapist, physiotherapist, obstetrician or nurse (Article 4.1). In this way, patients or consumers can check whether they are dealing with a qualified professional. Those entered on a BIG register are also subject to the law's disciplinary rules (Article 47). Healthcare professionals who move beyond their area of expertise in the course of their work and cause or are very likely to cause unnecessary harm to another person's health are punishable, even if they are not entered on a BIG register (Article 96). Performing reserved procedures in contravention of the stipulations of the BIG is also punishable (Article 97). Moreover, general criminal laws are applicable to anyone who has inflicted severe harm to other people (outside their professional work; Articles 307 and 208 of the Criminal Code).

2.3.3 *Medical Treatment Contracts Act (WGBO)*

A medical treatment contract is a contract in which a natural or legal person – the healthcare provider – in the course of carrying out a medical profession or busi-

ness, undertakes towards another person – the client- to perform medical procedures on the client or a third party (Article 7:446 of the Civil Code). Home-collecting tests and street-corner tests clearly involve both a. a natural or legal person carrying out a medical profession or business (*e.g.* a laboratory performing medical tests) and b. medical procedures (*e.g.* assessing someone's state of health). If the healthcare provider (the laboratory) agrees to assess the state of health of the client (the consumer) by means of a test, then a contract has therefore been concluded within the meaning of the WGBO. The employees of the legal entity (the laboratory) are to be regarded as the executors of the contract on behalf of the legal entity.

In short, the provisions of the WGBO govern the legal position of consumers in relation to the laboratory or the laboratory staff. This means, for example, that the laboratory is obliged to provide consumers with all the information they need to enable them to decide whether or not to allow the performance of the test. Another consequence is that the activities of the laboratory require a duty of care as a good healthcare provider and must be in accordance with its responsibilities arising from the professional standards applicable to healthcare providers (Article 7:453 of the Civil Code). This, of course, presupposes the existence of such standards.

Not all WGBO rules apply to home-collecting tests and street-corner tests. The provisions of 'central liability' (Article 7:462.1 of the Civil Code) do not apply if the laboratory that renders the service is not part of a hospital, because such a laboratory is not a hospital within the meaning of the law.

2.3.4 *Health Care Institutions Quality Act*

The Quality Act is a framework act that uses a general standard – the provision of 'responsible healthcare' – to place responsibility for the quality of healthcare within the institutions themselves. 'Responsible healthcare' is defined as "being of a good quality, effective, efficient and patient-oriented, and geared to the real needs of the patient" (Article 2). Theoretically, all healthcare institutions have to comply with the Quality Act, regardless of their funding arrangements.

Are suppliers and sellers of home-collecting tests and street-corner tests healthcare providers within the meaning of the Quality Act? The Act defines a 'healthcare provider' as "(i) the natural or legal person who operates an institution, (ii) the natural or legal persons who together form an institution" (Article 1.1c). 'Institution' is defined as "the organisation whose purpose is to provide healthcare" (Article 1.1b). And 'healthcare' is defined as "healthcare as defined

in or pursuant to the Health Insurance Act and the Extraordinary Medical Expenses Act" (Article 1.1a of the Quality Act).

The legislators did not intend for the Quality Act to apply only to healthcare reimbursed under one of the above laws; it also applies to healthcare that is comparable to the healthcare as defined in these laws.[26] What matters, then, is whether the intended services can be designated as this type of healthcare. One can argue about the answer to this question, and there are thus doubts about the scope of application of the Quality Act.

Parliament could remove this uncertainty by defining home-collecting tests and street-corner tests as healthcare within the meaning of the Quality Act. Article 1.2 states, "If required for the promotion of the quality of healthcare, a form of medical assistance can be designated as healthcare within the meaning of the Act by means of an Order in Council". An implementation decree on Article 1.2 of the Quality Act that designates certain forms of medical assistance as healthcare within the meaning of the Quality Act has been in effect since 1996. The decree could be amended in this respect, whereupon the institutions or laboratories would have to formulate quality policies that could be assessed by the Health Care Inspectorate.

The above doubts to not extend to regular healthcare institutions, or laboratories that form part of these, that offer services in the form of home-collecting tests or street-corner tests. These are certainly covered by the provisions of the Quality Act.

2.4 Regulations for self-tests as products and services

Article 38 of the Health Care Market Regulation Act (*Wet marktordening gezondheidszorg*, WMG) imposes an obligation on healthcare providers that also applies to suppliers of self-tests, at least on the assumption that these are also 'healthcare providers' (see also section 2.3.4). This obligation entails that healthcare providers must disclose information about the characteristics of their products and services in such a way that this information can be easily compared by consumers. This information must also refer to the quality of the product or service. The above stipulation can be enforced by the health care authority by administrative order or by imposing a penalty order (WMG Article 82).

2.5 Conclusions

The Committee has investigated which laws and regulations apply to self-tests. In doing so, it distinguished between tests as products and tests as services (hav-

ing oneself tested) because the relevant laws and regulations differ. What are the main conclusions?

The Netherlands is bound by the IVD Directive

- With regard to the product requirements for self-tests, the Netherlands is bound by the European IVD Directive. A member state may not tighten these requirements unilaterally because this would constitute an obstacle to trade, although member states do have some freedom to regulate the commercial practices (*e.g.* sale and advertising) surrounding these types of products.

The IVD Directive needs to be clarified

- The general 'essential requirements' set out in the IVD Directive are open to interpretation. The Committee adduces arguments to interpret them in such a way that they refer not only to the analytical validity, but also to the diagnostic validity and clinical utility, of a self-test.

The European assessment procedures are not transparent

- The procedures by which manufacturers and notified bodies perform a CE assessment take place behind closed doors. The files in question are currently kept secret and can only be requested for viewing by the Health Care Inspectorate if concerns arise. Secrecy impedes the professional identification of possible problems.

The IVD Directive gives very little guidance on information for consumers and clinicians

- The IVD Directive sets virtually no requirements on the information provided to consumers prior to the purchase of a self-test.
- There are no specific regulations for advertising self-tests (such as those that exist for prescription drugs), apart from the code of conduct adopted by the trade association, Diagned (www.diagned.nl).

Most tests fall within the CE assessment's low-risk category, even though they certainly carry risks

- Virtually all tests fall within the low-risk category of the CE assessment procedure. This is true, for example, for tests for cancer (apart from PSA tests) and genetic tests (apart from tests for phenylketonuria, Down's syndrome and histocompatibility). In these instances, the manufacturer can determine for itself whether the test meets the 'essential requirements'. As a result European test marketing is based on self certification.[244]

- The IVD Directive does not oblige the manufacturer to provide the results from studies with inexperienced users for the CE assessment procedure for do-it-yourself tests. Such an obligation currently only applies to the high-risk tests on List A and to self-tests for which performance evaluations have been conducted.
- An independent scientific committee should be responsible for overseeing the risk categories, and the current European system of agreement between civil servants should end.[244]

The regulations contain no clear definition of a high-risk diagnostic medical device

- The definition of high-risk diagnostic medical devices that fall under the sales channel regulation does not coincide with the products cited in List A and/or List B in the IVD Directive. This is confusing.

Some test forms seem to fall outside the current regulatory regime

- Some home-collecting tests and street-corner tests are not covered by public-law legislation such as the WBO and the Quality Act. At the very least, there are doubts about their applicability to this type of services. This can only be resolved with a legislative amendment.

Chapter 3

Criteria for the evaluation of self-tests

The statutory framework outlined in the previous chapter represents the parameters within which the government can shape its tasks to protect citizens from self-tests that do not promote health and may even harm it. But when is this the case? On what grounds can such a judgement be made? And how do these relate to the statutory requirements? In this chapter the Committee sets out which criteria it uses to evaluate the quality of self-tests.

3.1 Proven diagnostic value

A first condition for a good test is that a repeat of the test yields the same outcome. This characteristic (repeatability, reproducibility, reliability) is important, but not sufficient. By analogy, an archer who systematically hits a particular spot but misses the bull's-eye is doing his best, but he is not hitting the target. In other words, a test must also be valid (accurate). It is important to distinguish here between analytical validity and diagnostic validity. Analytical validity reflects the performances in a laboratory trial setting, for example how often is the test positive when a gene mutation being sought is actually present (the genotype)? Diagnostic validity goes one step further: how often is the test positive in people who have or will get the condition in question (the phenotype), and how often is it negative in people without that phenotype? A test may accurately show the presence or absence of a gene mutation, for example, but if people with that mutation virtually never get the disease, the test is not useful. The laboratory

analysis determining the presence of a particular biomarker (the 'assay') should be distinguished from the application of this assay for a particular purpose (eg, diagnostic, prognostic) in a particular population.

The validity of a test is determined by the test characteristics of sensitivity and specificity. A test's (diagnostic) sensitivity is its ability to identify *all* people with the disease in question, or the number of true-positive test results divided by the number of people with the disease (true-positives plus false-negatives). A test with a high sensitivity leads to few false-negative outcomes. A test's diagnostic specificity is its ability to identify *only* people with the disease, or the number of true-negative test results divided by the number of people without the disease (true-negatives plus false-positives). A test with a high sensitivity leads to few false-positive outcomes.

Contrary to what is often thought, the degree of sensitivity and specificity does not only depend on the characteristics of the test itself. The sensitivity also depends on the clinical spectrum of the disease among the people being tested.[27] A test is usually first 'benchmarked' among a series of patients who have been referred to a hospital. These will often have the disease in a severe, pronounced form. Among the general population, people will still have the disease at an early stage, and hence it will be far more difficult to distinguish between those who have the disease and those who do not. Because of this difference in clinical spectrum, a test with a high sensitivity in a hospital setting will perform less well when applied to the general population.

For users of self-tests, the predictive value of the test result is of overriding importance. The positive predictive value indicates the probability that people with a positive test result will indeed have the disease. This probability depends on the validity of the test, but moreover on the percentage of cases of the disease among the tested people (the prevalence of the disease). A test that performs well in a group with many cases of the disease may not be suitable for use among the general population. The probability of a false-positive test result is by definition higher among self-testers than among visitors to an outpatients' department. After all, the pre-selection by the general practitioner means that there will be more cases of the disease among the outpatients, and the probability of a correct test result will be higher than in the case of more-or-less random testing.[28] A physician will make the decision to refer a patient based on the patient's symptoms and medical history (anamnesis), and if necessary also on the outcome of a physical examination.

Just as with participants in organised population screening, the main motivation for self-testers is probably to seek reassurance that they do not have a particular condition. This means that the test must in every case meet the requirement

that the predictive value of a negative test result is high. A test that yields many false-negative outcomes is not very informative and gives people a false reassurance. People who use a self-test when it is almost certain that they do not have the disease will barely reduce the uncertainty, but do run a relatively high risk of an incorrect test result.[29]

It is true that self-tests are not only used as a screening test by people who do not have symptoms, but also by people who do have symptoms. This does not detract from the requirement of proven diagnostic value. It should also be stressed that severe symptoms require serious medical attention within the regular health service. If a person noticed blood in their faeces or urine, for example, it would be risky to rely on a self-test.

3.2 Proven clinical utility

A test must first of all give the user greater certainty about having or developing a particular condition. Furthermore, using the test must be of benefit to the user. Generally speaking, 'benefit' is taken to mean a health gain. In certain situations (*e.g.* pregnancy test, prenatal screening, or a test for an untreatable disease), the issue is not a health gain, but to offer sensible courses of action. The intended effect in the case of a health gain must be convincingly demonstrated in terms of mortality, disease burden or quality of life. After all, a test (explicitly or otherwise) offers a promise of a health gain. A test user should therefore be able to count on this promise being delivered.

This requirement of evidence-based effectiveness fits in with the general development that market parties demonstrate social responsibility concerning their products. Thus, the efficacy and safety of drugs must be well documented before they can be introduced on the market. This is done on the basis of clinical trials that can withstand or have withstood the peer reviews of scientific journals. Requirements have become more stringent and detailed information concerning efficiency must now also be given. Transparency in healthcare means, among other things, that medical specialists have to disclose their medical performances. Claims of health benefits for foods and food supplements, for example, must increasingly be substantiated, and this substantiation must be independently tested.[30]

To be convincing, information about the evidence of efficacy must be available to the public. This fits in with the obligation to provide information under consumer protection legislation (see section 2.2.4), and applies not only to consumers, but also to general practitioners and other physicians who are being consulted following a test outcome, as well as to health insurance companies.

3.3 Favourable risk-benefit ratio

Using a test may have the desired effects, but it may also have unwelcome effects. Ultimately, a test is only of value if the desired effects amply weigh up against the unwelcome effects (*e.g.* health impairment or risk) for the users themselves and for others. There is no point in testing if the benefit is cancelled out by the risk. All that is certain about tests which have not been proven to be effective are the disadvantages. Because there are no perfect tests, false-positive and false-negative outcomes are always likely, with all the implications that entails.

The use of self-tests is not likely to pose a direct danger to the user's safety, but it may pose an indirect danger to his or her physical and mental health. Health impairment can take many forms, such as temporary worry about the result, or unnecessary worry in hindsight if a result proves a false-positive. The follow-up examination or treatment may be burdensome and risky. Testing can lead to overdiagnosis and overtreatment or, on the contrary, to false reassurance and late treatment after a false-negative result. Testing can also lead to 'loss of amenity' (loss of enjoyment of life) because it may merely bring forward the moment of detection without allowing the user to live longer.

It is often unquestioningly assumed that the risk-benefit ratio is favourable, or at least not unfavourable. 'It doesn't hurt to try' does not, however, hold in the case of self-testing or screening. Users of self-tests are generally people without definite symptoms and with a low probability that they have the disease in question. This means that many people have to use the test before someone benefits and that the great majority of people will not benefit from the test. Under these circumstances, the risk of testing (for the many) will have to be very small indeed to remain favourable compared to the benefits (for the few). This fundamental law of a precarious, by no means inevitably favourable, risk-benefit ratio applies to all forms of early detection.

However, if someone does have symptoms (for example bowel pain and weight loss), then it is very much an open question whether self-testing offers benefits rather than causing harm.

3.4 Favourable cost-benefit ratio

Efficiency has to do with the costs of the test and the costs of all possible consequences of the use of the test. How does the deployment of resources compare to the potential net health gain? Efficiency can be considered from the consumer's perspective or from a social perspective. For consumers, the convenience of a

self-test, the avoidance of a doctor's appointment, or the reassurance of a negative test result may well easily outweigh the cost of buying the test. At a social level, one of the questions that arises is whether self-testing reduces the probability of a risky postponement of a doctor's appointment or actually increases it through a false-negative test result. Does self-testing inhibit the unnecessary use of healthcare services, or does it actually have a stimulating effect?

Efficiency is ideally expressed in terms of costs per gained life-year (cost-effectiveness) or costs per quality-weighted life-year (cost-utility). The efficiency and cost-benefit ratio of tests with unproven efficacy are by definition unknown. A very efficient test has a low (favourable) cost-effectiveness ratio.

Research on the efficiency of diagnostics in general and self-tests in particular is scarce. If nothing is mentioned on this in the following chapters, that is because nothing is known about the efficiency of the self-test in question.

3.5 Good test performances with inexperienced users

A specific criterion for do-it-yourself tests is that lay persons must also be able to perform the test in such a way that its diagnostic value is preserved. After all, diagnostic value can significantly decline if the test is not correctly applied.[2-4] Even when the instructions in the patient information leaflet are very clear, inexperienced users can easily make crucial mistakes, for example in timing the reading of the result. 'Stop Kidney Disease Early' ('*Stop beginnende nierziekte'*), a campaign launched by the Kidney Foundation in the autumn of 2006, led to an unexpectedly large number of false-positive test results, estimated at one in five participants. Part of the explanation was that the test (in the first morning urine) can only be accurately read in natural daylight. In artificial light – and bear in mind, the test was held in the autumn – the test results are more easily interpreted as positive.[5]

3.6 Adequate information for users

Quantified information on probabilities is part and parcel of informing the patient in the physician's surgery. The Committee finds it self-evident that information on self-tests, in particular, must meet high standards. To be able to assess the value of self-tests, consumers must receive balanced and adequate information. That is a precondition for exercising the right to self-determination. Do consumers have access to this information in time, or can they only obtain it after they have bought the self-test kit?

The code of conduct for the trade association of Dutch manufacturers, importers and suppliers, states that advertising for self-tests must be done so as to promote the rational use of the test, not mislead consumers on the effects, safety and applicability of the product, and to provide truthful and verifiable information (www.diagned.nl).

3.7 Embedding in the regulatory regime

A final set of criteria is whether the self-test requires a permit under the Population Screening Act (WBO), whether the test carries the CE marking, and whether (in the Committee's eyes) the outcome of the CE assessment procedure meets the general 'essential requirements' set out in the IVD Decree (and Directive).

The Committee has looked at publicly accessible sources, such as the Internet and articles in peer-reviewed scientific or professional journals. It did not take account of the non-public data which manufacturers, the notified body, or the Health Care Inspectorate have access to. The Committee was thus in the same position when evaluating the self-tests discussed in the following chapters as a consumer who is considering buying a self-test.

3.8 Conclusion

Self-tests must be assessed in the same way as tests in screening programmes

The Committee sees no reasons to assess a self-test any less critically than a test that is part of a screening programme. After all, both the use of self-tests and participation in population screening are promoted, explicitly or implicitly, as ways of achieving health gains. Users have the right to know whether there are sound reasons for that claim and what the downside might be.

A second reason is that the quality of self-testing is vulnerable. In a screening programme, a professional organisation safeguards the main links in the chain of information provision, choice of target group and screening interval, training and retraining of screening staff, quality control of the screening procedure, registration, and process and effect evaluations. The situation is different for self-tests.

Four general criteria apply to self-tests

No ready-made evaluation framework is available; there have only been initial steps in that direction.[31] The Committee based its evaluation of self-tests in this annual report on the following criteria: diagnostic value, clinical utility, risk-benefit ratio and efficiency. If nothing has been published in scientific and professional journals on these aspects, then the requirements that the quality of the tests must be objectively evaluated and that the outcome must be made public and must be verifiable have not been met. This is all the more serious because unpublished research tends to be of lower quality and often overestimates the results.[32]

How do these criteria relate to the requirements set out in the laws and regulations? According to the Committee, they agree with the general 'essential requirements' set out in the IVD Decree. After all, these requirements must ensure that it is clear what the test is used for, that the test works as intended (and delivers the indicated test performances in terms of reliability, diagnostic validity, etc), and that 'any risks which may be associated with their use must be acceptable when weighed against the benefits to the patient'.

These requirements generally apply to diagnostic medical devices. However, the evaluation of new diagnostic medical devices in the regular health service lags behind research into the effects of therapies. There has been a growing realisation over the last few decades of the need for critical evaluations of new diagnostic procedures.[28,33]

Three supplementary requirements are important for self-tests

In addition to the four above-mentioned criteria, the evaluation also focuses on several other requirements more specifically geared to self-tests: responsible application by inexperienced users, provision of adequate information, and meeting statutory requirements.

Chapter 4

Evaluation of do-it-yourself tests

In this chapter the Committee starts the evaluation of self-tests with do-it-yourself-tests: tests which consumers can perform themselves at home, without the intervention of anyone else in taking or collecting the necessary body samples and in reading the test outcome.

4.1 Do-it-yourself tests for glucose in urine or blood

There are do-it-yourself urine or blood tests for detecting diabetes and there are meters with which diabetes patients can monitor their blood sugar levels themselves. Diabetes is a serious and very common disease. On the basis of general practitioners' morbidity registrations, it is estimated that in 2003 there were more than 600,000 people in the Netherlands with diabetes, of which 90% had type-2 diabetes (www.nationaalkompas.nl). The costs to the Dutch health service in 2003 of diabetes and diabetes-specific complications, such as eye conditions and kidney problems, were estimated at EUR 735 million.[34] The total costs, including complications such as cardiovascular diseases, came to EUR 1.2 billion.

4.1.1 Clinical utility of screening

The efficacy of screening for diabetes has not been demonstrated.[35,36] Research on this is ongoing. A screening trial was started in the Rijnmond region (Greater Rotterdam) in late 2005-early 2006 to establish whether systematic screening for

diabetes reduces the risk of cardiovascular disease. In accordance with the Health Council of the Netherlands' recommendations, the sample group consists of men and women aged between 40-75 years with a large waist circumference. This form of obesity is a better predictor than obesity determined on the basis of the body mass index. A measuring tape and a questionnaire are used to estimate the respondents' risk. The group with a heightened risk is randomly divided into a screening group and a control group. The members of the screening group are invited to have their fasting blood glucose and lipid levels measured. Participants who probably have diabetes, according to this measurement, are then referred to their doctor for diagnosis and treatment. The control group is only given lifestyle advice. The study will take 10 years to complete, including a feasibility study, and will eventually include 62,000 people, equally divided between the screening group and the control group.

This population screening trial does not require a permit under the WBO.

In anticipation of the results of scientific research, the Netherlands Diabetes Association (DVN), the Netherlands Diabetes Federation (NDF), the Royal Netherlands Pharmacists Association (KNMP) and other organisations have launched publicity campaigns with free diabetes tests. In the autumn of 2007, a free finger-prick campaign was conducted nationwide in the branches of a major sports clothing chain. This involved a volunteer from the DVN taking blood from a person and measuring their blood glucose level. The whole procedure took less than a minute.

4.1.2 *Verdict on glucose tests for self diagnosis*

Do-it-yourself tests, like the Medi-Test glucose urine test strip, have been around for a long time. Urine tests are not very sensitive in detecting diabetes. Their sensitivity lies between 21% and 64%.[35]

Blood glucose tests are the most popular self-test kits, according to the Maastricht study by the Care and Public Heath Institute (CAPHRI).[4] An example is the Visual Glucose Home Test (www.kwaliteitsapotheek.nl priced at EUR 9 to EUR 13). This is a semiquantitative test on capillary whole blood requiring one drop of blood from a finger prick. According to the instructions, the test result should be read 50-75 seconds after the drop of blood has been applied to the test strip, by comparing the colour of the test section against a colour scale.

Comparative research has been conducted into a capillary glucose measurement in the laboratory with the oral glucose tolerance test – the 'gold standard' for diabetes – as the reference test. The sensitivity came out between 40% and 84% and the specificity between 66% and 98%.[37-40] This could mean that the test

does not recognise most cases of diabetes and that a positive result will be a false-positive in nine out of ten cases (on the basis of a prevalence of 3.8% and a specificity of 66%).

It must be assumed that these tests do not perform any better when applied as do-it-yourself tests, but the website does not provide any information on this. Nor does it state whether the test has CE marking (www.kwaliteitsapotheek.nl). The Committee was unable to determine, on the basis of an Internet search, what test performances are claimed by the manufacturers themselves. Manufacturers are not obliged to provide the 'notified body' with results from studies with inexperienced users. The Committee was unable to find any publications on such studies in peer reviewed medical jounnals.

Do-it-yourself tests for glucose are categorised as low-risk. This means that the CE assessment is left almost entirely to the manufacturer itself. Do-it-yourself tests fall outside the scope of the WBO.

The Committee concludes that the clinical utility and cost-effectiveness of screening for type-2 diabetes are still being researched. Glucose measurements from finger-prick blood with test strips produce widely varying test results under laboratory conditions. This is all the more serious because nothing has been published on the diagnostic value of test strips when used by inexperienced users. Because the diagnostic value cannot be ascertained, the test result cannot be interpreted. The Committee takes the view that the sale of test strips for glucose levels is at odds with the general 'essential requirements' of the IVD Decree.

Some people test themselves for diabetes by using the portable glucose meter used by a relative or friend with diabetes. Glucose meters all measure in capillary whole blood (obtained from a finger prick) and are not suitable for self-diagnosing diabetes mellitus.[41] Nor are they intended for that purpose. Glucose measurements (in veinous plasma) in laboratories are much more accurate. The use of portable meters (which are calibrated half for whole blood and half for plasma) can lead to confusion in diagnosis.

4.1.3 *Verdict on blood glucose meters for monitoring*

The 1980s saw significant progress in the self-measurement of blood sugar levels, namely from manual visual measurement to electronic measurement.[42] Subsequently many meters were equipped with software. Urine test strips are rarely used these days. The search for an ambulant feedback system in which a non-invasive glucose meter is linked to the automated application of insulin is still ongoing.[43]

In the 1980s the Netherlands Organisation for Applied Scientific Research (TNO) developed a guideline with quality criteria for portable and other glucose meters. This guideline was a voluntary agreement between manufacturers and professionals, and applied until the IVD Decree came into force in 2001. Under this guideline it was agreed with healthcare providers and insurance companies that only TNO-approved meters could be used for health insurance purposes. This approval is not a one-off check, but involves regular monitoring. The approval holder undertakes to submit his approved product annually for testing. Another important aspect is that regular checks are made to ensure that the measurements are performed correctly. Under this quality assurance programme, participants are sent two samples with unknown glucose concentrations every three months, each of these concentrations must be measured twice. After the participants return the measurements, they receive a detailed report. The introduction of CE marking made the pivotal role of TNO redundant.

Subject to certain conditions, glucose meters are suitable for monitoring. Accurate regulation of glucose reduces the chances of complications. Self-management improves the attitude of diabetics using insulin. This might also apply to type-2 diabetes patients who do not use insulin,[44] although this has not been demonstrated convincingly.[45] Self-management is probably chiefly valuable when it is embedded in structural diabetic care, within which education constitutes a major element. A systematic check revealed user mistakes among a quarter of 'self-measurers'.[46] This was due in particular to the use of expired or wrong glucose strips. Nearly all patients had questions about how to use the glucose meter.

Glucose values which vary by more than 7% from the reference values can lead to errors in the insulin dose.[47] Under the ISO standard, a meter's glucose value may not vary by more then 20% from the reference figure selected by the manufacturer. This means that two different meters could differ by 40% between them. In other words, someone with a glucose value of 10 mmol/l on the benchmark meter may register a value of 8 mmol/l on one approved meter and 12 mmol/l on another. In practice the variations are likely to be even greater if the instructions are not followed, if the strip preparation has changed over time without this being noticed, or if the self-selected reference level deviates more from the 'gold standard' for measuring glucose levels (hexokinase method calibrated using the ID-GCMS method).

Blood glucose meters are categorised as medium-risk in the IVD Directive. This means that they have to undergo a relatively onerous assessment procedure to obtain CE marking. The Committee takes the view that glucose meters are only suitable for monitoring if they pass not only the initial assessment but also subsequent regular checks of the meter, the test strips and the way in which the

measurement is conducted with blood from the patient. In this way it is possible to identify new patient-dependent interference factors for measuring glucose levels. The need for regular checks of blood glucose meters is insufficiently assured in the current CE marking system. The Committee recommends that this requirement be included in the preparations for the review of the CE marking system. The Committee was unable to find any publications on the efficiency of the use of blood glucose meters for monitoring.

4.2 Monitoring tests for blood coagulation time

Test equipment to determine how quickly blood coagulates is intended for people who are being treated with oral anticoagulation therapy. Setting the dose is precision work. Information on blood coagulation time can help patients to take the correct amount.

4.2.1 Thrombosis

Outpatient anti-coagulation treatment is supervised in the Netherlands by thrombosis clinics. In 2002 there were 63 such clinics, treating more than 326,000 patients: 73% with an arterial indication (cardiovascular diseases such as atrium fibrillation, heart attack with complications, heart valve replacement), and 27% with a veinous indication.[48]

Deep-vein thrombosis (DVT) and pulmonary embolism are responsible for a heavy disease burden and many deaths. The incidence of DVT in the general population is not known. An old US questionnaire-based study suggested that 5% of men over 70 years and 10% of women in that age group may have had DVT. A Swedish study came to a figure of 15% of the population.[49] Because of the often non-specific symptom pattern, mortality rates do not give a reliable picture. The likelihood of death within 30 days of a DVT episode is 5%. For pulmonary embolism the corresponding figure is 10%.[50] No figures are available on the specific costs of DVT and pulmonary embolism to the health service.

In its new consensus on the treatment of DVT and pulmonary embolism (*Behandeling diepe veneuze trombose en embolie*), the Institute for Health Care Improvement (CBO) provides evidence of major advances in the diagnosis and treatment of these conditions (www.cbo.nl). Hospital admission is usually no longer necessary for DVT. However, treatment with oral anticoagulants combined with supervision by the thrombosis services is burdensome. Although research into new anticoagulants which do not need laboratory control is ongoing, these new therapies will not become available in the coming years.

Oral anticoagulation therapy works well, but setting the dose is precision work. Too high a dose can lead to haemorrhaging; too low a dose to thrombosis. The blood coagulation time can be measured and the therapy can be checked with the INR test, which measures the prothrombin time, expressed in the 'International Normalised Ratio'. The test consists of adding a substance to the blood to make it coagulate, and measuring the coagulation time.

4.2.2 Verdict on the INR test

The patient can measure the blood coagulation time at home using a simple appliance. This brings a major improvement in terms of mobility. Coagulation meters can be taken as hand luggage when travelling. Even more important is that, subject to certain conditions, self-management is at least as safe as the standard treatment, measured at the incidence of thrombosis, embolism or serious haemorrhaging, or the so-called INR value.[9-11,51] INR is the standard used to allow for differences in prothrombin time measurements in different laboratories on the basis of different reagents.

Blood coagulation meters are categorised as low-risk in the IVD Directive. They determine the INR in a drop of finger-prick blood on a test strip after one minute (with the CoaguChek XS) or after two minutes (with the HemoSense INRatio system). The website for the second coagulation meter states that it has CE marking. Since 2002, patients deemed suitable for self-testing can receive training and support from the thrombosis services, and they learn to set the dose within certain INR values themselves.[48]

The Committee concludes on the basis of published research into clinical utility and safety that self-management can offer added value. It sees no reason to place coagulation meters ('low risk') in a lower risk category than blood glucose meters ('medium risk').

4.3 Do-it-yourself tests on occult blood in urine

There are test strips which can detect blood that is present in the urine but not visible to the naked eye. Such a presence could be indicative of bladder cancer or another cancer of the urinary tract.

4.3.1 Bladder cancer

Some 2,350 new patients were registered with invasive bladder cancer in the Netherlands in 2003, and almost as many with a non-invasive form (www.ikc-

net.nl). Each year 1,150 patients die of bladder cancer (www.cbs.nl). The costs of bladder and kidney cancer (not broken down further) to the Dutch health service were estimated at EUR 100 million in 2003.[34] The disease is often diagnosed on the basis of painless visible loss of blood in the urine (macroscopic haematuria).

Years ago it was already assumed that bladder cancer could be detected early with a test for invisible traces of blood in the urine in people who do not yet have symptoms (asymptomatic microhaematuria, AMH). Test strips – *dipsticks* – were developed which are used in the health service, but also as do-it-yourself tests. Does such a haematuria test indeed detect bladder cancer sooner, and if so, is the disease then easier to treat?

4.3.2 *Clinical utility of screening*

For screening to have an effect, then in any case appreciably more cases of the disease will have to be diagnosed among people with a positive test result than among those with a negative result. However, three patient-control type studies showed that bladder cancer was not diagnosed more often among people with asymptomatic microscopic haematuria (AMH) than among people without AMH.[52-54] Moreover, in autopsies, bladder cancer is not often observed at an early stage (unlike prostate cancer, for instance). This indicates that the chances of early detection of the disease are limited.[55] A calculation of the lead time (i.e. the period by which screening brings forward the moment of diagnosis) came out at only three months for AMH.[56] Correspondingly, no clear indications have been found that cases of bladder cancer detected via screening for AMH are detected at an earlier (more favourable) stage than would have been the case if the diagnosis had been made on the basis of symptoms.[57,58]

This implies that AMH screening has a low sensitivity for early bladder cancer, and that it would have to be repeated very frequently to have any effect. According to a study in Japan, a one-off haematuria test had a sensitivity of only 28% for bladder cancer.[59]

Moreover, there is the problem of low specificity. The initial test result is often positive, but at the decisive test (cystoscopy) this result usually proves a false-positive. How often this happens depends on the target group and the question of whether the screening consists of a single test strip or a series of ten or fourteen dipsticks on successive days. Between 2% and 24% of the participants present positive screening results under these conditions. The predictive value of this for bladder cancer is of a magnitude of 0.5 to 3.0% [53,59-61] or slightly higher.[55,57,62-64] The test performances among patients who have been referred for a

urological examination because of AMH are no better than among the general population.[65]

Scientific literature reports only two small, non-randomised studies into the efficacy of AMH screening for bladder cancer. A British study among men aged 60 and older showed no favourable effect of screening on bladder cancer mortality rates after an observation period of seven years.[63] But an American study among men over 50 did seem to point to a favourable effect after a period of 14 years.[55]

Test strips for AMH are categorised as low-risk in the IVD Decree. They are available, for example, as Bayer Multistix 5 (EUR 17 per bottle of 50 test strips) on several websites, such as www.daxtrio.nl (which has a Webshop Keurmerk quality mark), without stating whether the product has CE marking. These test strips can be used to screen for bladder or kidney cancer, but haemoglobin (the colourant of red blood cells) cannot be designated as a tumour marker, which means that the (Dutch) sales channel regulation does not apply.

4.3.3 Verdict on do-it-yourself tests for occult blood in urine

The Committee concludes that the efficacy of screening for bladder cancer, with test strips or any other method, has not been demonstrated. Suppliers of do-it-yourself tests for AMH do not warn that their clinical utility has not been established. Nor do they provide information on the test performances (which are often poor). Because of the high risk of false-positive and false-negative results, the test results cannot be interpreted. The efficacy of AMH testing for other cancers of the urinary tract has not been demonstrated either.

4.4 Do-it-yourself tests for albumin in urine

The next type of test which can be performed at home screens for albumin in urine. Loss of albumin through the urine (albuminuria) may point to chronic kidney disease.

4.4.1 Chronic kidney disease

The Netherlands has around 11,000 patients with renal replacement therapy (dialysis and transplant; www.renine.nl). The annual costs of this therapy amount to around EUR 400 million. Renal dysfunction can remain unnoticed for a long time, until the kidneys have become seriously damaged. Diabetes mellitus (types 1 and 2) and hypertension are the main causes of end-stage kidney failure. These

conditions account for one in three cases of end-stage renal disease (ESRD) in the Netherlands and other European countries, and for two in three in the United States.[55,66,67] A Norwegian study showed that people with type-1 diabetes had an 8% chance of nephropathy (persistent macroalbuminuria) during an average observation period of 24 years after diagnosis.[68] In Finland, it was calculated that people diagnosed with diabetes before reaching the age of 30 had a 2% chance of suffering ESRD within 20 years, and an 8% chance within 30 years.[69] Incidentally, these national figures are appreciably lower than those from previous small-scale studies in referral centres.

Albuminuria and impaired kidney function (i.e. an estimated glomerular filtration rate (eGFR) < 60 ml per minute) raise the probability of deteriorating kidney function or the development of cardiovascular diseases among people with diabetes or hypertension.[70-72] Between 20% and 30% of people with diabetes or hypertension have albuminuria (albumin concentrations 20 milligrams per litre in morning urine or a random sample) or impaired kidney function.[14,70,73-76]

Deteriorating kidney function can be slowed or prevented by careful regulation of blood glucose levels and above all of blood pressure.[77-79] Practice guidelines issued by the Dutch College of General Practitioners (NHG) advise doctors to test kidney function annually in diabetics and people using diuretics or ACE blockers.[78] The reality is rather different, however. A national representative study showed that less than 40% of patients with diabetes and only a quarter of people with hypertension had their kidney function tested every year. And less than 25% of patients with diabetes and 10% of people with hypertension were examined for albuminuria.[80]

4.4.2 *Clinical utility of screening for macroalbuminuria*

There have been calls to population screening for hidden kidney damage.[81,82] In the autumn of 2006, the Kidney Association (Nierstichting) conducted a national campaign entitled ‘Stop Chronic Kidney Disease Early’ (*Stop beginnende nierziekte*) (www.nierstichting.nl).[83] There was widespread interest in a free ‘kidney check’ for macroalbuminuria: more than 1.1 million people (8.7% of Dutch adults) reported for a test.[81,5] The participants were sent three traditional test strips or ‘dipsticks’ with a colour chart for a semiquantitative reading. They were advised to consult their doctor if two or three test strips were positive, equivalent to a protein excretion rate in urine of more than 300 mg/l. The campaign was explicitly aimed at effective prevention of end-stage kidney failure.[83] But what do we know about the effects and costs of screening?

Ten years ago the first round of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study was conducted in Groningen. Nearly half of the city's more than 85,000 residents aged between 28 and 75 years participated in this study. Macroalbuminuria (> 300 mg per day) was observed in 0.6% of the participants. In 75% of cases their doctors were not aware of this.[84] People with macroalbuminuria are at a heightened risk of developing chronic renal insufficiency, cardiovascular diseases or ESRD.[74,85-89] According to large American and Japanese studies, the probability of ESRD was increased by 12 to 15 times in case of a strong positive result (2+ or higher).[85,87]

However, the latter does not necessarily mean that screening is likely to have a major effect at population level. This is because people with a positive result (1+ or higher) constitute only a minority of those who subsequently develop end-stage kidney failure.[85] According to the American MRFIT study (1973-1975, 13,000 middle-aged men with at a heightened risk of cardiovascular diseases, observation period of 25 years), the figure was 19%. A Japanese study with an observation period of 17 years came out at 45%.[90] These would imply that a maximum of 19% or 45% of cases of ESRD could be prevented with screening for macroalbuminuria.[85] And this on condition that the screening programme is perfect in the sense that all members of the group take part, that a positive outcome leads to a formal diagnostic process in all cases, that treatment is given whenever required, and that treatment prevents the development of ESRD in all cases.

In practice this is an impossible combination. The evaluation of the 'Stop Chronic Kidney Disease Early' campaign showed that around 25% of participants whose 'kidney check' was positive visited their doctor.[5] Treatment compliance is generally only around 50% among people being treated for risk factors or chronic conditions which have few or no symptoms, such as hypertension and osteoporosis.[91-94] These percentages may of course come out higher when campaigns are less non-committal.

No research has been published which demonstrates the efficacy of screening. What is clear, however, is that screening has disadvantages. The commonly used test strips have a low specificity, between 70% and 90%. This is also true for new dipstick tests that measure lower albumin concentrations (microalbuminuria).[73,95-97] In a population screening, this inevitably leads to a low predictive value for a positive test outcome – in other words, many false-positive results, which would mean additional burdens for the participants and the health service. Whether repetition of the test would reduce the number of false-positive results without further reducing sensitivity has not been researched in any detail.

An unpublished pilot study for the 'kidney check' showed a specificity of 85%.[81] The evaluation of the Kidney Foundation campaign showed that 20% of

the participants had a positive 'kidney check'.[5] This percentage was much higher than expected, because the prevalence of macroalbuminuria in the general population is 0.6%.

The dipsticks used in the 'kidney check' are commercially available as Medi-Test, in combination with one to ten other indicators (www.macherey-nagel.com). A model calculation yields an unfavourable cost-effectiveness ratio for dipstick screening.[98] Incidentally, cost-effectiveness only becomes attractive once actual effectiveness has been proved.

4.4.3 *Clinical utility of screening for microalbuminuria*

Could screening for microalbuminuria be effective and efficient? The 'yield' could be much higher, because microalbuminuria is much more common than macroalbuminuria (occurring in 7% and 0.6% of adults respectively), and it is also a risk indicator for cardiovascular diseases.[72,89,99-102] However, a number of important questions still remain, for instance concerning test performances of dipsticks in screening exercises. These have been studied in high-risk groups, but only fleetingly thus far in the general population. An exception is a Japanese study of more than 2,300 people; 15% of the local population over the age of 40 years.[103] How this sample group was recruited is not explained, however. In case of a positive dipstick (a trace or more), the analytical sensitivity and analytical specificity to detect macroalbuminuria was 80% and 93% respectively. For the detection of microalbuminuria *and* macroalbuminuria the sensitivity fell to 15%, while the specificity remained the same.[103]

There is no research on the use of dipsticks as do-it-yourself tests. This is quite remarkable, because there are indications that the test performances depend on the user. In one study, more than 1,000 urine samples of diabetes patients, with albumin concentrations between 20 and 200 mg/l, were examined in different settings. Micral test strips used by laboratory technicians had a sensitivity of 91% for demonstrating heightened albumin levels (> 30 mg), while in doctor's surgeries the sensitivity was 66%.[12] Since the sensitivity in these doctors' surgeries ranged from 58-81%,[4] it is unlikely that inexperienced users will achieve much above 58%. A 'pee by post' may be a better alternative. After all, a quantitative measurement of the albumin concentration in a laboratory will be more reliable than a semiquantitative test strip at home, will yield fewer false-positive results and will therefore be cheaper in the end.[95] What is more, the experiences of sending urine samples through the post are good.

Another question concerns the natural course of microalbuminuria and chronic kidney disease. Population based studies have shown that the risk of

ESRD is smaller than thought. In the Norwegian HUNT II-study, 5% of the participants above the age of 20 years suffered from impaired kidney function (GFR < 60 ml per minute per 1.73 m^2). In a median observation period of eight years, 1.2% of the patients with impaired kidney function developed ESRD. The progression probability was low in particular in cases of impaired kidney function without the presence of diabetes or hypertension.[104] Furthermore, there is not enough evidence yet that people with microalbuminuria but without diabetes or hypertension should actually be treated.

Finally, it should be borne in mind that in the case of microalbuminuria the patient is significantly more likely to die of cardiovascular diseases than of ESRD. Screening for microalbuminuria could therefore also be advantageous from the perspective of preventing cardiovascular diseases. An indication in this direction was given recently by a therapy trial among members of the general population with microalbuminuria but without diabetes or hypertension.[105,106] The outcome was not statistically significant, however. The cost-effectiveness of screening came out well in one study, but this was based on assumptions about effectiveness.[105,106] Recommendations on screening for microalbuminuria are still premature, also from the perspective of preventing cardiovascular diseases.

4.4.4 Verdict on do-it-yourself tests for albuminuria

The Committee concludes that there is much uncertainty surrounding the diagnostic value and efficiency of test strips. The efficacy of macroalbuminuria or microalbuminuria screening in the general population for the early detection and treatment of hidden kidney damage has not been demonstrated. Nor is it certain whether the use of test strips for macroalbuminuria or microalbuminuria is of added value for the prevention of cardiovascular diseases. For that reason the guidelines do not recommend such a test to assess the risk for people without diabetes or hypertension.[107]

4.5 Do-it-yourself tests for prostate cancer

Twenty years ago a blood test for prostate-specific antigen (PSA) was introduced to detect prostate cancer. Do-it-yourself variants of the PSA test have become available recently.

4.5.1 *Prostate cancer*

Prostate cancer is the most common form of cancer among men in the Netherlands, accounting for 21% of new cancer cases. Some 7,900 men were diagnosed with prostate cancer in 2003 (www.ikc.nl). Every year around 2,400 men die of this disease (www.cbs.nl). The costs of prostate cancer to the Dutch health service were estimated at EUR 92 million in 2003.[34] The natural course of prostate cancer is fitful and unpredictable. Many men grow old with it and die of something else. Others die shortly after the disease has been diagnosed. The five-year survival rate averages around 80% (www.ikcnet.nl).

PSA is a protein which is excreted by prostate cells into the blood. A heightened PSA concentration may point to prostate cancer. PSA is accepted worldwide as a tumour marker. But among older men a heightened PSA level is often symptomatic of something else, such as a benign enlargement of the prostate.

4.5.2 *Clinical utility of screening*

Screening of the general population

Can screening reduce the mortality rate of prostate cancer and the disease burden? A search of the literature revealed two completed trials, conducted in Quebec (Canada) and Nörrköping (Sweden), with a total of more than 55,500 participants.[108] A meta-analysis of the results showed that screening had no effect on prostate cancer mortality.[108] But because there were serious criticisms of the quality of the trials, this may not be the last word. A definite answer is expected from two randomised trials which are still ongoing. The Prostate, Lung, Colorectal and Ovary cancer screening (PLCO) trial conducted by the National Cancer Institute (NCI) in the United States comprises 74,000 men aged between 60 and 75 years, half of whom are offered annual screenings with the PSA test and a digital rectal examination and half of whom receive only the usual healthcare. The findings of the first screening round were published at the beginning of 2005.[109] This showed that 8% of the screened men had PSA levels of 4 ng/ml or higher, and that 7.5% had suspicious findings for prostate cancer detected with the digital rectal examination. Some 1.4% of the screened men were diagnosed with prostate cancer, usually at an early stage (83% clinically localized). It was still too early to observe an effect on mortality rates.

Also started in 1994, the European Randomised Study of Screening for Prostate Cancer (ERSPC) is being conducted in eight European countries and is coor-

dinated from Rotterdam.[110,111] The ERSPC comprises nearly 200,000 men, mostly in the 55-70 age group. The men in the experimental group are offered a PSA test every four years. If their PSA levels are 3 ng/ml or higher, they are given a referral advice. Two or three screening rounds have been completed in most centres. The researchers believe that the ERSPC is large enough to demonstrate that screening has a potential favourable effect of at least 25% on prostate cancer mortality rates.[111] In addition to the effect of screening on mortality, the trial examines the implications for quality of life in order to estimate the cost-effectiveness of screening.[112,113] The outcomes of the trial are expected in 2010 or 2011.

In short, then, it is not yet known whether screening helps, whether it is efficient and whether it has a favourable risk-benefit ratio. The disadvantageous effects, however, are known. Firstly, there is a significant risk of false-positive results. Nearly 20% of the ERSPC participants in the Netherlands have heightened PSA levels, but for only one in four of these (4.7% of all participants) the decisive test (prostate biopsy) revealed the presence of prostate cancer. This means that the PSA test had false-positive results for 15% of the participants.[114] In other words, screening leads to many unnecessary follow-up examinations.

A second disadvantage of cancer screening in general, and of screening for prostate cancer in particular, is overdiagnosis. The number of prostate cancer patients rises sharply in countries where screening is undertaken. In the Netherlands the number of new cases per year has surged by nearly 50% over the past 15 years (after adjustment for population ageing and growth). Localised prostate cancer in particular is diagnosed ever more frequently.[23] Screening advances the diagnosis ‘prostate cancer’.[115] The length of this so-called ‘lead time’ depends on age, and is just over 12 years for a man aged 55 who has taken part in a single screening. Frequent repetition of the test lengthens the lead time even more. If screening makes sense, then the American practice of screening annually is not efficient. The ERSPC study has shown that it is not necessary to screen more than once every four years.[115,116] Men with low PSA levels (< 1 ng/ml) should not have to be screened for another eight years. If screening brings forward the diagnosis but does not extend life, then the only effect is that the patient will have to live longer with the awareness that he has the disease.

Screening may have an adverse effect on the quality of life. Temporarily, because of an unfavourable result of screening and because of unintended effects of the diagnostic process. Prostate biopsy may lead to blood loss in urine or sperm or to fever, but rarely to serious complications. Because of the risk of septicaemia, the patient is given a course of antibiotics. Primary treatment for prostate cancer (operation, radiation) lead to incontinence, impotence or bowel dysfunction in a substantial number of patients.[112,117] The possibility of overtreat-

ment cannot be ignored, and rises with repeated screening. In the first and second screening rounds of the ERSPC-Rotterdam, it emerged that 32% and 43% respectively of the detected cancers were dormant (indolent or minimal cancer).[118] These will almost certainly cause no problems for 10 years. This means that there is no need for an operation or radiation treatment, and that watchful waiting will suffice. Research is ongoing on how unnecessary treatment can be prevented by distinguishing more effectively between aggressive and non-aggressive cancers. To this end a prognostic nomogram has been developed which incorporates the PSA level, the prostate volume and the total length of cancer and no-cancer tissue in biopsy cores.[119,120]

In the meantime, unorganised screening for prostate cancer is booming. In the United States, for instance, 75% of men over 50 years of age have taken tests, and 54% do so regularly.[121] A similar proliferation becomes evident in the Netherlands.[122] One in five men over the age of 40 has taken one or more tests in the past five years, and for men over 70 this figure is nearly 40%, according to a questionnaire study in 2005. This showed an increase in testing in all age groups compared to 2001 (www.cbs.nl). PSA tests and variants on them are easily available. In some towns and cities, men's clinics and even sport fitness centres and occupational health and safety departments are offering PSA screening under the auspices of 'preventive medical examination' (PMO). Screening for prostate cancer requires a licence under the WBO.

Screening with do-it-yourself tests

Recently do-it-yourself tests have also become available on the Internet, from pharmacies and in chemist chains, at prices between EUR 6.50 and EUR 20. These are semiquantitative tests for PSA in finger-prick blood. The result can be read from a test line by comparing the colour reaction with a reference line. A control line indicates whether the quantity of blood used was sufficient to ensure a proper colour reaction.

Good information on the reliability and diagnostic value of the do-it-yourself tests is either absent or unverifiable. According to the supplier of the MiraTes Prostaat (PSA) ZelfTest, the 'agreement' between this do-it-yourself-test and a reference test is more than 98% (www.mirates.nl). But this figure says very little about the test's diagnostic value. This is because any test for a disease which is relatively uncommon will have a high percentage of true-negative results and will thus seem very 'reliable'. Moreover, the supplier does not state which reference test was used. There is no information on the risk of false-positive and

false-negative results with the do-it-yourself test. The Committee has not been able to find research results on this aspect in any specialist publications.

The information on the website seems balanced at first glance (www.mirates.nl). The website lists advantages and disadvantages of taking the test. It also warns that it is not proven that early detection of prostate cancer actually reduces the mortality rate of this disease. Even so, the Committee does not consider the information to be balanced. On the one hand, the disease is made out to be more serious than it is. The suggestion that prostate cancer is only rarely diagnosed at a curable stage does not square with an actual five-year survival rate of more than 80% (www.ikcnet.nl). And on the other hand, the benefit of early detection is exaggerated. Consumers who read '98% reliable' do not expect that around 80% of the positive results will prove to be false-positives, and that this figure will probably be even higher outside the setting of a scientific study.[114] Moreover, the website recommends screening from the age of 45 or 50 upwards, but does not explain what the benefit might be. Only 1% of deaths from prostate cancer in the Netherlands occur before the patient reaches his 55th year. The recommendation on the website to repeat the test annually is disingenuous, given the lead time of around 12 years.[115] Nor is it helpful to recommend screening in the case of urination problems. These symptoms are no reason to screen for prostate cancer. One in four men of this age has urination problems. The probability of having prostate cancer is the same for men with urination problems and those without.[123]

The Cobeco Bodytest PSA test kit is available for less than EUR 16 at www.kwaliteitsapotheek.nl. The information provided on the website is minimal. It is claimed that testing makes the chances of successful treatment 'many times greater'. The word 'cancer' is not mentioned. The Kruidvat chain sells a do-it-yourself test over the counter for EUR 6.50.

4.5.3 *Verdict on do-it-yourself tests for prostate cancer*

The Committee was unable to ascertain the diagnostic value of the MiraTes Prostaat PSA ZelfTest, the Cobeco Bodytest PSA test or the Kruidvat test. Whether these products have a CE marking is not mentioned. If they test for a tumour marker, they fall under the sales channel regulation. For CE assessment purposes, tests for the tumour marker PSA are categorised as medium-risk.

The Committee feels that the information provided by suppliers on their websites does not meet the requirement of balance and adequacy. Because of the lack of information on the risk of false-positive and false-negative outcomes, the test results cannot be interpreted. The sales channel regulation cannot change any-

thing in this respect, as long as there are no results from studies with inexperienced users. The Committee takes the view that the sale of do-it-yourself tests for prostate cancer is at odds with the general 'essential requirements' of the IVD Decree, because the clinical utility of early detection of prostate cancer is not proven, so that the risk-benefit ratio and efficiency are not known either, while the diagnostic value of do-it-yourself tests cannot be ascertained.

4.6 Do-it-yourself tests for bowel cancer

For decades now there have been faecal occult blood tests (FOBTs) for bowel cancer screening. Do-it-yourself variants of these tests have become available recently.

4.6.1 Bowel cancer

Colorectal cancer (bowel cancer) was diagnosed in 10,000 people in the Netherlands in 2003 (www.ikc.nl). Some 4,700 people died of bowel cancer in 2006 (www.cbs.nl). The five-year survival rate is 50-60% (www.ikc.nl). The costs to the Dutch health service of bowel cancer were estimated at EUR 232 million in 2003.[34]

4.6.2 Clinical utility of screening

Screening of the general population

Four randomised controlled clinical trials carried out abroad has shown that bowel cancer mortality rates can be reduced by 15-20% by FOBT screening. These trials involved screening on a two-year basis, an offer which was taken up by half of the intervention group. On the basis of the screening trials in the United Kingdom and Denmark, the costs of biennial population screening were calculated at GBP 1,600 per life-year gained.[124,125]

Other screening methods, such as immunochemical FOBT variants, are more sensitive for bowel cancer and polyps. However, immunochemical tests may have a larger number of false-positive outcomes than the standard test. The feasibility studies being conducted since 2006 in the regions of Maastricht, Nijmegen, Amsterdam and Groot-Rijnmond (Greater Rotterdam) are intended to give a better indication by 2008 of (i) the feasibility of a national population screening programme for bowel cancer and (ii) the advantages and disadvantages and the

optimum limit value of OC-Sensor, an immunochemical test, compared to the standard test.

The FOBT screenings in these experimental screening trials and feasibility studies are home-collecting tests. The faecal samples are collected by the participants themselves, but the test is read in a laboratory.

Screening with do-it-yourself tests

Immunochemical FOBTs have recently become available in the Netherlands as do-it-yourself tests, at a price of EUR 11. This means that the test can be read at home. What is the diagnostic value of these do-it-yourself tests?

There is a do-it-yourself test variant of ImmoCare-C, a semiquantitative test introduced in 1996 and affixed CE marking in 2004. But as yet very few experiences have been reported with ImmoCare-C. They only concern groups of patients referred for colonoscopies. The test is used in a screening project in the Austrian state of Burgenland. At the moment only a few preliminary results have been reported in a poster presentation at a conference. The Committee was not able to find any publications on the do-it-yourself test variant. It is not clear whether this do-it-yourself test has the CE marking.The manufacturer of a second do-it-yourself test, the CE-certified MiraTes Darm (FOB) ZelfTest (price EUR 11), claims a ‘reliability’ rate of 99% in terms of demonstrating the presence of blood in the faeces (www.mirates.nl). But it is not clear here what is meant by ‘reliability’. Does it refer to the reproducibility of the do-it-yourself test? And as applied by inexperienced users? The Committee suspects that the claim is more about the ‘agreement’ with another immunochemical FOBT (which one?) as a reference test. In any event, the reported 99% says nothing about the diagnostic validity of the test.

A second problem, according to the Committee, is that the precise purpose of these do-it-yourself tests is not clear. There is no section on the website dealing with the test’s aim (www.mirates.nl). Consumers cannot ascertain whether the objective is to detect 1) ‘blood in the faeces’, 2) ‘any bowel conditions’ (those specifically mentioned are inflammations of the colon, Crohn’s disease, intestinal polyps and bowel cancer), or only 3) intestinal polyps and bowel cancer. The test objective should be clear; any doubts on this score will lead to confusion. Feasibility studies for the planned national population screening programme for bowel cancer are being conducted in Maastricht, Nijmegen, Amsterdam and Groot-Rijnmond (with FOBT screening aimed at the third objective). Another source of confusion is that the test characteristics are linked to the test’s objective. On the assumption that the test’s objective is to detect blood (the first objec-

tive), then a positive test result would be a true-positive if there is indeed blood in the faeces, regardless of the cause (bleeding gums, haemorrhoids etc). In terms of the third objective, however, a positive test result would only be a true-positive if further examination (with a colonoscopy) reveals an advanced adenoma or bowel cancer.

A third problem is that the information about the MiraTes Darm (FOB) ZelfTest is incomplete. The most important information, on the test's accuracy compared to the 'gold standard' (colonoscopy) in detecting polyps and/or bowel cancer, is absent. A test with a perfect reliability, in the usual sense of reproducibility, is worthless if the diagnostic sensitivity and diagnostic specificity are low. How high these are and the positive predictive value for someone without symptoms are not mentioned, nor can these be verified in any other way. The information does not make clear precisely what test is being used and at what limit value the test result is positive. Because the different immunochemical FOBTs vary widely in their test performances, the screening outcome cannot be interpreted. Moreover, the Committee is not aware of any research into the diagnostic value of FOBTs when used as do-it-yourself tests.

FOBT do-it-yourself tests are categorised as low risk for CE assessment purposes. They do not fall under sales channel regulation. It is true that these are tests for cancer, specifically bowel cancer, but blood or haemoglobin are not tumour markers. The Committee concludes that the assessment procedure for these do-it-yourself tests is significantly less strict, and left largely to the manufacturer rather than the WBO regime which applies to the same test used as a home-collecting test.

4.6.3 *Verdict on do-it-yourself tests for bowel cancer*

The Committee concludes that the clinical utility of FOBT screening has been demonstrated in four trials. But it could not ascertain how well the FOBTs perform as do-it-yourself tests in inexperienced hands. Because of the lack of information on the risk of false-positive and false-negative outcomes, users cannot assess the benefit of such a test and the test results cannot be interpreted. The Committee therefore takes the view that the sale of FOBT do-it-yourself tests (that is, tests other than the home-collecting tests used in the planned national screening programme for bowel cancer) is at odds with the general 'essential requirements' of the IVD Decree/Directive.

4.7 Do-it-yourself tests for coeliac disease (gluten intolerance)

To detect gluten intolerance, a number of do-it-yourself tests for antibodies against coeliac disease are available.

4.7.1 Coeliac disease

Coeliac disease or gluten-sensitive sprue is a chronic digestive disorder. The cause is an intolerance of gluten proteins found in wheat, rye, barley and possibly oats. Coeliac disease is an autoimmune disease with a significant genetic component.[126] A Dutch population-based study among people aged between 20 and 60 years showed a diagnosis of 'coeliac disease' (gluten intolerance) in 0.016%.[127] This amounts to slightly more than 2,500 patients nationwide. Much more common, however, in 0.35% of participants, was undiagnosed coeliac disease.[127] This amounts to around 55,000 patients. A corresponding 'iceberg phenomenon' is also evident in other countries.

Serological diagnosis of coeliac disease became possible with a blood test for IgA antiendomysium antibodies (EmA). Somewhat better test characteristics than EmA may be achieved with measurements of IgA antitissue transglutaminase antibodies (tTG), which have a sensitivity of around 94% and a specificity of 99%.[128,129] However, the test sensitivity declines significantly with lesser degrees of villous atrophy.[130,131] If the result of the EmA or the tTG test is positive, the recommendation is to take biopts of the small intestine in order to conduct a tissue analysis to determine the existence of coeliac disease.

4.7.2 Clinical utility of screening

Screening of the general population

Given the iceberg phenomenon, it seems likely that screening for coeliac disease makes sense. After all, if people with undetected coeliac disease have the same disease burden as those who have been diagnosed with it, then screening should offer significant added value. This is not confirmed by research, however.[132,133] Hence it is doubtful whether screening offers any health gains. Moreover, following a gluten-free diet is a serious burden. This means that there are insufficient arguments for considering screening for coeliac disease.[134]

Screening with do-it-yourself tests

Do-it-yourself tests for coeliac disease are available on the Internet for around EUR 20. They include the CoeliaTest (www.glutentest.nl) and the Gluten Allergie Test. These are immunochromatographic tests for IgA antitissue transglutaminase antibodies (tTG) in finger-prick blood, which can be read in five minutes. Good test performances have been recorded in their use as point-of-care tests among small groups of patients with symptoms who were referred for biopsies from the small intestine.[135,136] However, the Committee is not aware of any publications on the diagnostic value of these tests as do-it-yourself tests in the general population.

The information on the supplier's website is quite extensive. It claims that the test is suitable for diagnosis and family screening. The test also has CE marking. Coeliac disease is described as a hereditary disease, although no indication is given of the significance of the genetic factor. There is no information on the lack of research into the effectiveness of screening for coeliac disease and into the test performances of do-it-yourself tests in the general population.

4.7.3 Verdict on do-it-yourself tests for coeliac disease

The Committee concludes that do-it-yourself tests for coeliac disease are categorised as low-risk for CE assessment purposes, and that they do not fall under the (Dutch) sales channel regulation. It also concludes that the clinical utility of screening for coeliac disease has not been demonstrated. The Committee does not know of the test characteristics of the application by inexperienced users. It takes the view that the sale of do-it-yourself tests for coeliac disease is at odds with the general 'essential requirements' of the IVD Decree.

Chapter 5

Evaluation of tests for a tumour marker

In this chapter the Committee discusses the tests for tumour markers, in view of their special prominence in the IVD Decree/Directive. In the previous chapter we looked at a do-it-yourself test for a tumour marker (PSA) and will now examine other types of self-tests.

5.1 Background information about biomarkers

Biomarkers are characteristic aberrations fixed in DNA, RNA and proteins, which are useful when determining the risk of disease, the nature of the disease, the choice of therapy and the response to it, following the course of the disease and ascertaining the genetic basis. This involves germline-specific or tumour-specific features such as reproduction, loss or translocations of chromosomes or chromosome regions, mutations, polymorphisms or modifications of genes, and expression levels of individual genes or groups of genes as measured by their RNA or protein. Biomarkers can also be functional proteins found in an unusual concentration in body fluids such as plasma, spinal fluid or urine.[23]

Tests for biomarkers for cancer (tumour markers) can serve different purposes.[23] With respect to prevention, they can indicate the risk of developing cancer, or the risk of having it. The former involves mutations and variations in the DNA. If a hereditary form of *e.g.* breast cancer or colon cancer is suspected, a test can be done to determine whether someone is a carrier of that type of mutation, and preventive measures can be considered. Another application is HPV screening for cer-

vical cancer. Tumour markers from the second category are generally proteins. The best-known example is the prostate-specific antigen (PSA).

With respect to diagnostics and treatment, tumour markers can provide information about the nature and severity of a certain type of cancer, or about the course of the disease and the success of the treatment (monitoring). For example, a successful treatment of patients with colorectal cancer or prostate cancer leads to a decrease in the quantity of carcino-embryonic antigen (CEA) or PSA, respectively. The diagnostic value and efficiency of a biomarker test depend on the objective for its use.

Given the explosion of knowledge about biomarkers, a huge increase in the number of commercially available tests is expected in the near future.[23] This could be a beneficial development for patients who want to monitor their disease themselves. If measuring the biomarker rapidly confirms whether a certain treatment is succeeding or not, the patient is spared unnecessary treatment.[23]

Tumour markers occupy a specific place in the legislation. The tumour marker PSA is included on the B-list of Annex II of the IVD Directive. This means that do-it-yourself tests for PSA for CE assessment belong in the 'medium-risk' category. The sales channel regulation does not apply to the provision of 'services'.

5.2 Test for a biomarker for cancer

5.2.1 Cancer

In 2006 there were 40,563 deaths in the Netherlands ascribed to the diagnosis group 'neoplasms' (cancer, www.cbs.nl), 30% of the total. In 2003 around 73,000 new cases of cancer were registered, of which 37,500 were men and 35,500 women. Every year the total rises by 1.5 to 2%, primarily due to population growth and ageing of the population. If you correct for these factors, there is no evidence of an increase (www.ikcnet.nl). Deaths from cancer have declined since the 1980s, especially in men. In women the drop has stagnated, primarily due to the rising death rate from lung cancer among women.

In 2003, EUR 2.4 billion, or 4.1% of the total health care costs in the Netherlands, were devoted to the diagnosis group 'neoplasms' (www.kostenvanziekten.nl). There was an increase in expenditure of nearly 5% a year for this group in the 1994-1999 period, and almost 11% in the 1999-2003 period. The increase in expenditure was greater than average in the health care sector in both periods (4.3% and 9.6%, respectively).[137]

5.2.2 *Clinical utility of screening with the AMAS test*

Twenty-five years ago, an American couple introduced the AMAS (anti-malignin antibody serum) test. With an alleged sensitivity and specificity of 95%, people with cancer could be effectively distinguished from people without cancer.[138] The test was praised on the Internet by Dutch companies in terms of screening, diagnostics and monitoring. It was claimed that for people with complaints or symptoms which could suggest cancer (regardless of the type), no further testing was necessary if the result of the AMAS test remained under 135 microgram per millilitre (www.kanker-aktueel.nl). The test (USD 135) entailed sending a serum sample to the inventors' laboratory in Boston, USA.

In 1991 they reported that trials were being conducted in the UK and elsewhere to assess the value of the AMAS test for the early detection of breast cancer, lung cancer and ovarian cancer.[138] Their outcomes have never been published in scientific journals. Hardly any publications have appeared that scientifically support the other claims. They concern mostly women referred for biopsy due to the suspicion of breast cancer.[139,140] The researchers concluded that the AMAS test is not sensitive enough to spare women from undergoing a biopsy if there are symptoms of breast cancer, and in addition there were too many false-positive outcomes to be useful for screening.[139] The specificity was around 65%.[139,140] This corresponds to 99 of every 100 positive outcomes being false-positive with AMAS screening, given the relatively small risk of breast cancer in women over the age of 50 in the general population (around 5 per 1,000).[141] How sensitive the test is for cancer in the general population has not been explored.

5.2.3 *Verdict on the AMAS test*

The Committee concludes that the claimed performance of the AMAS test for screening for cancer is unsupported. This street-corner test is categorised as 'low-risk' for CE assessment, so long as the test, or tests for cancer, is not registered on the A- or B-lists of the IVD Directive. The AMAS test is not a do-it-yourself test and does not fall under the sales channel regulation. Whether the AMAS test has CE marking cannot be ascertained from the Internet. Offering this test for screening purposes is forbidden without WBO approval.

5.3 Tests for biomarkers for cervical cancer

Up to now, screening for cervical cancer has been based on morphological examination of cells (cytology) in a smear from the cervix. Recently, tests for tumour markers have become available: DNA of the high-risk types of the human papilloma virus (hrHPV).

5.3.1 Cervical cancer

Each year, around 600 women are diagnosed with cervical cancer in the Netherlands, and about 200 women die from this disease (www.ikc.nl, www.cbs.nl). In this respect, the Netherlands has a favourable position within Europe.[142] The estimated costs to the Dutch health service due to cervical cancer in 2003 were EUR 52 million.[34] The death rate from cervical cancer has been declining in the Netherlands since 1962.[143] This decline amounts to 60%, at least half of which can be ascribed to screening.[144] Since 1996, women between the ages of 30 and 60 years have been invited to participate in the population screening for cervical cancer every five years.

5.3.2 Clinical utility of cytological screening

Nowhere has the efficacy of screening for cervical cancer been examined with randomised controlled trials. The decision-making is based on observational research (case-control studies, cohort studies, research into the occurrence of cervical cancer after a negative smear result, research into the cytological prior history of women with this disease or who have died of it) and modelling. There is very convincing evidence in support of the effectiveness of screening for cervical cancer.[143,145-152] Death due to cervical cancer is usually (in about 60%) associated with non-participation in screening and much less with a false-negative screening result.[153-157] Conventional (cytological) screening is not successful in detecting a certain type of cervical cancer, adenocarcinoma.[151]

5.3.3 Clinical utility of screening for human papilloma virus

DNA of a high-risk type of the human papilloma virus (hrHPV) is almost always demonstrable in cervical cancer and often also in CIN.[158] HrHPV is considered an essential but not sufficient cause of cervical cancer.[159] Most young people become infected with HPV at some point. Usually, the infection does not lead to cellular

aberrations, and the immune system removes the virus. In 96 to 98% of women over 30, hrHPV is no longer evident.[160,161] Sometimes the virus persists. The associated risk of tissue aberrations (CIN) is great.[162] But even most aberrations disappear spontaneously. It usually takes at least 15 years before an infection transforms into cancer.[159]

Screening of the general population

A great deal of research is being done into the efficacy of hrHPV testing for triage or primary screening.[163,164,165] In 1998 a randomised screening trial involving 44,000 women was started in the Neteherlands. The second round of this POBASCAM (Population Based Screening Amsterdam) trial will be concluded shortly.[163] In 2008, the Health Council of the Netherlands will present separate recommendations about the new developments in the screening and about possible inclusion of HPV vaccination in the national vaccination programme.

Screening non-responders

One important problem is reaching the target group.[157] In 2003, 66% of the general population participated in the screenings. This means that a total of 77% of the target population (79 % in 2006) is reached once every five years (including opportunistic screening).[166] The participation is lower among non-Western immigrant women, women under the age of 40 and women in urban areas or those with a low social-economic status, while some of these groups (such as women born in Surinam or Morocco) actually have an increased risk of cervical cancer.[167,168]

In the national screening programme, women in the target group are invited either by a GGD (Municipal Health Service) or by their own GP. In the latter case, the participation is 8 to 13% higher than when invited by the GGD. This difference can be as high as 20% if the GP sends a reminder to women who have not yet responded to the initial invitation.[169] The effect of an invitation by the person's GP on the level of participation is greater than average in subgroups with a poor response rate, especially non-Western women who also belong to another subgroup.[170]

The government memorandum entitled *Langer gezond leven (Live a longer, healthy life)* aims to increase the participation in the organized screening programme to 75%.[171] Especially high-risk women are difficult to reach. Alternatives to the usual letter of invitation, such as phoning or a publicity campaign, generally have little effect.[172,173] Preparing personal invitations that address the

motives for not participating (computer tailoring) work no better than the standard approach. Sending material in a reply envelope so that women can conduct their own vaginal smear will not help if the smear has to be analysed in the normal way (cytologically). This form of test allows many aberrations to slip through.

Success is expected from self-sampling if the sample obtained can be tested for hrHPV. The (relative) sensitivity of an hrHPV home test is equivalent to that of an hrHPV test on material collected by a physician, and at least as good as a conventional cervical smear.[174-178] In addition, a home test could be a welcome alternative for a speculum examination.[174,175,179,180]

In 2006, a trial with the home test was conducted in North-Holland and Flevoland among 44,500 women who had not responded earlier to an invitation to participate in the screening programme.[181] A preliminary study revealed that 34% had used the home test.[176,182] It also emerged that they belonged to the group at risk. Almost three times as much high-grade CIN was found as among regular participants in the screening programme.

5.3.4 Verdict on the HPV home test

If these findings are confirmed in the main study, nationwide implementation of home-collecting testing for non-responders would significantly improve the effectiveness and efficiency of the screening programme. There are various home-collecting tests for hrHPV with CE marking. Offering this screening service requires authorisation, because the test is aimed at cancer. At the start of 2008, the Health Council of the Netherlands will make separate recommendations about the new developments in the screening for cervical cancer and about possible incorporation of HPV vaccination in the national vaccination programme.

5.4 Tests for new biomarkers for prostate cancer

5.4.1 Prostate cancer

Information about prostate cancer can be found in Chapter 4 section 4.5.1.

5.4.2 Clinical utility of screening

If an increased PSA value is found when screening for prostate cancer, prostate biopsies (sextant biopsy) are taken to ascertain whether or not cancer is present. Due to the low specificity of the PSA test, three out of four prostate biopsies, an uncomfortable intervention, are shown in hindsight to have been unnecessary.[114,119] A second

limitation of PSA as a tumour marker is that it cannot be used to distinguish tumours that remain latent from tumours with a biologically aggressive nature.

A great deal of research is being done with other blood tests for proteins to improve this situation.[183] However, the specificity of these tests is not high either. In the past few years markers at the DNA and RNA level have appeared. One promising candidate is marker PCA3, a prostate cancer-specific gene which was discovered by the Nijmegen/American research group.[184,185] PCA3 levels are strongly increased in prostate cancer cells and the gene is overexpressed in more than 95 % of prostate tumours. PCA3 messenger RNA (mRNA) is not or rarely overexpressed in normal prostate tissue and tissue of a benign prostate enlargement.

PCA3 does not code for a protein. It is thus not possible to develop a protein-antibody test for it. A urine test is available for determining the quantity of mRNA copies of PCA3. The PCA3 score is measured in the first urine excreted after a light prostate massage (digital rectal examination). Research in men being considered for a prostate biopsy due to a raised PSA value showed that they perform better on the PCA3 score than the PSA test.[184,186-188] Nothing has yet been written about the value of the PCA3 score as a screening test. In August 2007 the Minister authorised a scientific study into this, linked to the ERSPC.[189]

5.4.3 Verdict on testing for new biomarkers for prostate cancer

The Committee concludes that, aside from the PSA test, no new biomarker test for prostate cancer is available as a home-collecting test. The PCA3 test is still undergoing trials, has CE marking and is available as the Progensa PCA3 test.

5.5 Tests for biomarkers for bladder cancer

5.5.1 Bladder cancer

Information about bladder cancer can be found in 4.3.1.

5.5.2 Clinical utility of screening

A great deal of research is being done concerning genes involved in the development and the course of progress of bladder cancer. The ability to demonstrate markers in urine is important because this method is non-invasive and could be used in the creation of a screening option.[23]

Various tumour markers are found in the urine of bladder cancer patients. The Minister of Health, Welfare and Sport has recently authorised a screening

trial in the Rotterdam region.[190] A total of 22,500 men aged between 50 and 75 years are being invited to take part in this trial. Participants are required to conduct a dip-stick test for 14 days to look for blood in the urine. A positive outcome will lead to tests for tumour markers. If one of these further tests is positive, cystoscopy will be performed (exploratory examination of the bladder) to determine whether bladder cancer is really present. Using the outcome of cystocopy as the golden standard, the properties of the tumour markers will be determined.

5.5.3 *Verdict on tests for biomarkers for bladder cancer*

The Committee concludes that biomarker tests for bladder cancer are still being developed and not available as a self-test.

5.6 Tests for biomarkers for breast cancer

5.6.1 *Breast cancer*

Breast cancer is the commonest tumour in women in the Netherlands. One in three new cases of cancer is breast cancer. In 2003 this corresponded to 11,700 women (www.ikcnet.nl). About 3,350 women die from this disease each year (www.cbs.nl). The costs to the Dutch health service for breast cancer in 2003 were estimated at EUR 199 million.[34] Women aged between 50 and 75 years are invited every two years for the screening programme for breast cancer. The cost of this screening programme amounted to EUR 42 million in 2005.

Genetic research is advancing rapidly. In the past few months alone, 22 new breast cancer genes were found.[191,192] Nonetheless, it is not expected that the genetic screening will change greatly as a result in the near future. The five genes published in *Nature* are polymorphisms, each of which slightly increases the risk of developing breast cancer, while little is known about their mutual interactions. The 17 other genes are spontaneous mutations which cannot be inherited. Biomarkers are already being used in clinical genetics (especially BRCA1 and BRCA2), diagnostics (gene expression profiles, in research) and treatment of breast cancer (ESR1, PR, ErbB-2).[23]

During follow-up examinations of women treated for breast cancer, CA 15-3 and sometimes other markers (CEA, CA 125) are used for monitoring tumour growth and the effect of treatment. The efficiency of routine use of these tumour markers is still unclear. It has not been shown that the detection of metastases with a test for CA 15-3 increases the survival rate. Use of the test is thus not recommended.[193,194]

If CA 15-3 is determined in new patients with breast cancer before they undergo surgery, the result is positive in 15 to 30% of cases.[195,196] The sensitivity seems especially low in patients with early-stage breast cancer and only increases once the tumour has grown and metastasised.[196] It is clear that a test which is unsuitable for the diagnosis of breast cancer is equally unsuited for self-diagnosis.

5.6.2 *Clinical utility of screening*

Some companies offer preventive examination into CA 15-3 as a street-corner test (www.vandervlugthealth.nl, www.medicontrol.nl). Are there any arguments in favour of this? If a test has a sensitivity of 15 to 30 % in women already diagnosed with breast cancer after experiencing symptoms, it follows due to differences in the clinical spectrum of the disease that the sensitivity will be even lower when applied as a screening test in the general population. This means that most patients with breast cancer would be missed, and in particular those with early disease at a more tractable stage. In addition, the test may give a positive result with certain benign diseases (especially hepatic diseases) and in 5% of healthy people.[193] Assuming a specificity of 95% and a sensitivity of 20%, it can be calculated that 98 of the 100 positive results would be false-positive.

5.6.3 *Verdict on tests for biomarkers for breast cancer*

The Committee feels that offering tests for CA 15-3 for the early detection of breast cancer conflicts with the general ‘essential requirements’ of the IVD Decree, given its poor diagnostic value and the unproven effectiveness of screening for breast cancer with a test for CA 15-3.

The Committee was unable to ascertain whether street-corner tests for CA 15-3 have a CE marking. These tests are categorised as ‘low-risk’ for the CE assessment. Although a tumour marker is involved, they are categorised as street-corner tests (and thus a service) so they do not fall under the sales channel regulation. Because the test targets cancer (breast cancer), providing it without authorisation is forbidden by the WBO.

5.7 Tests for biomarkers for bowel cancer

5.7.1 *Bowel cancer*

Information about bowel cancer can be found in Chapter 4 section 4.6.1.

5.7.2 Clinical utility of screening

For bowel cancer, biomarkers are used in clinical genetics (MSI, MMR-proteins, APC), diagnostics and the monitoring of the effect of treatment (CEA). Except in connection with trials, no use is made of markers in the treatment of people with bowel cancer.[23]

Considerable scientific research is being done to find reliable biomarkers to develop a screening test.[197] Aside from DNA tests on faeces samples, there are also stool and blood tests searching for proteins (CEA, CA 19- 9, MCSF, TATI). These simple tests are not suitable for screening for bowel cancer. For example, CEA (*carcinoembryonic antigen)* has been known for 35 years.[198] Nonetheless, such tests are offered on the Internet (www.vandervlugthealth.nl) as part of preventive health examinations. The price of individual tests is not listed on the website.

Developments in microarray technology ('biochips'), mass spectroscopy and bioinformatics enable large numbers of proteins to be measured precisely and identified directly at the same time. Their application can define protein profiles in blood or stool samples that are specific for bowel cancer and advanced (high-risk) adenoma. These patterns can be used to identify new candidate genes and explore their utility as a marker. Another possibility is to test the protein profiles for their utility as a marker.[199]

A home-collecting test for bowel cancer can already be bought on the Internet. The PreGen-Plus, available for USD 575, targets 23 markers in stool samples (www.dnadirect.com). It is claimed that the test is a more effective screening method than FOBT screening.

5.7.3 Verdict on tests for biomarkers for bowel cancer

The Committee could not find any support for this claim for the PreGen-Plus. Nor has it found any useful, well studied biomarker tests for bowel cancer screening.[119]

Chapter 6

Evaluation of genetic self-tests

In this chapter we examine genetic tests for susceptibility to specific diseases. Two types of genetic tests are first distinguished and the latest developments are described. Five self-tests are then considered.

6.1 Background information about genetic tests

6.1.1 Types of genetic tests

Presymptomatic diagnostics

Genetic tests can be directed at determining the existence of a hereditary condition or genetic predisposition for a certain condition, predicting the course of the disease, or estimating the sensitivity of the disease to medical treatment. The last two objectives will not be dealt with here. Determining the existence of a hereditary condition before any signs develop is called presymptomatic diagnostics. This examination informs members of a high-risk family who have the mutation in question that the chance is great that they will develop the condition later in life. For example, carriers of BRCA mutations have a 45 to 65% risk of developing breast cancer and a 10 to 40% of ovarian cancer.[200] This concerns monogenic, Mendelian-inherited diseases with extensive penetrance. Other examples include Huntington's disease and certain inherited forms of bowel cancer (FAP, HNPCC).

Self-tests are not feasible for these diseases and are not necessary in the Netherlands. The essential knowledge about the mutation in the family is only available to family members with the patient's permission and in a clinical-genetics centre or its associated Outpatients' Department for hereditary cancers.

Susceptibility tests

Presymptomatic diagnostics can thus assist families at risk to take sensible measures. It provides important information, for relatives as well. In such conditions, the genotype can be synonymous with the diagnosis. However, the case is different with susceptibility tests.[244] Susceptibility tests concentrate on inherited genetic variants that increase susceptibility to common diseases, such as cancer, type-2 diabetes, osteoporosis, cardiovascular diseases and congenital abnormalities such as spina bifida. The development of these multifactorial disorders involves various genetic factors. In addition, environmental factors influence the concerned genetic variations. The thus-far rarely reproducible findings from association studies have such a slight effect on the risk of developing the disease that they are useless for counselling purposes.

6.1.2 Limitations of susceptibility tests

The development of new technologies to rapidly obtain information about a range of characteristics from large groups of people is racing forward. The unravelling of multifactorial disorders, however, is still in its infancy. A first problem is statistical in nature. Increasingly larger studies are needed to rule out false positive results, because certain interactions between commonly occurring gene variants in the common epidemic diseases (that are thus are also common in the control group) are usually involved. The influence of genetic factors is generally overestimated. Quite often, large replication studies reveal that the risk of developing a disease is considerably smaller than was assumed based on the easily available research on a small scale. For example, 85 variants of 70 genes that had previously been reported to be associated with the predisposition for a cardiac infarct or another disease of the coronary arteries were examined in a large validation study. This association could not be confirmed for even one of the gene variants.[201] Of greatest concern is the fact that at least six of these markers are being offered as clinical tests to assess risk of cardiovascular disease.[243] An additional difficulty is that an association that has been determined in a certain ethnic group may not be found in another ethnic group. Nearly all gene-disease associations have been found in people of European origin.

A second problem with susceptibility tests is the occurrence of pleiotropy: the condition in which a gene has more than one expression. Susceptibility genes are often associated with an increased risk of developing various diseases. However, they can also have opposing effects, increasing the risk for one disorder and decreasing the risk for another. As a result, preventive treatment meant to reduce the risk for disease A may increase the risk for disease B.

A third point is that a positive outcome can be explained as an unavoidable fate. Even in the recent prevention memo from the Ministry of Health, Welfare and Sport, *Kiezen voor gezond leven* (Choose a healthy life*)*, genetic predisposition is presented as something you are powerless to change (www.minvws.nl/images/preventienota). Due to the often exaggerated focus on 'heredity' and lack of knowledge about genetics, the risk of developing a disease can easily be overestimated by forgetting the role of untested (and perhaps not yet even understood) genetic factors and the contribution of environmental factors.

Finally, a negative test result can give the person a feeling of having a free rein to keep on with an unhealthy lifestyle, as if directives concerning a healthy diet and recommendations concerning not smoking apply only to people with the wrong genes.

The question of which susceptibility tests can usefully contribute to predictive medicine still requires considerable scientific research. Although major scientific progress has been made, clinical applications are still mostly unclear. The main impact of the new markers will probably be from the insights provided into disease mechanisms.[244] Given the limited knowledge available, susceptibility tests are unlikely to meet the requirement that a test be informative and clinically useful.

6.1.3 *Recent applications*

In the meantime, genetic screening options continue to grow. One recent example, but not from the self-test field, is the expansion of neonatal screening (the heel prick test of newborn children). Although there will not be many other useful applications for genetic screening in the near future, there is a proliferation of genetic tests in the USA, available for USD 100 to USD 500 per test or more than USD 1,000 for test combinations (www.redorbit.com). Many self-tests are put on the market when only one or two genetic risk factors, which hardly affect the risk of developing the disease, are known. For example, there is a diabetes test on sale for USD 300 (deCODE T2™, www.dnadirect.com) that focuses on only one of the many relevant factors.[202] The thousand-dollar genome has also made its appearance. The Icelandic company Decode Genetics recently announced a test, called deCO-

DEme, which examines your entire genome after receipt of a saliva sample and USD 985.

There is little oversight at the federal level, despite warnings from government agencies such as the Food and Drug Administration, the Centers for Disease Control and Prevention, and the Federal Trade Commission, a consumers' watchdog against unfair commercial practices (www.ftc.gov).[203] The US Government Accountability Office conducted a random sampling of genetic tests marketed on the Internet and concluded that the companies involved were misleading consumers and could not substantiate their claims.[204] Half of the American states allow direct-to-consumer (DTC) genetic testing. The intervention of a caregiver is required in some states, although this is often not an independent physician but one working for the supplier of the tests.

Since 2005, genetic tests have been marketed via Internet in the Netherlands (www.mijnapotheek.nl, www.veilabs.nl, www.quaok.nl). One company wants to give consumers the possibility to predict their risk of developing a severe disease based on their DNA profile (www.geneticom.nl). This offer is accompanied by rousing advertising texts such as, "Cardiovascular diseases, diabetes, cancer and other dreaded diseases develop in one person and not in another. ... But the predisposition for many known and dreaded diseases has been determined by DNA research. ... Lifestyle, eating fat, smoking are involved, but the 'susceptibility' to the development of diseases lies in our genes. ... It is difficult to imagine a more effective basis for prevention. ... Now you can take control of your right to early prevention".

Elsewhere you can pay EUR 335 to have a cheek swab sample, obtained with a cotton bud, examined and receive recommendations on the results (www.mijnapotheek.nl). The assortment includes home-collecting tests for genetic predisposition to coeliac disease (gluten intolerance), lactose intolerance, thrombosis and osteoporosis (bone demineralisation). In the near future, it is said there will be tests for the predisposition to high blood pressure, Crohn's disease (regional enteritis) and dyslexia.

For people over 40 years old who are not sleeping well or seem less interested in sex, there is an 'effective' anti-aging medication containing dehydroepiandrosterone (DHEA), if you are willing to provide a blood sample for a DNA test. This 'extremely complex' research takes place in a specialised laboratory in Vienna (Genosense Diagnostics, TUV-certified, ISO 9001-2000 certificate, CE marking not known) and takes three months (www.quaok.nl). The result of the test is a lifestyle recommendation.

For nutritional advice, consumers can order a test kit for about EUR 200 that they can use to carry out a cheek swab at home (www.mycellf.com). The com-

pany claims to be able to give a 'personal' recommendation for a healthy diet based on any aberrations in 19 genes.

By examining previous meta-analyses and HuGe reviews, Janssens *et al.* assessed the scientific evidence for the usefulness of commercially available genomic profiles. They identified seven companies that offer predictive genomic profiling. The seven companies tested at least 69 different polymorphisms in 56 genes. Of the 56 genes tested, 24 (43%) were not reviewed in meta-analyses. For the remaining 32 genes, they found 260 meta-analyses that examined 160 unique polymorphism-disease associations, of which only 60 (38%) were found to be statistically significant. Even the 60 significant associations were generally modest. Furthermore, genes in cardiogenomic profiles were more frequently associated with noncardivascular diseases than with cardivascular diseases, and though two of the five genes of the osteogenomic profiles did show significant associations with diseases, the associations were not with bone diseases. Their conclusion was that there is unsufficient scientific evidence to conclude that genomic profiles are useful in measuring risk for common diseases or in developing personilized diet and lifestyle recommendations for disease prevention.[242]

Providing genetic tests counts as screening within the meaning of the WBO, but is not subject to authorisation under current legislation. They are, for the CE evaluation, 'low-risk' tests (Table 1). Because is it a home-collecting test, a genetic self-test does not fall under the sales channel regulation of the IVD Decree, as this Decree covers only products.

6.2 Tests for genetic predisposition to coeliac disease

6.2.1 Coeliac disease

Information about coeliac disease can be found in Chapter 4 section 4.7.1.

6.2.2 Clinical utility of screening

Do-it-yourself tests for coeliac disease were discussed in 4.7. There is now a home-collecting test of the genetic predisposition to coeliac disease (www.mijnapotheek.nl).[1] This does not even involve blood sampling. For EUR 335 you are sent coded test material, and you can have a cheek swab sample examined in a laboratory in Germany. The supplier receives the coded test results from the laboratory after one or two weeks and forwards this to a (Dutch) physician, who contacts the client to discuss the result. A contract is entered into for the testing.

People with the HLA-DQ2 or -DQ8 gene should have ‘a high risk’ of developing coeliac disease. According to research in European countries such as Norway, Italy and Spain, a large proportion (around 30 %) of the general population has one of the genes but only a fraction develops coeliac disease.[205-208] It is estimated there are 55,000 people with coeliac disease in the Netherlands, this includes undiagnosed cases.[127] This means that 99 out of 100 people with the genetic predisposition do not develop the disease. The question is, what should people do with a positive, uninformative result?

Is a negative test result of value for excluding the presence of the disease? That may be possible in certain cases of doubt. [209,210] However, hard facts about the predictive value are lacking. The research into disease genes is still going on. English and Dutch researchers recently identified a new region of genes on chromosome 4 that could cause coeliac disease.[211]

6.2.3 Verdict on tests for genetic predisposition to coeliac disease

The Committee concludes that a self-test of genetic predisposition is premature.[1] Research has not yet revealed whether the test could be valuable for certain groups at risk, as the supplier claims. The test does not have CE marking. The test is a population screening within the meaning of the WBO, but it does not require authorisation.

6.3 Tests for genetic predisposition to lactose intolerance

6.3.1 Lactose intolerance

Lactose is a milk sugar that is digested in the small intestine. The enzyme lactase splits lactose into glucose and galactose. If too little lactase is produced, lactose arrives in the large intestine, where it is broken down by bacteria. This process produces gasses (carbon dioxide, hydrogen and methane) that can lead to the development of symptoms such as flatulence, cramp, pain, diarrhoea.

Newborn children have a high lactase activity and can absorb large quantities of lactose. The ability to produce lactase decreases in most children around the world as they grow older. This is then considered a lactase deficiency (adult-onset hypolactasia, lactase nonpersistence), unfortunate terms for a normal process. People with lactase deficiency can suffer from lactose intolerance when consuming excessive amounts of milk or other dairy products. Some people retain the ability to continue producing lactase. Especially in northwest Europe, this is the normal

state.[212-214] It is ascribed to an autosomal-dominantly transmitted mutation that prevents the normal age-related reduction in lactase activity.

6.3.2 *Screening for lactose intolerance*

A home-collecting test of the genetic predisposition to lactose intolerance recently became available (www.mijnapotheek.nl).[1] For EUR 335 you receive a coded test kit and have a cheek swab sample you collect yourself examined in a laboratory in Germany. The recent identification of two polymorphisms (C/T_{13910} and G/A_{22018}) associated with the persistence of lactase or its decline has enabled the development of these tests. People with the CC or GG genotype have a genetic predisposition to lactose intolerance, and people with another genotype do not.[213]

The test features are excellent according to studies using the lactase activity in small-intestine biopsies and the sucrase:lactase activity ratio as golden standards.[213,215,216] This research was, however, limited to small numbers of patients with abdominal symptoms who had been referred for further diagnosis. This does not give a definitive answer about the test's performance in the general population and provides no more information about the risk run by people with a genetic predisposition to lactose intolerance who suffer symptoms as a result. Epidemiological research on a large scale with people from different backgrounds is needed to determine its utility as a screening test or self-test.

In northwest Europe, 6 to 20 % lactase deficiency is found.[66,212,214] At least equally large is the percentage of people with vague abdominal symptoms.[217,218] Does it make sense to use a test for genetic predisposition to lactose intolerance? What should the tested person do with the result? The signs of lactose intolerance are aspecific and occur even if there is no lactose intolerance. Various studies have shown that the suspected diagnosis of 'lactose intolerance' must be rejected for more than half of the patients.[212,219,220] This will occur more often with home diagnosis. On the other hand, many people with lactase deficiency are not affected by the moderate consumption of dairy products or can develop some tolerance.[219,221-223]

A potential benefit of a test of genetic predisposition is that a negative test result excludes a genetic predisposition to lactose intolerance as the cause of aspecific symptoms. The utility of this depends on the need for such a test (low), the costs of the test (high) and the properties of the test (unknown). The need is limited because the diagnosis is easily made, and there are already sensitive diagnostic tests available that are rarely used in practice.[224] A disadvantage could be that a negative test result may lead to the symptoms not being taken seriously and no physician being consulted, even though the symptoms could be concealing a

treatable disorder, such as coeliac disease or Crohn's disease. In addition, aside from people with a CC or GG genotype, heterozygotes (CT/GA) could also have severe lactose intolerance. The disorder also occurs in TT/AA families.[225] This shows that other hereditary factors are involved along with the two known polymorphisms.

What should be done if the test gives a positive result for aspecific symptoms? Can we then conclusively assume that the symptoms are actually due to the genetic predisposition? As both aspecific abdominal signs and a genetic predisposition to lactose intolerance occur relatively often, the symptoms can easily be incorrectly ascribed to genetic predisposition. This could lead to another, severer disorder that is causing the symptoms being overlooked or diagnosed late. A second disadvantage is that milk and other dairy products have to be avoided, leading to a shortage of calcium and to osteoporosis.[226] This disadvantage can also occur when an asymptomatic person is tested and appears to have a predisposition to lactose intolerance.

6.3.3 Verdict on tests for genetic predisposition to lactose intolerance

The Committee concludes that a DNA test for lactose intolerance could be of benefit for clinics. It is not yet known whether the test is also suitable as a self-test. Little is known about the test's performance and about the penetrance of a predisposition to lactose intolerance in the general population. No research has been done into the clinical utility and efficiency of the active detection of people with a genetic predisposition to lactose intolerance. The test marketed on the Internet does not have a CE marking.

6.4 Tests for hereditary predisposition to thrombosis

6.4.1 Thrombosis

Information about thrombosis can be found in Chapter 4 section 4.2.1.

6.4.2 Clinical utility of screening

Factor V is a protein involved in the activation of blood clotting. Factor V Leiden (FVL) is produced by a mutation in the factor V gene. FVL is the most commonly occurring genetic risk factor for venous thrombosis. About 5 % of the Western population is a carrier of this autosomally transmitted mutation, while 1 in 5,000 people is homozygous for FVL (this is less than expected due to foetal mortality). It

is mostly homozygous carriers who have a considerably increased risk of developing thrombosis and, when pregnant, of spontaneous miscarriage or growth retardation of the unborn child.[227] Heterozygotes have a 5- to 8-fold greater risk of venous thrombosis. FVL is involved in 20 to 50 % of cases of thrombosis.[228]

There is a home-collecting test available, the Trombo Check genetic test (EUR 335). This focuses on FVL and other thrombophilic aberrations, such as the prothrombin G202 10A mutation (www.mijnapotheek.nl). Carriers of the latter mutation run a threefold elevation in the risk of thrombosis.[229] Does the use of the self-test make sense?Screening of the general population is not being considered. The chance of developing thrombosis is relatively increased for a heterozygote, but the risk remains small in absolute terms.[228] Nine of ten carriers never suffer thrombosis.

Does it make sense, therefore, to test groups at risk, for example because of a family history or because someone has to undergo an operation? No, it makes no sense even here. The risk of developing thrombosis does not depend solely on genetic factors. There are also triggering factors to consider, such as an operation or pregnancy. A pregnancy proceeds normally in most women.[230] In addition, even if there are triggering factors such as operations, the policy would not change if thrombophilia becomes evident. Testing is superfluous.

Does it make sense to test women who want to take the contraceptive pill? If they are found to have a predisposition to thrombosis, they could reduce the risk of developing thrombosis by not taking the pill. Thrombosis occurs very rarely, however, in young women. Many women would have to be tested, and many women would have to refrain from taking the pill to prevent just one death from pulmonary embolism.[231] In addition, the chance of pregnancy increases, which in itself increases the risk of thrombosis and embolism.[227]

Is a self-test useful for patients who have suffered deep venous thrombosis or pulmonary embolism? Carriers of FVL have a definitely increased chance of recurring thrombosis.[232] According to the new CBO consensus, *Behandeling diepe veneuze trombose en embolie* (Treatment of deep venous thrombosis and embolism), even testing after the first thrombosis has taken place is unnecessary because the treatment does not depend on the test outcome (www.cbo.nl).

6.4.3 *Verdict on tests for genetic predisposition to thrombosis*

The Committee concludes that there are no arguments in favour of providing self-tests for hereditary predisposition to thrombosis. The self-test cited above has no CE marking.

6.5 Tests for genetic predisposition to osteoporosis

6.5.1 Osteoporotic fractures

Osteoporosis is a skeletal disorder characterised by a low bone mass and a deterioration of the micro-architecture, leading to an increased risk of bone breaks. Annually, around 84,000 people aged over 55 years break a bone (hip, vertebra and wrist) as a result of osteoporosis.[233] This problem will only increase with the aging of the population. The risk of dying in the year following a hip fracture is considerably larger than for peers without a hip fracture. The annual treatment costs connected with osteoporotic fractures amount to EUR 500 million.

The guideline states that when someone consults a physician and is found to belong to a high-risk group (persons with one or more vertebral fractures, women over 50 years old with a fracture), testing for osteoporosis must be considered.[233,234] This testing can include a bone density measurement (DXA, QCT).

Despite the availability of effective therapy, it has not yet been possible to reduce the number of osteoporotic fractures in the population. A significant obstacle is the unpredictability of the risk of a fracture. A bone density measurement has a low sensitivity, of the order of 50 %. The weakest link is compliance. This is not high in the short term, and the treatment has to be continued for 5 years. Within a year the compliance is low in half the cases. After two to three years it has reached 75 %.[91-93] The compliance of self-testers could be better, but this possibility has not been explored.

6.5.2 Clinical utility of screening

Screening of the general population

Screening for osteoporosis is not recommended.[233,234] No experiments have been done to assess the efficacy and appropriateness of screening (and preventive treatment with hormonal supplement therapy, bisphosphonates or other medication) of the general population or groups at risk. Hormonal supplement therapy was discredited in mid-2002 as long-term use increased the risk of breast cancer, cardiovascular disease and thrombosis.[235] There are few data about the use of bisphosphonates in the middle term. It is recommended not to prescribe bisphosphonates for longer than 5 years.[233,234] This seems to be long enough in most cases, although it is not known whether this applies to women in high-risk groups as well.[236]

Can screening for a predisposition to osteoporosis be recommended? Tests of the genetic predisposition to osteoporosis are available via the Internet. For EUR 335 you can receive a test kit, take a cheek swab sample with a cotton bud, return it in a test tube after drying, and have it tested in a laboratory in Germany. The samples are coded before mailing. The Internet pharmacist receives the coded results and forwards this to a (Dutch) physician, who communicates the results to the client and gives advice.

The test focuses on four factors (collagen, r-calcitonin, r-vitamin D3, r-oestrogen) and should be chiefly useful (according to the supplier) for menopausal women, when osteoporosis is suspected, and for family members of already known osteoporosis patients. Scientific research into the meaning of these factors for the risk of osteoporotic fractures has not revealed a clear picture.[237-239] The University of Edinburgh has just started a study of the general population and certain families to improve their insight into the hereditary factors involved in the development of osteoporosis. The information provided by the supplier on the Internet makes it seem that the genetic predisposition to osteoporosis is mostly understood. The supplier emphasises that a negative test result 'almost certainly excludes' osteoporosis.

6.5.3 Verdict on tests for genetic predisposition to osteoporosis

The Committee finds that the claims about the diagnostic value and the clinical utility of testing of the genetic predisposition to osteoporosis are not supported. The test has no CE marking.

6.6 Genetic predisposition to hypertension

6.6.1 Cardiovascular diseases

Blood pressure, smoking and cholesterol level are (along with hereditary predisposition [first-grade relatives with cardiovascular disease before the age of 60], age and gender) the classic risk factors for developing cardiovascular diseases.

In 2006 almost 42,000 people died in this disease category (www.cbs.nl). This is 32 % of all deaths in the Netherlands. The costs of cardiovascular diseases in the Netherlands were estimated at EUR 5.3 billion in 2003.[34] Among members of the Dutch population aged 20 to 60 years, around one-fifth suffers from hypertension (140/90 mm Hg or higher).

6.6.2 *Tests for genetic predisposition to hypertension*

An Internet pharmacist announced that a test of the genetic predisposition for hypertension was about to be added to his arsenal. This will only be useful if the test provides added value. However, no research has been performed into whether a test of the genetic predisposition (together with the classic risk factors) will improve the risk profile and prevention of cardiovascular diseases. It is also unknown whether people who know that they have a genetic predisposition can adhere better to lifestyle recommendations. The question is how people deal with the knowledge about hereditary predisposition. Such knowledge can also have negative consequences. On the one hand, it is easy to exaggerate the importance of a hereditary predisposition, and 'predisposition' can be considered inevitable. On the other hand, a favourable test result can feel like being given a free rein to continue with an unhealthy lifestyle.

Before we can investigate the utility of a genetic test, we need to know which hereditary factors are significant, how they influence each other and how they interact with non-genetic factors. Numerous publications about association studies have appeared (genome-wide association studies), but they do not yet provide a serious foundation for making a judgement.[240]

6.6.3 *Verdict on tests for genetic predisposition to hypertension*

The Committee feels that a self-test of genetic predisposition is premature. The purchase of a sphygmomanometer or the consulting of a physician offers cheaper alternatives than a genetic test (EUR 335). If there is any cause to be worried about blood pressure, it is best to include other important risk factors for cardiovascular diseases in the evaluation.

Chapter 7

Conclusions

Some self-tests offer added value

Of the examples discussed in this annual report, the HPV home test for cervical cancer and tests that monitor blood glucose levels and blood coagulation times can be said to have added value. The FOBT, which is used as a home-collecting test in population screening for bowel cancer in several trial regions(not the do-it-yourself test), also deserves mention. A fifth possibility of added value is the *Chlamydia* home test (not the do-it-yourself test). A population screening trial that will investigate the value of home tests for infection with *Chlamydia trachomatis* will be started in three regions in 2008. These are all self-tests that take place with professional kwowledge, input and supervision. Table 1 provides an overview of the Committee's verdicts on the selected self-tests.

The other evaluated self-tests have not been scientifically supported

The Committee is unable to recommend the other 17 evaluated self-tests on the basis of scientific research into their diagnostic value, clinical utility, efficiency and risk-benefit ratio (Table 1). This applies to new tests as well as tests that have been routinely used for decades, and even holds on the basis of no more than scientific research into their diagnostic value. It is worrying that in the absence of sufficient knowledge, such self tests are being marketed directly to the public.

Table 1 Quality of self-tests.

	Diagnostic validity	Clinical utility	Favourable benefit / risk ratio	Efficiency	Tested with lay persons	Adequate information	Mention of CE marking of conformity	Risk category for conformity assessment procedure	Fulfils the 'essential requirements' of the IVD Directive	Sales channelling	WBO permit required	Comments
Self-test kits												
Blood glucose: self diagnosis	N	N	N	N	N	N	?	L	N	N	N	
Blood glucose: monitoring	Y	Y	Y	?	Y	Y	Y	M	Y	N	N	A
Prothrombin time test	Y	Y	Y	?	-	Y	Y	L	Y	N	N	A
AMH test for bladder cancer	N	N	N	N	N	N	?	L	N	N	N	
Albuminuria test for renal damage	N	N	?	?	N	N	Y	L	N	N	N	
PSA test for prostate cancer	Y	?	?	?	N		?	M	N	Y	N	
FOBT for colorectal cancer:	Y	Y	?	?	N	N	Y	L	N	N	N	
Coeliac disease self-test	N	N	N	N	N	N	Y	L	N	N	N	
Tumour markers												
AMAS test for (breast) cancer:	N	N	N	N	N/A	N					Y	
HPV self sampling cervical cancer:	Y	Y	Y	Y	Y	Y	Y	L	Y	N/A	Y	A
CA 15-3 test for breast cancer:	N	N	N	N	N/A	N	?	L	N	N/A	Y	
CEA test for colorectal cancer:	N	N	N	N	N/A	N	?	L	N	N/A	Y	
PreGen-Plus for colorectal cancer:	N	N	N	N	N/A	N	N	L	N	N/A	Y	
Genetic self-tests												
Genetic predisp. to coeliac disease	N	N	N	N	N	N	N	L		N/A	N	
Gen. predisp. to lactose intolerance	N	N	N	N	N	N	N	L	N	N/A	N	
Hereditary risk of thrombosis	N	N	N	N	N	N	N	L	N	N/A	N	
Gen. predisp. to osteoporosis	N	N	N	N	N	N	N	L	N	N/A	N	
Gen. predisp. to hypertension	N	N	N	N	N	N	N/A	L	N	N/A	N	

A = added-value; N = no; Y = yes; N/A = not applicable; ? = research into this is currently underway, or unknown; L = low-risk; M = moderate; H = high

These self-tests likewise fail to meet the general ‘essential requirements’

The Committee finds that these tests also fail to meet the general ‘essential requirements’ of the IVD Directive (or it was not possible to properly examine this.) The Committee bases this conclusion on its interpretation that the general ‘essential requirements’ refer not only to a test’s analytical validity, but also its diagnostic validity and clinical utility. The clinical content of these self-certification dossiers is thought to be low, as tasts that were rejected by the US-FDA as lacking any evidence of diagnostic validity have claimed CE marking in Europe.[244]

The Committee has the impression that self-tests are not seriously assessed according to the general ‘essential requirements’ before being placed on the market. Either the required assessment is not carried out, or the requirements are interpreted in a minimal manner. The Committee takes account of the possibility that the notified bodies conduct their assessments in accordance with the stipulations of the IVD Directive, but that these stipulations are chiefly aimed at assessing technical aspects and not enough at assessing compliance with the general ‘essential requirements’. The Committee also wonders whether the notified bodies have sufficient skills in the area of medicine and epidemiology to carry out this type of assessment. The regulatory system is not felt to currently deliver the clinical evidence that consumers and clinicians need.

Manufacturers are almost always allowed to themselves decide whether the ‘essential requirements’ have been met

European test marketing is based on self certification. Most self-tests are not subject to independent pre-market review. For all tests not named on List A or List B, the manufacturer is allowed to decide itself whether its product meets the ‘essential requirements’ of the IVD Directive, and it can itself affix the CE marking to this product. Only the assessment of the supplementary requirements for do-it-yourself tests must be left to a notified body. The competent authorities’ assumption that the manufacturer will take the appropriate social responsibility calls into question the credibility of the assessment system. The arguments used (in preamble 22 of the IVD Directive) are that in vitro diagnostic medical devices do not pose a health risk and that the results obtained can often be confirmed by other means. But these arguments cut no ice, as far as the Committee is concerned.

The risk classification schema lacks consistency

The list-based approach to classification is neither consistent nor effective for risk classification of novel tests.

It is not easy to ascertain whether the requirements have been fulfilled

Manufacturers must prepare technical files as part of the CE assessment. These files are not public, however, and can only be requested for viewing by the Health Care Inspectorate. Consequently, consumers can usually not find out whether a self-test has the CE marking and what quality standards it complies with before they buy the product on the Internet.

The IVD Directive leaves it entirely up to the manufacturer to describe the purpose of the self-test. This leads to claims of outstanding test performances that have little to do with the test's actual aim. In the case of genetic tests, for example, the precise aim and the associated diagnostic value is often not specified, or it is even stressed that the test is not intended to detect a disease or predisposition to it. Consumers themselves then have to establish the link with the conditions in question. In the website advertising and the patient information leaflets for the FOBT and PSA test, for early detection of bowel cancer and prostate cancer respectively, the aim of the tests is described as demonstrating the presence of blood in the faeces or PSA in the blood. Information on the test performances is restricted to the 'agreement' of the index test with an (unknown) reference test. However, this measure gives no sound information on the test's diagnostic value. This masks the risk of false-positive and false-negative test results.

Information provision to consumers and doctors is inadequate

In certain respects the IVD Directive works against transparency of data. Evaluative data is treated as confidential. The Committee finds that the information on self-test kits provided by manufacturers or suppliers on the Internet is generally inadequate to enable consumers to take well-considered decisions whether or not to buy a self-test. Descriptions of the precise aim of the self-test and its anticipated clinical utility, health risk and diagnostic value are often missing.

The information is often restricted to little more than the price and instructions for use. Advertising seems to be more important than informing. CE marking seems more often an excuse to omit information rather than a guarantee of objective and balanced information. For instance, the website www.thuistesten.nl

sells 12 do-it-yourself tests, including allergy, blood type, candida, syphilis and pregnancy tests, with not much more explanation than that all tests have CE marking and that laboratory tests have shown them to be “more than 99% reliable”. This ‘reliability index’ says little about a test’s diagnostic value.There are virtually no guarantees that consumers will be able to properly interpret the result of a self-test. After all, test results cannot be interpreted without an indication of the risk of false-positive and false-negative outcomes.

The sales channel regulation, under which ‘high-risk diagnostic medical devices’ can only be supplied by a physician or pharmacist, does not seem very effective. Of the evaluated tests, only the do-it-yourself test for PSA is subject to this regulation, and this test turns out to be freely available from a certain chemist chain.

The growth in do-it-yourself testing diminishes the importance of the WBO as an assessment framework

The importance of the WBO as an assessment framework may be diminished as a result of the growth in do-it-yourself testing. Self-testing and screening actually have many similarities. Legally, however, do-it-yourself tests are commercial products; they therefore cannot be made subject to the WBO permit requirement on top of the assessment regulations in the IVD Decree, because this would constitute an obstacle to trade. However, certain services in the contexts of home-collecting and street-corner testing are covered by the WBO. If these services are intended to detect cancer or an untreatable condition, then they require a licence under this law. This also applies to tests for a genetic predisposition to cancer or an untreatable condition.

There is no research on the efficiency of self-tests

All kinds of advantages and disadvantages have been attributed to self-tests. On the one hand it is claimed that self-testing means that users are better able to decide whether to consult a physician. On the other hand, because of the high incidence of false-positive results, the use of self-tests may lead to significant unnecessary demands on healthcare services. No research is yet available on these aspects.

Chapter 8

Recommendations

8.1 Adaptation of regulations, enforcement and information provision

The Committee proposes to the Minister that the recommendations in this chapter relating to the IVD Directive be included in the preparations for the review of the CE marking system.

A number of recommendations relate to the regulatory regime. Nevertheless, the Committee sees the solution to the identified problems not only in terms of improving compliance with and strengthening the regulations on self-testing. There are limits in the Internet age to the enforceability of statutory rules. This underlines the importance of reliable public information (to be stimulated by the government) on the sense or otherwise of self-testing, and of a public debate on the issue. Professional associations, consumer organisations, patient associations as well as the trade association (Diagned) can play a major role here.

The Committee recommends that the information on self-testing in this annual report be widely distributed.

8.2 Improve self-tests as products

More clearly define 'essential requirements'

- The Committee feels that self-tests should be assessed for diagnostic validity and clinical utility before they are admitted to the market. In its view, this follows naturally from the general 'essential requirements' of the IVD Direc-

tive. If it emerges that the requirements 1 and 3 as they are currently formulated do not refer to the diagnostic validity and clinical utility, then the Committee recommends that these requirements be revised at the EU level so that they do refer to these criteria. The Committee underlines the importance of a clear and meaningful formulation of the general 'essential requirements'. There is a great need for more detailed information on these requirements that unambiguously sets out what is meant by the employed concepts. It should be mandatory for manufacturers to state the test's intended clinical purpose.

Study the conformity assessment procedure

- The Committee recommends that a study be made of how manufacturers and notified bodies operate with regard to the CE assessment procedure. How do they interpret the general 'essential requirements', and what role do these requirements play in the assessment? The findings of such a study could be brought into the review of the IVD Directive. In any case, the CE assessment procedure must be structured in such a way that a check regarding the general 'essential requirements' is guaranteed at all times, and the bodies conducting the assessment must be adequately equipped to fulfil their task. The Health Care Inspectorate also has a role to play here. An EU member state has an obligation to take appropriate steps in every case where the CE marking has been wrongly assigned (Article 17 of the IVD Directive). Incidentally, the Committee is allowing for the possibility that this tightening of the assessment regime may require changes to the prescribed conformity assessment procedures.

Revise the risk classification

- EU should adopt a more comprehensive and more consistent risk classification schema, in order to ensure that more tests be subject to pre-market review. The Committee recommends that the classification in risk categories be structured so that the competent authorities can more quickly respond to new market developments. This can be achieved by replacing the specific listing of conditions in the classification in risk categories by a generic listing. (This in effect supports a position already adopted by the Netherlands at EU level.) Tests for cancer and genetic tests should be added to List A or List B as a matter of urgency.

Create preconditions for proactive policies

- The Committee points out the problem of adapting the IVD Directive to the rapid technological and commercial developments taking place. This adaptation will take years, while developments in this market segment are very fast-moving. The Committee therefore recommends that the EU creates the preconditions in this area for more proactive policies by the member states.

Always include results with inexperienced users in the assessment procedure

- The Committee recommends that the obligation on manufacturers, within the context of the CE assessment procedure, to provide the results from studies with inexperienced users should be applied to all do-it-yourself tests.

Possibly restrict the availability of harmful tests

- If a high-risk do-it-yourself test has no proven benefit, but does have many disadvantages (many false-positive test results, overdiagnosis or overtreatment), the Committee recommends that the Minister of Health, Welfare and Sport should consider restricting the availability of such a test under Article 13 of the IVD Directive. This states that if the availability of a product needs to be restricted *in order to ensure protection of health and safety and/or to ensure that public health requirements are observed*, then a member state may take any necessary transitional measures, for example tightening the essential requirements or banning the product.

Aim for self-regulation in post-marketing surveillance of new self-tests

- The Committee recommends that the Health Care Inspectorate continues to urge manufactures to actively seek out the experiences of consumers and patients with their products within the framework of the post-marketing surveillance of do-it-yourself tests. The Committee realises, however, that stronger post-marketing surveillance in a lay environment will always have its limitations. In light of these limitations, the Committee recommends a form of self-regulation in which manufacturers, expert healthcare professionals and other directly or indirectly involved parties track the performance of and experiences with new self-tests for a certain period (one year, for example) in order to monitor the correct use. This could be organised on a voluntary basis. This would certainly not constitute an unwarranted imposition on the free market. Another option might be to set up an independent reporting centre where consumers/patients could lodge any complaints.

Introduce a requirement for regular checks of blood glucose meters in the IVD Directive review

- The need for regular checks of blood glucose meters is insufficiently guaranteed in the current CE marking system. The Committee recommends that this requirement be brought into the review of the IVD Directive.

8.3 Improve the supply of self-tests as products

Investigate the effect of the sales channel regulation

- The Committee recommends that research be undertaken to see whether the sales channel regulation is achieving its objective. One question in this context is whether Internet-based pharmacies are (given the required expertise in oncology, genetics and epidemiology) suitable outlets for selling high-risk products.

Draft production information in such a way that it is possible to make a well-considered choice

- The Committee takes the view that the product information provided in advance of a purchase and in the patient information leaflet should, at the very least, include details of the test's aim, diagnostic value and clinical utility (including a quantified indication of the risk of false-positive and false-negative results). What matters above all is that consumers can make a well-considered choice on the basis of understandable information as to whether or not to buy the test, thereby fleshing out the right to self-determination. The Committee recommends that the sales channel regulation be tightened to this effect.

8.4 Improve self-tests as services

Consider the scope of the WBO

- Some forms of genetic screening already require a permit under Article 2 of the WBO or Article 2 of the Special Medical Procedures Act (WBMV). The Committee recommends that research be undertaken to investigate to what extent other forms of genetic screening should be made subject to the WBO's permit requirement.

Place home-collecting and street-corner tests within the scope of the Quality Act

- The Committee recommends that the services that institutions and laboratories offer in the form of home-collecting tests and street-corner tests should be designated as ‘healthcare’ within the meaning of the Quality Act so that there is no doubt that these institutions and laboratories fall within the scope of this law when they offer this type of test. The applicability of the Quality Act gives the Health Care Inspectorate an instrument to supervise these institutions.

Formation of quality policies by manufacturers

- Suppliers and sellers of home-collecting tests and street-corner tests will have to formulate their own quality policies within the applicability of the Quality Act. These are policies for which the Health Care Inspectorate can hold them accountable. The Committee recommends that the diagnostic medical devices industry helps to develop such policies, following on from the code of conduct formulated by Diagned, the industry’s trade association. Given the applicability of the WGBO to this type of service, the professional groups involved will also have to give thought to what constitutes ‘healthcare by a good provider’ (Article 7:453 of the Civil Code) in this context. If they do not yet have an appropriate professional standard in this respect, they should ensure that such a standard is formulated as a matter of urgency. The Committee recommends that close attention be paid in the formulation of quality policies and professional standards to the question of what information consumers and patients require to take a well-considered decision on whether or not to have themselves tested. This information could cover the advantages and disadvantages of having the test performed, the opportunities for testing in the regular health service, a quality comparison, when to consult a physician, etc.

8.5 Improve information on self-tests

Provide users and clinicians with appropriate information

- Oblige manufacturers to make information available to all stakeholders. Because the test performances are correlated with the intended aim, the Committee recommends that suppliers be obliged to describe the test’s intended clinical purpose in the information for users (in terms of the disease or condition being tested for and not in terms of ‘reliability’ or ‘agreement’ with an

unnamed reference test). Regulators should ensure easy access to all the relevant clinical evidence.

Report CE marking

- The Committee recommends that suppliers undertake (or be obliged) to mention in the advertising (on the Internet or elsewhere) for their tests that the tests have CE marking. As far as the Committee is concerned, the introduction of a separate quality mark besides CE marking is superfluous and confusing under the conditions set out by the Committee.

Ensure that advertising is evidence-based

- The Committee recommends that manufacturers and other suppliers be obliged to proceed in an evidence-based way in their advertising for do-it-yourself tests, in analogy with the requirements currently made for advertising products that make a health claim. Such an obligation could be laid down in the IVD Directive. The basis for the regulation of advertising for home-collecting and street-corner tests will have to be enshrined in a public law. In short, the Committee recommends that advertising for these kinds of products and services be subjected to stricter standards than those that currently apply. Arrangements for supervising compliance with these standards will also have to be made.

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Annexes

Annex **A**

The committee

- J.A. Knottnerus, *chairman*
  President of the Health Council, The Hague
- J.H. Dekker
  General Practitioner, University Medical Centre Groningen
- S.W.J. Lamberts
  Professor of Internal Medicine, Erasmus MC, Rotterdam
- Y. van der Graaf
  Professor of Clinical Epidemiology, University Medical Centre Utrecht
- W.P.Th.M. Mali
  Professor of Radiology, University Medical Centre Utrecht
- J.L. Severens
  Professor of Medical Technology Assessment, University of Maastricht
- A.L.M. Verbeek
  Professor of Clinical Epidemiology, University Medical Centre St Radboud Nijmegen
- W.A. van Veen, MD, *secretary*
  Gezondheidsraad, The Hague
- C.J. van de Klippe, Doctor of Law, *secretary*
  Gezondheidsraad, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **B**

Expert consultations

The Committee consulted the following experts:

- E.M. van Ardenne-Stachiw
  Lawyer, Amersfoort
- G.J. Dinant
  Professor of Family Practice, University of Maastricht
- J.C.J. Dute
  Professor of Health Law, Erasmus MC, Rotterdam; University of Amsterdam
- J.K.M. Gevers
  Professor of Health Law, Academic Medical Centre/University of Amsterdam
- G.R.J. de Groot
  Professor of Health Insurance Law, Free University Amsterdam; Lawyer, The Hague
- L.P. ten Kate
  Professor Emeritus of Clinical Genetics, VU Medical Centre, Amsterdam
- M.H. Prins
  Professor of Clinical Epidemiology, University of Maastricht
- H. Rigter
  Professor Institute of Public Health, Erasmus MC, Rottterdam
- F.R. Rosendaal
  Professor of Clinical Epidemiology, University Medical Centre Leiden

- R.J. Slingerland
  Clinical Chemist, Isala Klinieken, Zwolle
- E.M.A. Smets
  Clinical Psychologist, Academic Medical Centre, Amsterdam
- D. Stemerding
  Lecturer, science and society, University Twente, Enschede
- F. Sturmans
  Professor Emeritus of Epidemiology, Geertruidenberg

Annex **C**

Glossary

Accuracy

See ‘Validity’.

Agreement (reliability index)

The degree to which the results of an index text match the results of a reference test. This can be expressed as the sum of the number of true-positive results and the number of true-negative results divided by the total number of tested people. This measurement depends more on the prevalence of the condition than on the diagnostic value of the test. The percentage of true-negative results and the ‘reliability’ will be high for conditions with a low prevalence.

Analytic validity

Accuracy of an assay identifying the biomarker. See ‘Sensitivity’ and ‘Specificity’.

A priori probability

The probability of a person having or developing a particular disease before the test result is known, measured against the prevalence of the disease in the population to which the tested person belongs.

Bias

A distortion of research results owing to systematic flaws in the structure or execution of a study. See also ‘lead-time bias’, ‘selection bias’ and ‘overdiagnosis’.

Biomarker

A characteristic defect or anomaly at DNA, RNA or protein level, used to determine the probability of disease, the presence or nature of the disease, the choice of therapy and the reaction to it, the course of the disease and the determination of heredity. These are germline-specific or disease-specific characteristics such as multiplication, loss or translocations of chromosomes or chromosome areas, mutations, polymorphisms or modifications of genes, as well as expression levels of individual genes or groups of genes measured in terms of RNA or protein. Biomarkers may also be functional proteins found in abnormal concentrations in body fluids such a blood plasma or urine.[23]

Direct-access test (DAT)

Allows the consumer to order a battery of laboratory tests previously available only with a physician's order.

Direct-to-consumer (DTC) test

A home-collecting test that is marketed and sold on the Internet and whose test result is reported directly to consumers, without the intervention of an independent healthcare professional.

Do-it-yourself test

A self-test that an inexperienced user or lay person can perform themselves at home, without the intervention of a physician or laboratory.

False-negative result

A test result that was negative in a subject who possesses the attribute. It should be stressed that this is not a value judgement ('unjustified good news'). The 'false-negative' category comprises not only 'missed' diseases or risk factors, that is, those that were undoubtedly present or present at a preliminary stage during the screening but were not identified. They also include cases where the disease was already present but not detectable, or even when there is subsequent development of the disease.

False-positive result

A test result that was positive in a subject who does not possess the attribute for which the test is conducted. Further diagnosis shows that the presumed disease or risk factor is not present ('false alarm').

Genetic screening

Screening for the presence of or risk for disorders with a strong genetic component ('heritable disorders').[241]

'Gold standard' (reference test)

A test that is generally accepted as most accurately representing the actual situation (i.e. presence or absence of a disease or risk factor).

Home-collecting test (home test)

A self-test in which a person takes or collects a body sample (urine, faeces, blood or saliva) from himself or herself and has this tested in a laboratory.

Index test

The test whose diagnostic value is being investigated.

In vitro diagnostic medical device

A medical device for the diagnosis of body samples.

Lead-time bias (sojourn bias)

A phenomenon whereby the active detection of disease brings forward the moment of diagnosis. For instance, prostate cancer is discovered ten years earlier with PSA screening.[115] If this does not change the time of death, the interval between diagnosis and mortality is extended, so that the survival period seems longer. But this is not a case of 'life-years gained'. Rather, the man in question knows for ten years more that he has prostate cancer.

Length-time bias

An error which is due to the fact that slowly progressing disease processes are more likely to be detected by screening than more rapidly progressing disease processes.

Mendelian inheritance pattern

A term to describe a high probability of a child being born with the hereditary disease in question: 25% in the case of a recessive mutation in both parents and 50% in the case of a dominant mutation in one of the parents.

Monitoring test

A test in which the patient himself or herself monitors a previously diagnosed condition (for example, the self-management of glucose levels by diabetics).

Monogenetic

Relating to a single gene, inherited under Mendel's laws. Examples of the more than 5,000 monogenetic diseases that are most common in the western world are familial hypercholesterolemia (FH), phenylketonuria (PKU), cystic fibrosis (CF) and classical haemophilia.

Multifactorial

Relating to several hereditary factors as well as to environmental factors, such as lifestyles. The most common forms of cancer, cardiovascular diseases, diabetes, hypertension and many other conditions where hereditary factors play a role are multifactorially determined.

Mutation

A change in the nucleotide sequence in a gene. Germline mutations are hereditary, can be found in the DNA of the reproductive cells, and spread to all the body's cells during embryonic development.

Negative predictive value

The probability that a person with a negative test result does not have the condition being tested for. In other words, the retrospective probability of the absence of the condition, or the percentage of true-negative results among all test-negatives.

Negative test result

A test result that is favourable and that indicates that the probability of having or developing the disease in question is low.

Overdiagnosis

There is a possibility that defects and anomalies are detected through screening that would never have actually led to disease. This may happen as a result of lead time (for instance, a woman who has been diagnosed with breast cancer through screening dies from something else before the breast cancer would have come to light in a situation without population screening). A second possibility is that a defect or anomaly is regarded as an early stage of disease, but proves not to be so. In early diagnoses of cancer, the line between benign and malignant growth is not always clear. A third possibility is that the defect or anomaly detected through screening (for instance a carcinoma in situ or an advanced adenoma) can be regarded as an early or preliminary stage of a disease, but would never have led to the awareness of the disease in a situation without population screening.

Penetrance

Frequency of expression of a genotype.The extent to which a genetically determined condition is expressed in an individual.

Point-of-care test (POCT) (near-patient test)

A test that is not performed in a hospital or laboratory, but wherever healthcare is provided (such as physician's or specialist's surgery, at home or elsewhere).

Polymorphism

A frequent (> 1%) inheritable variation in a particular gene sequence in a population. Some polymorphisms are advantageous, in that they can, for example, slightly reduce the probability of developing a particular condition. Others are disadvantageous, in that they can slightly increase this probability.

Positive predictive value

The probability that a person with a positive test result indeed has the condition for which they have been tested. In other words, the retrospective probability of the presence of the condition, or the percentage of true-positive results among all test-positives.

Positive test result

A test result that is unfavourable and that indicates a raised probability of having or developing the disease in question.

Predictive genetic tests

A generic term for presymptomatic and susceptibility tests.

Presymptomatic diagnosis

A diagnosis based on DNA evidence of monogenetic diseases that only manifest themselves at an older age, such as Huntington's disease. Carriers of the mutation in question have a high probability of developing the condition.

Qualitative test

A test whose result is positive or negative.

Quantitative test

A test whose result is a numerical value.

Reliability (reproducibility)

The extent to which a test will give the same result when repeated under the same conditions (either by the same person at a different time, or by different people independently of each other).

Reproducibility

See 'Reliability'.

Safety

The probability that a person's health will be impaired owing to an incorrect use of a self-test, a false-positive or false-negative test result, or an incorrect interpretation of the test result.

Screening (early detection, population screening)

The testing of apparently healthy people with the aim of separating them into a subgroup with a high probability and a subgroup with a low probability of having or developing a particular disease. Screen-

ing does not pretend that it can diagnose or exclude the disease or a preliminary stage of the disease. People with a positive (unfavourable) test result are referred to their physician for a formal diagnosis. The initiative lies with the person or institution offering and performing the screening. The purpose of screening is to use early detection to improve the treatment outcome or to widen the options for action.

Selection bias

A distortion of research results owing to systematic flaws in the selection of participants in a scientific study. Thus, people who use screening or self-testing may form a selection from the general population (for example, in terms of socioeconomic status and inclination towards preventative behaviour), so that they are already at an advantage regardless of the screening programme. In that case, patients will appear to live longer and survival rates will yield a distorted picture of the clinical utility of testing. Another type of selection bias occurs because people with a rapidly progressing disease processes will be less inclined to use screening or self-diagnosis.

Self-test

A generic term for do-it-yourself tests, home-collecting tests and street-corner tests. This annual report only considers tests on blood, urine, saliva and another body samples (taken or collected by means of an in vitro diagnostic medical device), not (for example) self-examination of the breasts or monitoring of blood pressure or peak flow at home.

Semiquantitative test

A test whose result is higher or lower than a particular limit value (the test's cut-off point).

Sensitivity

The ability of a test to identify people with a particular disease or risk factor as such, or put another way, the number of true-positive test results divided by the number of people with the disease in question (true-positives plus false-negatives). A test with a high sensitivity leads to few false-negative outcomes. This diagnostic sensitivity should be distinguished from 'analytical' sensitivity, which reflects a test's performance in a laboratory trial setting (for example, the ability to demonstrate a particular amount of haemoglobin in faeces or hCG in urine). The analytical sensitivity of a genetic test is its ability to identify people with a particular mutation (the genotype of interest) as such.

Single-nucleotide polymorphism (SNP)

A genetic variation that relates to only a single nucleotide. The human genome contains more than 3 million of SNPs.

Specificity

The ability of a test to identify people who do not have a particular disease or risk factor as such, or put another way, the number of true-negative test results divided by the number of people without the disease in question (correct negatives plus false-positives). A test with a high specificity leads to few false-positive outcomes. This diagnostic specificity should be distinguished from 'analytical' specificity, which reflects a test's performance in a laboratory trial setting. The analytical specificity of a genetic test is its ability to identify people without a particular mutation as such.

Spectrum bias

A distortion of the test performances in scientific research because of an incorrect choice of the spectrum of people with the disease and those without the disease. The diagnostic value of a test intended for people from the general population, with a broad disease spectrum, should not be investigated only in patients with relatively serious conditions.

Street-corner test

A self-test in which the necessary body samples are taken by a third party, for instance in a pharmacy or supermarket.

Susceptibility test

A test for hereditary factors that slightly raises the probability of a person subsequently developing a particular multifactorial condition.

True-negative result

A test result that was negative in the first instance (i.e. absence of the disease or risk factor), and that is subsequently confirmed in a further diagnosis.

True-positive result

A test result that was positive in the first instance (i.e. presence of the disease or risk factor) and that is subsequently confirmed in a further diagnosis.

Tumour marker

A biomarker used to detect cancer. Tumour markers are usually proteins that are associated with a particular form of cancer and are excreted from tumour cells.[23]

Validity

The extent to which a test can distinguish between people with a disease or condition and people without the disease or condition. Or put another way, the extent to which the results of a test agree with those of the 'gold standard' as a reference test.