Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*

Personalised medicine products
Evaluation of the regulatory framework

RIVM Report 360211001/2014

M. Weda et al.

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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RIVM Report 360211001/2014

Colophon

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This investigation has been performed by order and for the account of the Ministry of Health, Welfare and Sport (VWS), within the framework of Onderzoeksprogramma Geneesmiddelenketen

This is a publication of:

National Institute for Public Health and the Environment
P.O. Box 1│3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

Publiekssamenvatting

Personalised medicine producten: een evaluatie van de wettelijke kaders

Personalised medicine is een relatief nieuw en populair begrip in de medische wereld. Het staat voor een behandeling van de patiënt op basis van zijn individuele kenmerken, een zogenaamde behandeling op maat, in plaats van de traditionele *one-size-fits-all*-benadering. Voor een optimale en adequate behandeling op maat wordt een geneesmiddel gekoppeld aan *in vitro* diagnostica (IVDs; bijvoorbeeld genetische tests). Op die manier kan op basis van het genetisch profiel van een patiënt voor bepaalde medicijnen of doseringen gekozen worden, waarmee de patiënt beter kan worden behandeld. Momenteel gebeurt dit vooral bij de behandeling van kanker.

Er bestaan echter verschillende wettelijke kaders voor medicijnen en genetische tests. Uit onderzoek van het RIVM blijkt dat lacunes in de informatievoorziening over de genetische tests en een gebrek aan eenduidigheid tussen de wetgevingen optimale keuzes voor behandeling in de weg kunnen staan. Zo kan de kwaliteit of opzet van een genetische test van invloed zijn op de nauwkeurigheid waarmee het genetisch profiel van een patiënt wordt bepaald. Daardoor zal een bepaalde patiënt na gebruik van de ene test wel en de andere test niet geselecteerd worden voor een behandeling met een geneesmiddel of een dosering. Dit kan een risico vormen voor optimale en adequate behandeling. Het RIVM stelt dat dit risico alleen kan worden ingeperkt als de wet- en regelgeving van geneesmiddelen en IVD’s aan elkaar worden gekoppeld. Verder blijkt dat het noodzakelijk is professionals in de gezondheidszorg te trainen om adequate behandeling op maat te stimuleren. Het RIVM doet aanbevelingen om de risico’s zo veel mogelijk te beperken.

In september 2012 heeft de Europese Commissie een voorstel gedaan om de wet- en regelgeving voor IVD’s te herzien. Hoewel hierin rekening wordt gehouden met personalised medicine producten die behandeling op maat mogelijk maken, blijven lacunes bestaan om ze adequaat te gebruiken.

Trefwoorden: personalised medicine, behandeling op maat, genetische biomarkers, companion diagnostics, pharmacogenomic test, *in vitro* diagnostica (IVDs), wettelijke kaders

Abstract

Personalised medicine products: evaluation of the regulatory framework

In personalised medicine, patients are treated with medicinal products according to their individual characteristics, such as genetic background, instead of a traditional one-size-fits-all approach. Genetic screening of patients for effective and safe treatment with medicinal products is performed using *in vitro* diagnostic devices (IVDs), including genetic tests. Therefore, in personalised medicine, medicinal products and IVDs are linked. However, different regulatory frameworks exist for these two components of personalised medicine. The current report states that: to adequately control the risks of personalised medicine products, the legislation of medicinal products and that of IVDs should be linked.

This report describes the gaps between these two sets of legislation. One of these gaps is the incompleteness and lack of uniformity of information in the summary of product characteristics (SPC) of medicinal products, the instructions for use of the IVDs and Dutch clinical practice guidelines. The need for comprehensive and uniform information across these documents was confirmed by Dutch healthcare professionals. A potential hazard resulting from lack of (uniform) information occurs when in daily practice an IVD is used that differs from the one applied in the pivotal clinical trials of the medicinal product. A difference in IVD tests may result in a different selection of patients, and thereby different, and potentially less optimal, treatment. In addition, legislation does not cover the simultaneous development of a medicinal product and IVD. Finally, the results of vigilance activities (the monitoring of adverse drug reactions, product defects, etc.) are not exchanged between the authorities responsible for medicinal products and those responsible for IVDs. In the European Commission's September 2012 proposal for revised IVD regulation, both medicinal products and IVDs are mentioned; however, gaps remain. Research also reveals that the training of healthcare professionals in the use of personalised medicine techniques needs to be improved.

For this report, literature and database research was performed, as well as expert consultation. Additionally, the current regulatory frameworks for medicinal products and IVDs were reviewed. If the regulatory frameworks for medicinal products and IVDs were sufficiently linked, the potential hazards of personalised medicine products may be minimised. Specific recommendations for minimizing these hazards are provided in this report.

Keywords: personalised medicine, genetic biomarkers, companion diagnostics, pharmacogenomic test, *in vitro* medical device, regulatory framework

Contents

Summary

Personalised medicine is a new medical model for classifying, understanding, treating and preventing disease on the basis of data and information on individual biological and environmental differences. In personalised therapy, genetic information plays a major role and is used to tailor treatment with a medicinal product to the genetic make-up of an individual patient. Treatment in personalised medicine is more effective or causes less harmful side-effects than generic, one-size-fits-all treatment. *In vitro* diagnostic devices (IVDs) – specifically, pharmacogenomic tests – are needed to determine the genetic biomarker that predicts the efficacy of a medicinal product.[1] Therefore, in personalised medicine, medicinal products and IVDs are linked. However, the regulatory frameworks for medicinal products and IVDs differ. The aim of this project was to evaluate the adequacy of the regulatory frameworks to control the potential hazards[2] of personalised medicine products.

In step 1, an inventory was made of the personalised medicine products marketed in Europe, using the databases of the European Medicines Evaluation Boards. Information on genomics testing contained in healthcare professionals' guidelines was also reviewed. The results show that the majority of medicinal products with companion diagnostics are indicated for oncology. When testing is required, the specific biomarker to be tested for is named in the summary of product characteristics (SPC) and often in Dutch clinical practice guidelines as well. However, the SPC seldom states the required test or testing principle to determine the biomarker. The CE-marked testing devices that are available on the market sometimes differ in testing principles from those that were used in the clinical trials of the medicinal products. In this report, the following failings were identified: lack of information on testing devices and testing principles in guidelines; and the availability of multiple testing devices for one biomarker, sometimes with testing principles that differ from the one that was used in the clinical trials. Using different testing devices or testing principles may result in the stratification of a different population from the one used in the clinical trial, potentially leading to a shift in benefit–risk balance.

In step 2, healthcare professionals practising personalised medicine on a daily basis were interviewed. The interviewees perceived lack of knowledge among healthcare professionals nationwide regarding personalised medicine techniques, including the evaluation of test performance and interpretation of results, as contributing to the general reluctance to use personalised medicine as a treatment option. Training of healthcare professionals would help to widen the implementation of personalised medicine, resulting in more patients benefiting from tailored treatment. As was also identified in step 1, interviewees perceived the variety of tests and testing principles available (commercially and in house) for the same biomarker as a potential problem, which could result in the stratification of a different population from the one used in the clinical trial of the medicinal product.

[1] For some medicinal products, pharmacogenomic tests must be carried out before treatment; for others, testing is optional. In this report, we use the term 'companion diagnostics' in cases where testing is required.
[2] 'Hazard' is defined as a potential source of harm to the patient. 'Harm' is defined as damage to health. 'Risk' is defined as the combination of the probability of occurrence of harm and the severity of that harm.

In step 3, the regulatory frameworks for medicinal products and IVDs were reviewed. For both medicinal products and IVDs, clinical trials are required to test performance. For personalised medicine products, where the two components are linked, this means that there is a duplication of effort. We suggest the adaptation of legislation or the introduction of 'soft legislation' to reduce the number of clinical trials required in these cases. Also, joint meetings should be organised during the development process of products used in personalised medicine, in which representatives of the pharmaceutical and diagnostics industries as well as the relevant regulatory authorities take part.

In September 2012, a new proposal for IVD regulation was published by the EC in which companion diagnostics were specifically addressed. It requires the involvement of a medicines evaluation agency during the process of evaluating an IVD for release onto the market, without specifying further requirements. Additionally, vigilance activities need to take the relationship between medicinal products and companion diagnostics into account.

In conclusion, the risks of using personalised medicine due to the different regulatory frameworks of the two components that are identified in this report indicate that legislation must apply consistently to both the medicinal product and the relevant IVD. If such consistency is achieved, the potential hazards of personalised medicine products may be adequately controlled and the regulatory framework may support the safe use of personalised medicine.

1 Introduction

1.1 Background

Personalised medicine is attracting increasing attention from the healthcare industry as well as from policy makers and regulators. The expectation is that the use of personalised medicine will dramatically reduce healthcare expenditure as well as improving the efficacy and safety of medicinal products for individual patients [1]. In oncology, molecular diagnosis facilitates the selection of a treatment that is most likely to improve an individual's chance of survival. Advances in HLA genotyping have improved transplant outcomes and improved predictions of the potential for a patient to experience a hypersensitivity reaction. The genotyping of drug metabolising enzymes enables dose adjustments that permit individual patients to be treated more effectively or with less harmful side-effects [2].

Personalised medicine is a new medical model for classifying, understanding, treating and preventing disease on the basis of data and information on individual biological and environmental differences [1]. Personalised medicine moves away from the one-size-fits-all approach towards a tailored approach based on the biological make-up of each patient. In the case of medicinal products, the purpose is to tailor their use to the individual patient. The use of genetic information plays a major role in this and distinguishes personalised medicine from the traditional way of preventing and treating diseases.

Since human DNA was completely decoded in 2000, the concepts of personalised medicine have been brought into practice at an increasing pace [1]. The development of new genetic testing principles and molecular diagnostics has further boosted the development of personalised medicine. For molecular diagnostics in personalised medicine, the new *in vitro* diagnostic medical devices (IVDs) need to be used along with the medicinal product. IVDs use the molecular distinctiveness of a patient to identify whether they will experience a benefit or unwanted side-effects from treatment with a particular medicinal product [3]. This has led to the realisation that implementing personalised medicine requires a high degree of collaboration amongst the research community, drug and diagnostics manufacturers, regulators, health technology assessors, healthcare professionals and patients [4, 5].

Genomics alone cannot completely predict an individual's phenotype. Environmental, social and lifestyle factors are also influential. A future perspective on personalised medicine integrates all these factors [1]. This report will, however, focus on molecular diagnostics, i.e. the use of genomics in personalised medicine. It will address the regulatory frameworks that apply to medicinal products and IVDs, which are used together in personalised medicine, in order to explore whether potential hazards[3] for patients in the use of personalised medicine are sufficiently limited by those regulatory frameworks. Both medicinal products and IVDs are governed by European Union (EU) legislation. The main objectives of Community legislation on both categories are the elimination of obstacles to the free movement of products and the

[3] 'Hazard' is defined as a potential source of harm to the patient. 'Harm' is defined as damage to health. 'Risk' is defined as the combination of the probability of occurrence of harm and the severity of that harm.

safeguarding of public health and consumer safety. Nonetheless, the regulatory systems differ in many respects, as has been found for medical devices in general [6]. For personalised medicine this raises uncertainties regarding the presence and suitability of links between IVD and medicinal product legislation: since IVDs are linked to medicinal products, there must be sufficient assurance that a specific IVD will allow a healthcare professional to make the right decision on the use of the relevant medicinal product in each particular case.

1.2 Aim of this study

The overall aim of the project was to evaluate the adequacy of the regulatory frameworks to control the potential hazards of personalised medicine products. For this purpose, the field of personalised medicine in the Netherlands was explored by: (1) making an inventory of the available personalised medicine products and IVDs, and (2) selecting and interviewing healthcare professionals practicing personalised medicine on a daily basis. The threats to the safe use of personalised medicine were identified and the current regulatory frameworks for medicinal products and IVDs evaluated to establish whether the potential hazards are, or could be, adequately controlled. The legislation for IVDs is currently under revision to ensure an appropriate level of scrutiny before testing devices are released onto the market. Both the current and the proposed legislation were taken into account.

1.3 Definitions and scope

There is no universal definition of the term 'personalised medicine'. In fact, the term is often used interchangeably with 'genomic medicine', 'stratified medicine', 'precision medicine' and 'targeted therapy' (see Figure 1.3.1) [1].

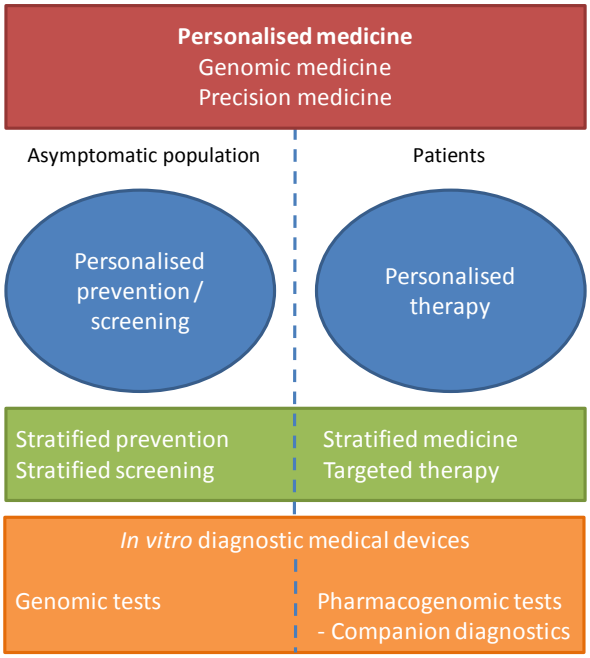


Figure 1.3.1 Definitions of personalised medicine

IVDs play a major role in personalised medicine. IVDs can be used for population screening, diagnosis, treatment monitoring and the evaluation of medical interventions. In personalised medicine, IVDs are used to provide information about a patient's predisposition to a specific disease (personalised

prevention/screening) or about their likely response to treatment (personalised therapy). This report focuses on personalised therapy.

The terms 'pharmacogenetics' and 'pharmacogenomics' are also often used interchangeably, but their meaning is different. A pharmacogenomic test is defined as a test for drug exposure and/or response in relation to 'variations in DNA and RNA characteristics' [1]. Pharmacogenetics is a subset of pharmacogenomics and studies only variations in DNA sequence. For this report the term 'pharmacogenomics' is therefore more appropriate. Companion diagnostics are also a subset of pharmacogenomic tests, but in a different sense. A companion diagnostic is defined as a pharmacogenomic test specifically intended to select patients with a previously diagnosed condition or predisposition as eligible for a targeted therapy. In this report, companion diagnostics refers to the pharmacogenomic tests that must be carried out to select patients before the start of treatment with a medicinal product.

Biomarker information may be important in judging the possible effects of a medicinal product, but may also be relevant in assessing the possibility of interaction between medicinal products using (partly) the same metabolic pathways (e.g. CYP enzymes). In terms of the scope of our study, medicinal products with pharmacogenomic information on biomarkers that is relevant only to their interactions with other medicines are excluded.

2 Methods

Four activities were performed:

- Preliminary step, literature survey;
- step 1, inventory of available products and product information;
- step 2, semi-structured interviewing of healthcare professionals;
- step 3, review of legislation.

The details of these steps are outlined below. At steps 1 and 2, any potential hazards related to the use of personalised medicine were identified. These potential hazards were used as input for step 3. In step 3 it was explored whether the two regulatory frameworks that currently exist for medicinal products and IVDs are adequate and sufficiently aligned to limit potential hazards to patients.

2.1 Preliminary step: literature survey

As a preliminary activity, we searched for literature dedicated to legislation on personalised medicine by checking Pubmed as well as the 'grey literature' via Google and the websites of the European Medicines Agency (EMA), the European Commission and the U.S. Food and Drug Administration (keywords: personalised medicine, legislation, regulatory, pharmacogenomics). No formal search strategy was applied, since this step was meant only to provide a general picture of activities in this area prior to the activities in steps 1, 2 and 3. The results are not reported separately, but all relevant references are included in this report (see reference list).

2.2 Step 1: inventory of available products and product information

Here, we made an inventory of the products used in personalised medicine and the devices used for companion diagnostics/pharmacogenomic tests marketed in Europe, and we reviewed the information on genomics testing contained in healthcare professionals' guidelines. The aim of this step was to gain insight into the types of product on the market and the type of information that accompanies these products and is contained in healthcare professionals' guidelines. The information was gathered between January and August 2012.

First (step 1a), information on medicinal products was derived from the relevant summaries of product characteristics (SPCs), available from the websites of the European Medicines Agency (EMA) or the Dutch Medicines Evaluation Board (MEB). The U.S. Food and Drug Administration's Table of Pharmacogenomic Biomarkers in Drug Labeling [7] was used as a starting point for identifying medicines with pharmacogenomic information in the drug label that have been registered in the European Union. This table contains about 120 drug substances, but for some substances the pharmacogenomic biomarkers are relevant only to the pharmacodynamic/kinetic interaction of the medicine with other medicines; these substances were not relevant to this research. These data were supplemented by information derived from the Dutch pharmacists' database KNMP Kennisbank. For each medicinal product with pharmacogenomic information in the SPC the following characteristics/information were collected:

- active pharmaceutical ingredient;
- therapeutic area;
- year of authorisation;
- type of registration procedure used;

- biomarker(s) mentioned in the SPC;
- clinical effect related to the biomarker;
- pharmacogenomic test information;
- test mandatory or not;
- type of action to be taken by healthcare professionals in response to test result;
- description of the action;
- other relevant information (such as literature references on pharmacogenomics included in the SPC).

Second (step 1b), information on pharmacogenomic tests was gathered by searching the internet to discover the available CE-marked testing devices and to find the instructions for the use of these devices. Since no registers of CE-marked devices are available, a snowball method was used, starting with the website of the Pharmacogenomics Knowledge Base. This website shows the FDA-approved pharmacogenomic testing devices. Thereafter, a search via Google was performed, using a combination of the keywords 'name biomarker' AND 'name medicine' AND 'test', 'kit' or 'assay' AND 'CE mark'. Finally, a list of companies that offer tools, technologies, services and tests in the companion diagnostics sector was used as the basis of a search of company websites [8]. For each device the following characteristics/information were collected:

- Device name;
- Biomarker(s) tested for;
- Year of CE marking;
- Manufacturer;
- Intended use;
- Used in clinical trials of medicinal products or not;
- Testing principle;
- Instructions related to the interpretation of results;
- Other relevant information (such as limitations of the test).

Third (step 1c), Dutch clinical practice guidelines were screened for available information on pharmacogenomic tests. The list of medicinal products with pharmacogenomic information in the SPC generated in step 1a was used as the starting point. For each therapeutic area, healthcare professionals' guidelines were searched for on the internet. The list of websites visited to find these guidelines is presented in Annex 1. For each set of guidelines the following characteristics/information were collected:

- Subject of the guidelines;
- Year of adoption;
- Organisation that prepared the guidelines;
- Personalised medicine products mentioned;
- Pharmacogenomic test information;
- Test mandatory or not;
- Description of action to be taken by healthcare professionals in response to test result;
- Level of agreement of information on tets and action in the guidelines with information in the SPC of medicinal products;
- Other relevant information (such as dosing advice).

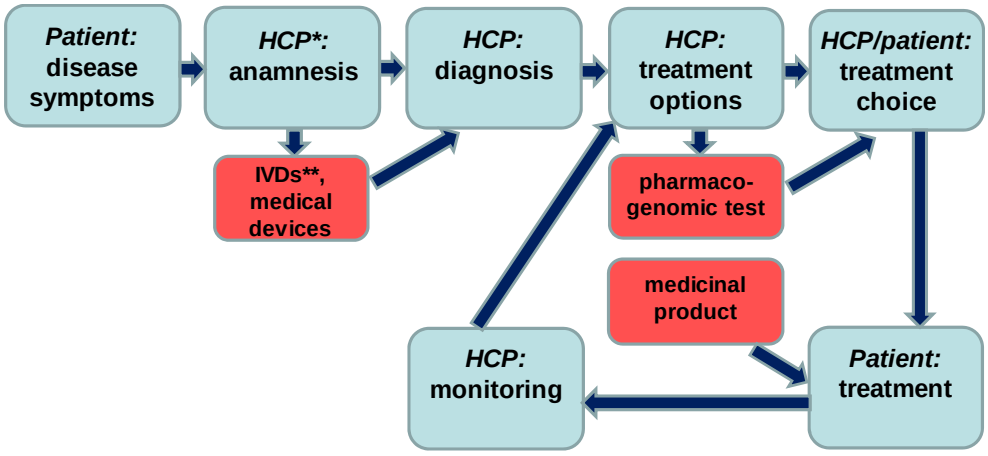
2.3 Step 2: semi-structured interviewing of healthcare professionals

As a second step, an inventory was made of healthcare professionals in the Netherlands practising personalised medicine on a daily basis. Seven key individuals were identified who are active in the field of (implementing)

pharmacogenomics in the Netherlands – key in that each of them represented a different profession in the healthcare system that deals with personalised medicine. With the selection of these professionals we aimed to cover the entire field of personalised medicine practice in healthcare and to reflect the main medicinal product categories found in step 1. The interviewees had the following professional backgrounds:

- Pathologist;
- Clinical-chemist;
- Hospital pharmacist;
- Psychiatrist;
- Oncologist, clinical pharmacologist;
- Hospital pharmacist, clinical pharmacologist;
- Director of company developing genomic tests.

The list of interviewees is provided in Annex 2.
The aim of this step was to explore whether professionals are aware of potential hazards to patients when practising personalised medicine. A semi-structured interview was applied. In order to identify the topics of interest (in order to prepare the interview questions), a model was made for the treatment decision process in the case of personalised medicine (see Figure 2.2.1). On the basis of this model all steps specifically related to the use of a medicinal product and/or a pharmacogenomic test were identified as topic of interest.



* HCP = healthcare professional; ** IVD = *in vitro* diagnostic device
Figure 2.2.1 Treatment decision process

In principle, all steps are critical for the treatment choice, but not all steps are specifically related to the use of a medicinal product and/or pharmacogenomic test. The following steps were identified as potentially critical for treatment decisions in the case of personalised medicine, including the topics of interest between brackets:

1. Diagnosis of disease (information available from clinical practice guidelines);
2. Consideration of treatment options (information available from clinical practice guidelines);
3. Use of a pharmacogenomic test (choosing a test, performing the test, interpreting the test results);
4. Final treatment choice (other available sources than clinical practice guidelines).

Questions were formulated for each of these topics. The full list of questions is shown in Annex 3.

The interviewees had the following professional background and are all actively involved in the field of personalised medicine:

- Pathologist;
- Clinical-chemist;
- Hospital pharmacist;
- Psychiatrist;
- Oncologist, clinical pharmacologist;
- Hospital pharmacist, clinical pharmacologist;
- Director of company developing genomic tests.

All interviews were audio recorded and the recordings were transcribed. The main findings per topic were identified by two researchers independently and were then cross-checked and reviewed for consistency.

2.4 Step 3: review of legislation

The third and last step of the project was an analysis of marketing authorisation legislation for medicinal products and IVDs. The aim of this step was to investigate whether the legislation sufficiently enables the right treatment choices to be made in the case of personalised medicine. In other words: when a pharmacogenomic test (i.e. an IVD) is used in practice, does the relevant legislation ensure that the test result generated by the IVD does not negatively influence the risk–benefit balance of the medicinal product's use established during the marketing authorisation procedure of this product? Legislation must sufficiently and consistently link the IVD and the medicinal product.

As a first attempt to identify the theoretical hazards related to the combined use of a pharmacogenomic test and a medicinal product, we searched for keywords related to diagnostics in medicinal product legislation (keywords: *in vitro* diagnostic, companion diagnostic, medical device, diagnostic device, *in vitro* companion diagnostic device, in house, targeted) and for keywords related to medicinal products in current IVD legislation (keywords: medicinal product, medicine, drug product, companion, in house, EMA, targeted). Since this did not reveal any relevant links between medicinal products and IVDs in the current legislation, the project team looked at the points where the medicinal product effect and the IVD result link to each other:

Pre-market approval:

- In the performance of clinical trials as part of development of the medicinal product and/or IVD;
- In the assessment of clinical trials by drug regulatory agencies and/or notified bodies;
- In labelling.

Post-market activities:

- In clinical use in daily practice;
- In vigilance activities[4];

[4] In this report, vigilance activities are defined as the reporting of incidents to the competent authorities and investigation of these incidents. Incidents can occur with medicinal products and with companion diagnostics, or a combination of the two.

- In innovation activities (changes to existing products or development of new products);
- In their availability on the market.

The inventory of available products (see Step 1 above) and the outcomes of the interviews (see Step 2 above) were taken as basis when considering theoretical hazards.

After the theoretical hazards had been identified, the current legislation on medicinal products and IVDs as well as the EC's September 2012 proposal for the regulation of IVDs were reviewed to establish whether the (newly proposed) legislation contains adequate provisions to deal with the hazards identified. This was done by checking the legislative documents for provisions related to the hazards. Whenever possible, the hazard was illustrated by a case example.

3 Results and discussion

3.1 Step 1a: inventory of available medicinal products

A total of 43 medicinal products with pharmacogenomic information in the SPC were identified. A complete overview of products and their characteristics is given in Annex 4.

3.1.1 Pharmacotherapeutic areas

The greater part of the products (19) are indicated for oncological diseases (see Figure 3.1.1.1). According to the SPCs of the medicinal products, testing for the pharmacogenomic biomarkers is either required or not required before the start of treatment. The total number of 'required' and 'not required' tests for oncology products is 21 instead of 19, because for each of two oncology products, Gefitinib and Tamoxifen, two independent pharmacogenomic tests (that need to be followed up by different actions) are mentioned in the SPC. The group of 'other' areas included cardiology, dermatology, endocrinology, haematology, rheumatology and infectious diseases.

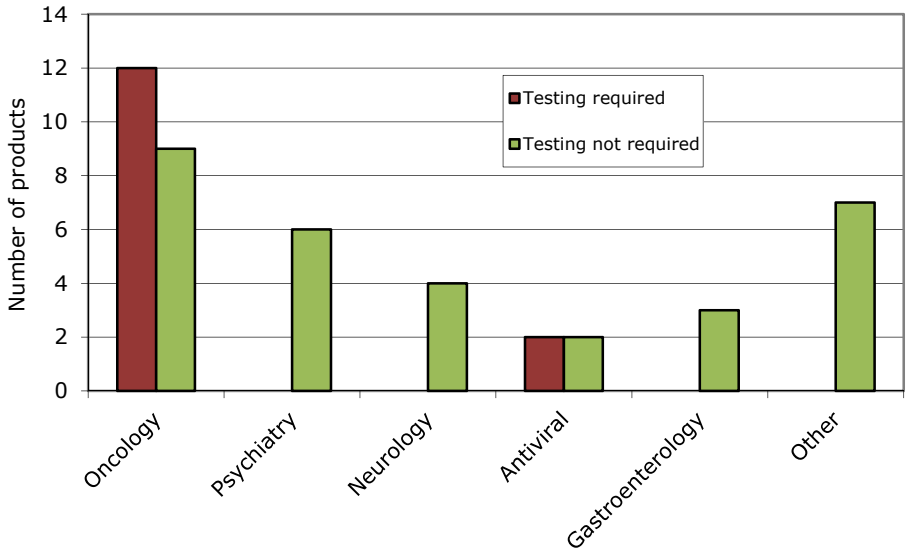


Figure 3.1.1.1 Medicinal products by therapeutic area

3.1.2 Recommended actions

The actions recommended in the SPCs are shown in Figure 3.1.2.1. When testing is required, this is in most cases used to decide whether the product is indicated for (i.e. should be prescribed to) the patient in question or not. When testing is not required, the SPC may still give advice in case testing is actually performed. Dose adjustments, usage warnings and monitoring recommendations are generally included in the SPCs but usually do not explicitly indicate what the healthcare professional should do.

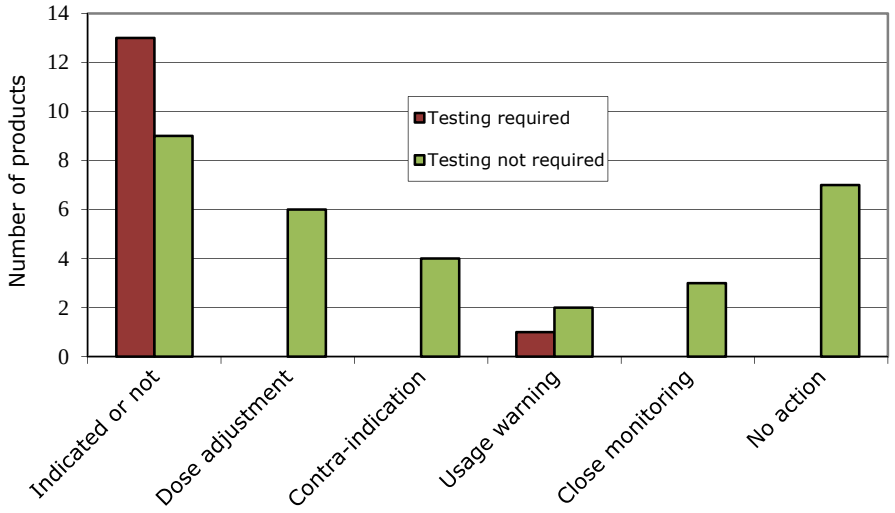


Figure 3.1.2.1 Recommended actions mentioned in SPCs

3.1.3 *Information on biomarkers and testing in SPCs*

The biomarkers mentioned in the SPCs are shown in Figure 3.1.3.1. The biomarkers marked as 'testing required' fall under our definition of a companion diagnostic. The other biomarkers ('testing not required') are pharmacogenomic tests. Since in several SPCs more than one biomarker is mentioned, the total number exceeds 43. The companion diagnostics for the identification of biomarkers that need to be tested for before the start of treatment are all related to oncology products, with the exception of those for CCR5 and HLA-B*5701 (which are indicated in the SPCs of antiviral products).

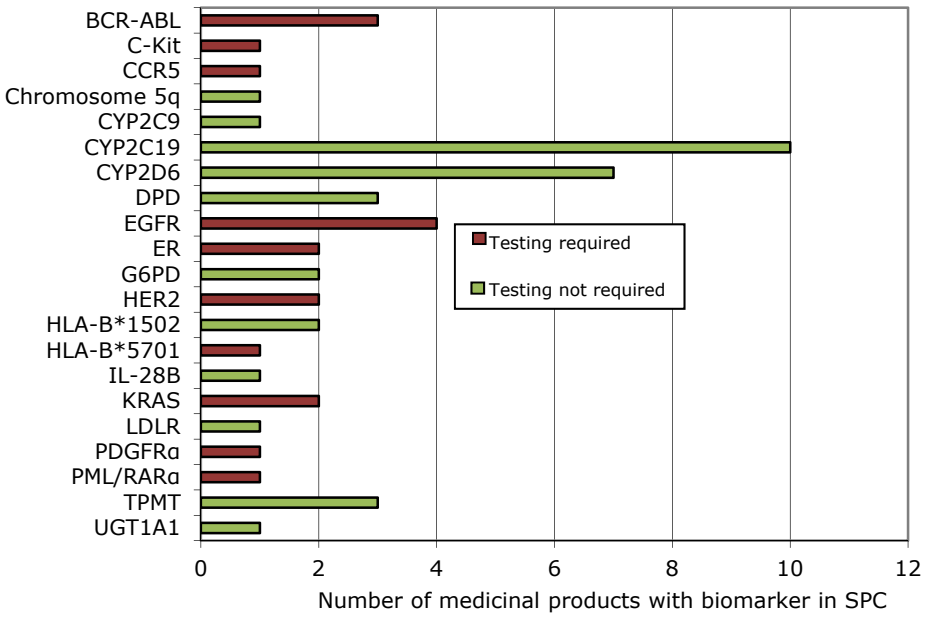


Figure 3.1.3.1 Biomarkers mentioned in SPCs

The information on the biomarkers given in the SPCs of all of the 14 medicinal products requiring a test before the start of treatment is shown in Figure

3.1.3.2. For 11 out of these 14 products no information about the test to be used is given or the SPC states only that 'a validated test should be used'.

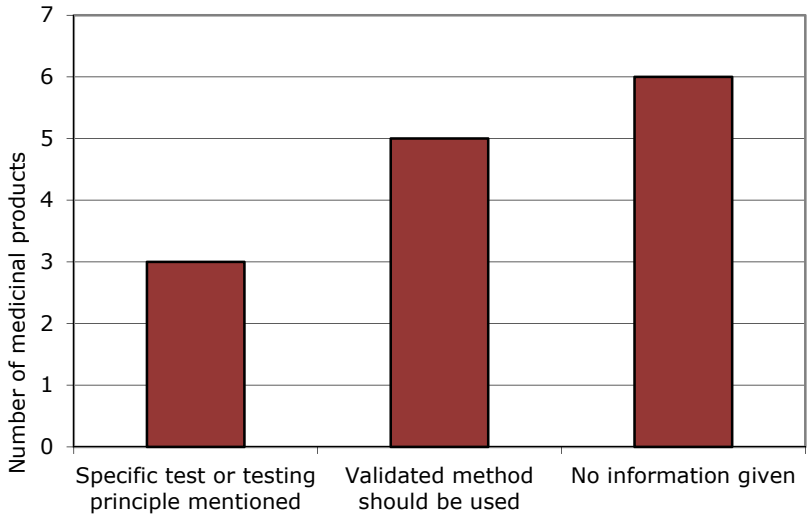


Figure 3.1.3.2 Information on device or testing principle for companion diagnostic

3.1.4 Identification of potential hazards

For medicinal products for which testing is optional the pharmacogenomics information in the SPC is apparently of limited, or yet unknown, clinical relevance. Nonetheless, in our opinion, for this group of products, a comprehensive summary on the available knowledge in the SPC is relevant. This information may stimulate the generation of clinical data that may in the future provide sufficient evidence to recommend required instead of optional testing.

For medicinal products with obligatory testing, therapeutic choices in clinical trials are based on a specific test/ testing principle, leading to the designation of stratified groups. If no test or testing principle is prescribed in the SPC, the choice is up to the healthcare professional (e.g. clinical chemist, pharmacist or pathologist). When the test or testing principle applied in daily practice differs from the one used in the clinical trials (on which the benefit–risk balance is based), it can be expected to lead to another group being stratified and to a shift in the benefit–risk balance.

3.2 Step 1b: inventory of IVDs

In relation to the biomarkers mentioned in the SPCs of the 43 medicinal products, information was gathered for 45 CE-marked testing devices. Information on commercial pharmacogenomic tests is not readily available: a publicly accessible database with CE-marked testing devices and up-to-date instructions for use is missing. A complete overview of testing device characteristics is given in Annex 5. Out of 45 CE-marked testing devices, 33 fall under the definition of a companion diagnostic (which means, in terms of this report, that testing of the biomarker is required before the start of treatment). For one biomarker (CCR5) no CE-marked testing device was found.

3.2.1 Biomarkers and testing principles

The most common testing principles of the 45 testing devices (either companion diagnostics (required) or pharmacogenomics (optional)) are shown in Figure

3.2.1.1. For the 33 devices used for companion diagnostics the numbers of devices using each testing principle are presented in Figure 3.2.1.2. For several biomarkers more than one testing device (up to nine per biomarker), with differing testing principles (up to four per biomarker), are available on the market.

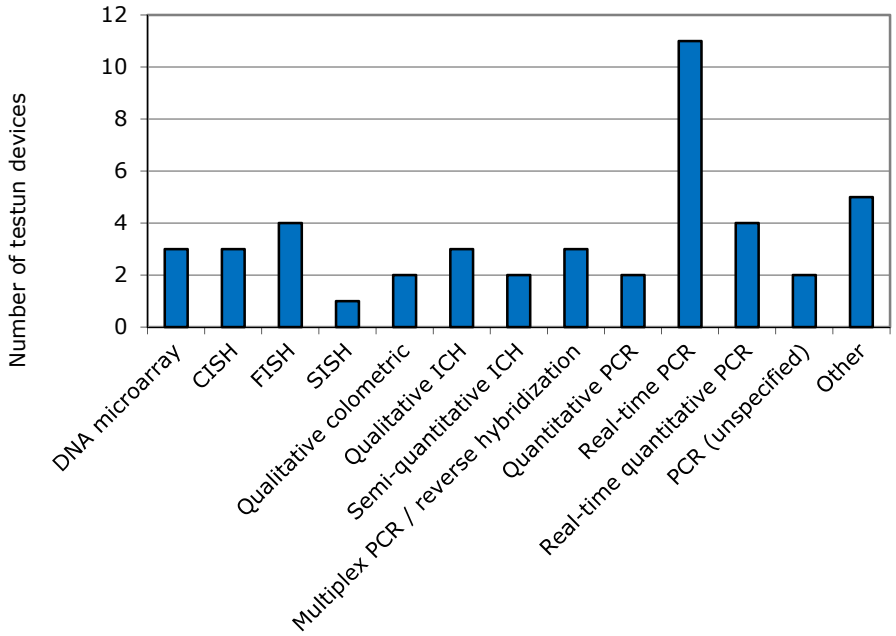


Figure 3.2.1.1 Information on testing principles

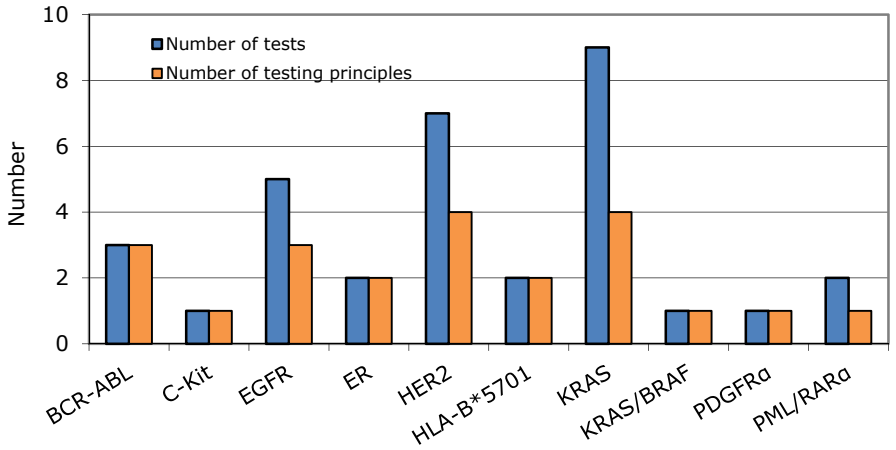


Figure 3.2.1.2 Information on CE-marked companion diagnostics

3.2.2 *Testing principles used in clinical trials of medicinal products*

For only 2 of the 45 CE-marked testing devices, the testing principle corresponds with the testing principle used in the clinical trials performed on the medicinal product, according to the European Public Assessment Reports (EPARs) (see Figure 3.2.2.1). In 10 cases, the testing principle of the CE-marked testing device does not correspond with the testing principle used in the clinical trial. In all other cases, no testing principle is mentioned in either the information on the

CE-marked testing device or in the EPARs, or there is no EPAR available ('Not applicable').

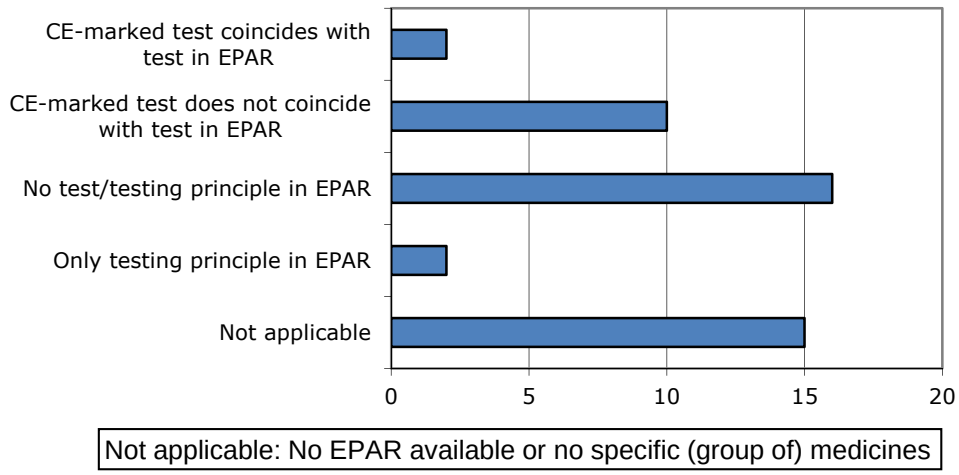


Figure 3.2.2.1 Correspondence of testing principles in CE-marked testing devices and tests used in clinical trials according to the EPARs

3.2.3 Information on medicinal products in instructions for use

For 26 of the 33 companion diagnostics, specific medicinal products or groups of products are mentioned in the instructions for use of the testing device. The intended use for the other seven companion diagnostics devices is only to determine a specific biomarker; their instructions for use do not provide information on the specific medicinal products for which the biomarker is required to be tested for.

3.2.4 Identification of potential hazards

In the case of a companion diagnostic, the therapeutic decisions in clinical trials are based on a specific test/device/testing principle, leading to the definition of a stratified group. When the testing principle applied in daily practice differs from the one used in clinical trials (on which the benefit–risk balance is based), this may lead to another group being stratified and to a shift in benefit–risk balance. This may be the case when a new testing principle is developed after market approval of the medicinal product or when the CE-marked testing device used in clinical trials is no longer available (in which case a test developed in house will be used). In such cases, information on the patient stratification generated by the test or testing principle used in the clinical trial should be provided.

3.3 Step 1c: personalised medicine in Dutch clinical practice guidelines

Information on pharmacogenomic tests was gathered from 34 clinical practice guidelines. A complete overview of guideline characteristics is given in Annex 6.

3.3.1 Characteristics of available guidelines

The number of guidelines per therapeutic area is given in Figure 3.3.1.1. The level of agreement between the information provided in the guidelines and the information in the SPC of the medicinal products mentioned in the guidelines is shown in Figure 3.3.1.2. For example, if for a specific medicinal product pharmacogenomic testing is required and the guideline also indicates that this

must be done before the start of treatment, this implies that the guideline and the SPC are fully agreement. If a biomarker is mentioned in the SPC but not in the guideline, then there is no agreement between the two documents. If the biomarker is mentioned in the SPC as well as the guideline, but the advice given differs, then there is partial agreement.

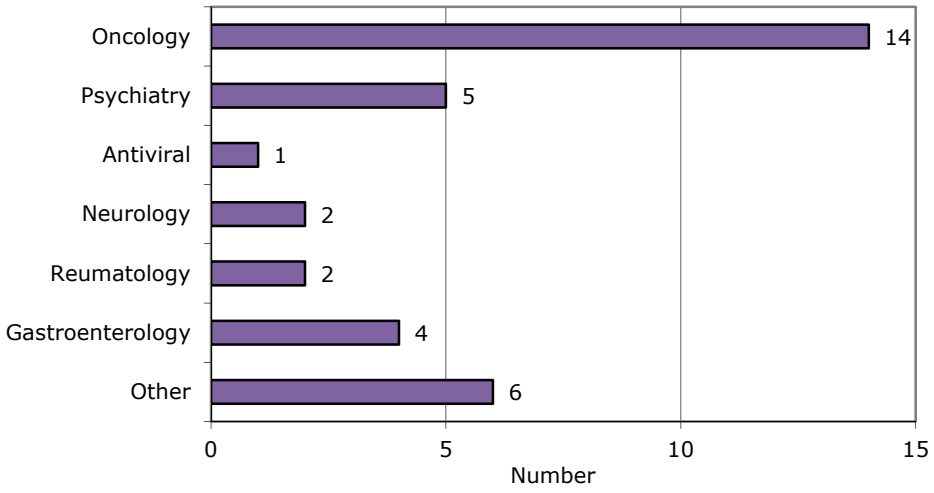


Figure 3.3.1.1 Number of guidelines per therapeutic area

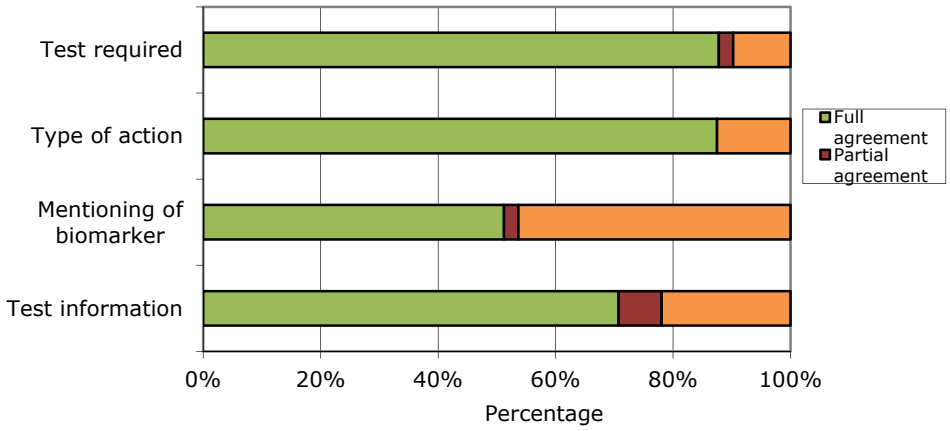


Figure 3.3.1.2 Level of agreement between guidelines and SPC

3.3.2 Identification of potential hazards

If a discrepancy exists between the information in clinical guidelines and SPCs, healthcare professionals may base their treatment decision on the one that does not give information on biomarker testing. In this case, there is a risk that treatments that are effective or those that have less harmful side-effects are withheld from patients.

3.4 Step 2: semi-structured interviews

The heterogeneity of the group of interviewees regarding their profession was sufficient to cover a broad area of expertise in personalised medicine. Sufficient

saturation was achieved, since the last interviews did not provide new themes and insights, and did not show large variation in interviewees' responses.

The interviewees mentioned the following potential hazards and hindrances relating to the practice of personalised medicine:

1. In relation to the diagnosis of disease and choice of treatment:
   - Lack of pharmacogenomics knowledge among healthcare professionals;
   - Absence of complete (public) information on the possible influence of pharmacogenomics on the clinical outcome of the use of a medicinal product (more explicitly: the fact that information is not included in the SPC not only when the level of evidence is still limited or when pharmacogenomics has been shown to have no influence, but also, in some cases, when pharmacogenomics has been fully proven to have influence).
2. In relation to the choice of pharmacogenomic test:
   - lack of knowledge of testing principles;
   - lack of information on/studies related to differences in testing devices.
3. In relation to the performance of the test:
   - inter-laboratory variability in testing results;
   - variability in results between testing devices with differing testing principles;
   - lack of knowledge of testing devices, leading to unreliable results;
   - time needed to perform a test is too long to take timely decisions on pharmacotherapy.
4. In relation to the interpretation of the test results:
   - inter-individual variability in the interpretation of test results;
   - inadequate communication of test results to healthcare professionals.
5. In relation to information for the treatment
   - advice in the SPC is not always clear;
   - not using existing knowledge, leading to a delay in the implementation of pharmacogenomics in practice;
   - lack of evidence/studies investigating the relationship between pharmacogenomics and clinical effects.

Most of the hazards and hindrances perceived by the interviewees are related to knowledge (education, level of evidence, research), to laboratory quality assurance (accuracy and variability of testing results, communication of results) and to the implementation of tests (too much time needed for a test, not using existing knowledge). Only three of the hazards/hindrances mentioned (absence of complete (public) information on the possible influence of pharmacogenomics on the clinical outcome of a medicinal product, advice in SPC is not always clear and variability in results between testing devices with differing testing principles) are directly linked to the regulatory framework for the market approval of personalised medicine products, and only the last of these three is specifically related to the link between legislation on the testing device and on the medicinal product (see further *Step 3: review of legislation, 3.5.3*, third point of hazard 4).

3.5 Step 3: review of legislation

3.5.1 Medicinal products

The regulatory system for the market authorisation of medicinal products is based on the provisions of Directive 2001/83/EC [9]. This Directive is

supplemented by 13 other Directives, 21 Commission Regulations and several other legal reference documents [6]. The legislation is characterised by a high degree of technical detail, following the 'old approach' of 'total sectoral harmonisation' [10]. The legislation is supported by an extended series of Community guidelines, which are published in The Rules Governing Medicinal Products in the European Union [11]. The main objectives of this EU Community legislation are to eliminate obstacles to the free movement of products and to safeguard public health and consumer safety. There is no specific mention of personalised medicine or any related terms, such as pharmacogenomics, pharmacogenetics or biomarkers, or reference to the use of IVDs in combination with medicinal products.

The framework of the pharmaceutical legislation is supplemented by scientific guidelines. These guidelines do not have any legal force, but are to be considered as a harmonised European Community position, which aims at facilitating the assessment, approval and control of medicinal products in the European Union [12]. Alternative approaches may be followed, but these need to be appropriately justified.
For medicinal products, wholesalers must guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and deliver the supplies requested within a very short time over the whole of the area in question [8]. Any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State shall cease to be valid [8].

Box a Definition of medical device
'Medical device' means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:
- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception.

and which does not achieve its principle intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

3.5.2 In vitro *diagnostic devices*

3.5.2.1 Current legislation

IVDs are medical devices (see *Box a* for definition of 'medical device'). The current EU regulatory framework for IVDs consists of Directive 98/79/EC (the *in vitro* diagnostic medical device directive; IVDD) [13]. The main purpose of this directive is the same as for medicinal product legislation (i.e. to eliminate obstacles to the free movement of products and to safeguard public health and consumer safety). The definition of an IVD in this directive is outlined in Box b. Pharmacogenomic tests and companion diagnostics are not specifically mentioned, but fall under the scope of this directive. The IVDD is meant only for IVDs that are placed on the market (for payment or free of charge). IVDs developed and manufactured by health institutions (e.g. hospitals) for use within the same institution (without transfer to another legal entity) are exempted.

The IVDD follows the so-called New Approach to Community legislation. A new regulatory technique and strategy was laid down by the Council Resolution of 1985 on the New Approach to technical harmonisation and standardisation, which established the following principles:

- Technical requirements are limited to 'essential requirements' that products placed on the Community market must meet if they are to benefit from free movement within the Community;
- The technical specifications of products that meet the essential requirements set out in the directives must be laid down in harmonised standards;
- The application of harmonised or other standards remains voluntary, and the manufacturer may always apply other technical specifications to meet the essential requirements; however, a justification for so doing is needed;
- Products designed in compliance with harmonised standards benefit from a presumption of conformity with the corresponding essential requirements.

Box b Definition of IVD

'*In vitro* diagnostic medical device' means any medical device that is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

- concerning a physiological or pathological state, or
- concerning a congenital abnormality, or
- to determine the safety and compatibility with potential recipients, or
- to monitor therapeutic measures.

New Approach European Commission directives define the 'essential requirements', with respect to health, safety and environmental protection, that goods must meet when they are placed on the market. In the IVDD, the essential requirements specifically address topics like chemical and physical properties, infection and microbial contamination, manufacturing and environmental properties, and self-testing.

IVDs must meet the essential requirements set out in annex I of the IVDD. Depending on the product's risk class, an IVD manufacturer may choose from a number of modules (conformity assessment procedures) to demonstrate compliance with the requirements in the directive, including the essential requirements. The procedures range from product design examination, through EC-type examination (a notified body reviews a representative sample of production) and EC verification (demonstrating compliance with a representative sample of products) to production quality assurance or a quality assurance audit. Most conformity assessment procedures combine two or more of these modules.

IVDs are grouped into four risk classes:

1. Highest-risk IVDs, subject to conformity assessment by a notified body, including an examination of the design of the IVD: e.g. IVDs used to determine the blood groups ABO system, rhesus (C, c, D, E, e), anti-Kelland IVDs for markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D;
2. High-risk IVDs, subject to conformity assessment by a notified body: e.g. tests for rubella, toxoplasmosis, cytomegalovirus, chlamydia and PSA;
3. Low-risk IVDs, including all devices that are not highest-risk nor high-risk devices and not subject to conformity assessment by a notified body (no direct risk to patients and used by competently trained professionals);
4. Self-tests, for which notified body assessment is required to check the adequacy of the design and instructions for use, related to the use of the device by non-professionals.

The highest-risk devices and high-risk devices are listed in annex II of the IVDD. New devices not listed in annex II automatically fall into the category of low-risk devices.

The large majority of IVDs, including pharmacogenomic testing devices and companion diagnostics, are classified as 'low-risk'. For this class, the manufacturer self-assesses conformity with the essential requirements, compiles a technical file with all relevant documents, prepares a declaration of conformity, applies the CE mark to his product and places the product on the market.

3.5.2.2 Proposal for new European IVD legislation

In September 2012, the European Commission published a proposal for a Regulation on *in vitro* diagnostic medical devices [14, 15], intended to replace the IVDD.

Compared to the IVDD, the main changes proposed are:

- That the Regulation becomes national legislation in the member states without the need for each member state to transpose it into national law. This allows for quicker and more uniform implementation.
- A change in legal format: from Directive to Regulation;
- Extension of the scope with explicit reference to genetic tests and companion diagnostics;
- More detailed and stringent rules for notified bodies;
- A qualified person within the manufacturer's organisation must be responsible for regulatory compliance;
- Introduction of an identification and traceability system (Unique Device Identification);
- Further development of Eudamed (European databank of medical devices);
- Introduction of a new risk rule classification system, based on Global Harmonisation Task Force principles, which replaces the list of 'high-risk' IVDs in annex II) (see IVD risk classes, 3.5.2.1);
- The need for clinical evidence to support adequate performance of the IVD, including scientific validity of the analyte, analytical performance and, if applicable, clinical performance;
- Clinical performance studies whose results may influence patient management or treatment decisions ('interventional clinical performance studies') are subject to regulatory approval;
- In the case of companion diagnostics, the notified body must consult a medicinal product-authority regarding the suitability of the device in relation to the medicinal product concerned (also in the case of post-market-approval changes);
- More detailed and stringent requirements for post-approval follow-up (by the manufacturer), market surveillance and vigilance.

Companion diagnostics and pharmacogenomic testing devices are classified as risk class C. They must be assessed by a notified body before they can be released onto the market. Moreover, for companion diagnostics, the European Medicines Agency (EMA) or the medicinal product authority of a member state must be consulted regarding the suitability of the device in relation to the medicinal product concerned (it is not further specified what needs to be done by this authority). The notified body shall give due consideration to the opinion expressed by the EMA or the medicinal products-authority concerned and communicate its final decision to that authority. Before any changes that might affect the suitability of the device in relation to the medicinal product concerned

are made, the manufacturer shall inform the notified body of the proposed changes, and it shall consult the EMA or the medicinal products-authority that was involved in the initial consultation.

It is noted that the proposed Regulation does not apply to class C IVDs that are developed and used in house (i.e. within a single health institution, such as a hospital), provided that manufacture and use are managed by the health institution's single quality management system, and the health institution is compliant with standard EN ISO 15189 'Medical laboratories - Requirements for quality and competence' or an equivalent recognised standard [16]. Health institutions manufacturing and using in house tests must report any serious incidents and safety corrective actions to the competent authority of the member state in which the health institution is located.

3.5.3 *Identification of potential hazards*

Evaluation of the adequacy of the regulatory framework for controlling the risks of using personalised medicine products has led to the identification of six hazards within the current legislation for medicinal products and IVDs. The estimated risks posed by these hazards are illustrated using practical cases, when available. A distinction was made between hazards at the pre-market-approval and post-market-approval stages.

Pre-market approval

1. The IVD used in the early clinical trials on medicinal products differs from the IVD used in the pivotal clinical trials, e.g.:
    - the CE-marked IVD was modified during development of the medicinal product, which may not have been noticed during assessment for market authorisation of the medicinal product, due to the absence of a requirement for information and communication on these changes.

Hazard 1: the IVD used in the early clinical trials on the medicinal product differs from the IVD used in the pivotal clinical trials

Consequences: This could lead to differences in the selection of patients. A new type of IVD could differ in analytical and clinical performance (sensitivity, specificity or detection threshold) and therefore select different populations. This may affect the benefit–risk balance.

Estimated risk: This situation is not likely to occur. During the marketing authorisation process of the medicine, clinical assessors will notice the use of new IVDs with other testing principles. No examples have been found of major changes in existing IVDs. When the situation does occur, the risk for patients is small, since market approval decisions are mainly based on the pivotal clinical trials.

Conclusion: There is no need for risk control and no need to amend regulations.

2. A new medicinal product (whose treatment success involves a genomic biomarker) and a new device are simultaneously developed, with the result that the requirements for the clinical trials of the medicinal product may be different from the requirements set out in the IVDD and it is unclear whether there will be a separate benefit–risk assessment for

the medicinal product used in combination with the IVD and the IVD as such (the IVD always requires a risk assessment).

Hazard 2: a new medicinal product and a new device are simultaneously developed

Consequences: Clinical trials for medicinal products are subject to specific and detailed requirements, which are described in guidelines of the EMA. Moreover, EMA guidance is available on (genomic) biomarkers. In the proposed IVD regulation, clinical trials demonstrating the adequate performance (the so-called clinical performance) of the IVD are required, but the requirements for these studies are not specifically described. Consequently, the lack of coordination between the requirements for the clinical performance of medicinal products and IVDs causes the need for more clinical trials. This may not only be a duplication of work; it would also lead to increased costs and, obviously, if patients are involved, would be unethical.

Estimated risk: The estimated risk is high, as this situation is likely to occur, but it could be avoided by either adapting legislation or making 'soft legislation' (i.e. guidelines or other documents with agreed viewpoints on clinical trials requirements and assessments).

Conclusion: Pre-market approval, there is a risk for patients of being recruited in clinical trials that could have been avoided if the clinical requirements for medicinal product approval and market access for IVDs were aligned.

Post-market activities

3. The labelling of the medicinal product and the IVD are not consistent and/or coherent, e.g.:
    - the SPC of the medicinal product does not mention what (kind of) IVD to use – for example, fulvestrant is an injectable oestrogen receptor antagonist used for the treatment of hormone receptor-positive metastatic breast cancer. The SPC does not mention a specific IVD or testing principle to determine the hormone receptor status of the tumour. For oestrogen receptor testing more testing principles exist, based on IHC and PCR. No details are given of the expression levels of the hormone receptor on the tumour, as is given for Trastuzumab in cases of HER3 tumour expression (see box on Hazard 4);
    - the SPC of the medicinal product mentions an IVD that is no longer available on the market;
    - the instructions for the use of the IVD mention a medicinal product for which no testing need is indicated in the SPC.

Hazard 3: labelling of the medicinal product and the IVD are not consistent and/or coherent

Consequences: Different groups may be selected, depending on the test or threshold, resulting in different benefit–risk balances.

Estimated risk: This situation is likely to occur and there is a risk for patient safety in cases where use of the alternative IVD (not mentioned in the SPC and/or used in the clinical trials) leads to a different treatment decision from that made when the IVD used in the clinical trials was applied, although this is partly solved by clinical practice guidelines on tumour ER-status testing.

Conclusion: Risks may be controlled when available IVDs and their clinical performance are compared to the one used in the clinical trials/mentioned in the SPC. A (new) testing principle demonstrating better (or at least comparable) stratification should be evaluated against the principle(s) used successfully in the clinical trials of the medicinal product. Information on this standard and the performance of the new or other IVDs should therefore be included in the SPC, which is currently not always the case.

4. The IVDs on the market differ from the IVD used in the clinical trials on the medicinal product, e.g.:
    - the CE-marked IVD changed during the marketing of the medicinal product;
    - another CE-marked IVD for that product becomes available – for example, the HER2 protein expression on breast tumours is an important therapeutic target for breast cancer treatment. Only patients with HER2 over-expression or amplification are eligible for Trastuzumab treatment. Originally, HER2 status was assessed on protein levels using IHC, but many more HER2 testing technologies became available after market approval of Trastuzumab. Currently there is no consensus on which technique is the best;
    - an in-house developed test is used instead of a CE-marked test;
    - a CE-marked IVD is used for a medicinal product for which it has not been evaluated ('off-label' use of the IVD).

Hazard 4: the IVD on the market differs from the IVD used in the clinical trials of the medicinal product

Consequences: The choice of testing strategy will likely be based on local preferences that consider both practical and economic issues. These local preferences might influence the patient population and thereby the benefit–risk ratio per centre.

Estimated risk: This situation is likely to occur and there is a risk to patient safety in cases where the local testing strategy used scores negative, whereas the IVD used in the clinical trial would score positive, or vice versa.

Conclusion: Risks might be controlled if testing strategies were comprehensively described in SPCs and clinical guidelines – in this case, by clinical practice guidelines on tumour receptor-status testing. See also box on Hazard 3.

5. Vigilance activities are insufficiently linked, e.g.:
    - an adverse event or efficacy problem is erroneously assigned to one component (medicinal product or IVD), while it was actually caused by the other;
    - lack of (public) information, transparency and communication with the medicinal product marketing authorisation holder or authority in the case of problems with the IVD;
    - lack of (public) information, transparency and communication with the IVD manufacturer or authority in the case of problems with the medicinal product.

Hazard 5: vigilance activities are insufficiently linked

Consequences: When the results of an IVD test determine individual sensitivity to adverse reactions to a medicine, inadequate performance of such an IVD could have severe consequences. This may be the case with 5-Fluorouracil (5-FU), a medicinal product that can cause serious adverse effects in patients with a DPD mutation. Different DPD tests (non-CE marked) are currently used. If one hospital uses a device that is less sensitive than the one(s) used in other hospitals, more adverse reactions of 5-FU can be expected in this hospital.

Estimated risk: This situation is likely to occur but it is unknown whether this happens in practice; the risk to patient safety is therefore unknown. When reporting problems with medicines to the Netherlands Vigilance Center Lareb, no information has to be provided on the IVD used to determine the medicinal product choice. Moreover, information on adverse events associated with IVDs is not systematically collected in Europe. This applies to both in-house and CE-marked devices.

Conclusion:It would be logical to report problems with IVDs to medicinal product agencies and problems with medicinal products to notified bodies as well.

6. Non-availability of the IVD, e.g.:
    - the IVD is not yet CE-marked, while the medicinal product has already been approved;
    - the CE-marked IVD is withdrawn from the market;
    - problems with the production or distribution of the CE-marked IVD occur, but this is not communicated to the medicinal product marketing authorisation holder or authority; if the availability of the IVD on the market is abrogated, there is no legal requirement to communicate this to the medical product marketing authorisation holder or authority.

Hazard 6: unavailability of the IVD

Consequences: Suboptimal and/or delayed treatment may be the consequence of the unavailability of an IVD. This may also be the case when equipment required to perform the IVD test or a part of the IVD test is withdrawn, causing abrogation of the IVD.

Estimation of risk: This situation is likely to occur, as is demonstrated by reports by the FDA of recalls of IVDs, but risks to the safety of patients are unknown since it is unknown whether alternative IVDs or in-house tests could replace the original IVD. When IVDs are unavailable, alternative IVDs or in-house tests may be performed.

Conclusion: Information on suitable alternative IVDs should be provided in SPCs and guidelines.

3.5.4 Hazards addressed in new European IVD legislation

Article 40 of the September 2012 proposal for a Regulation on IVDs partly addresses the first two points of hazard 4 (changed IVD or new IVD with either a similar or different testing principle): in the event of a new IVD or a change in an existing IVD intended to assess patient eligibility for a treatment with a specific medicinal product, the notified body must consult a medicinal product authority. However, no communication on this new or changed IVD is foreseen with the marketing authorisation holder of the medicinal product . Communication on this may be important for the interpretation of vigilance data of the medicinal product and to update information available on the allowed (testing principles of the) IVDs in the SPC. The other hazards are not specifically addressed in the September 2012 proposal. Therefore, there is a need for a review of the provisions for companion diagnostics in the proposed Regulation. Issues such as how to deal with in-house testing should also be addressed.

4 Reflection

Personalised medicine can be used for screening purposes in the general population (personalised prevention/screening), for disease prevention or to stratify patients for the purpose of maximal efficacy or minimal toxicity of treatment [1, 2]. This report is dedicated to personalised therapy and the use of IVDs therein to select patients on the basis of their genetic make-up for appropriate medicinal treatment. Pharmacogenomic tests are carried out with IVDs, which are used to identify variations in DNA and RNA characteristics to guide medicinal treatment decisions. We have defined companion diagnostics in this report as pharmacogenomic tests that *must* be carried out before a patient is treated with the medicinal product. In this report, we have explored the legislation on personalised medicine products and IVDs with the aim of evaluating the adequacy of the regulatory framework to control the hazards and risks of personalised medicine products. First, an inventory was made of medicinal products that make mention of pharmacogenomic tests in their SPCs and of the CE-marked pharmacogenomic testing devices that are available on the market. The information in the SPCs of the medicinal products, the information retrieved from CE-marked pharmacogenomic testing devices and information on personalised medicine in Dutch clinical practice guidelines were all evaluated for potential hazards and risks. Second, Dutch healthcare professionals practising personalised medicine on a daily basis were interviewed to explore whether they were aware of risks to patients when practising personalised medicine. Third, current European medicinal product and IVD legislation and the proposal for new IVD legislation published by the EC in September 2012 were evaluated to identify whether potential hazards are (or will be) sufficiently controlled or whether they (will) still exist.

Step 1: inventory of available products and product information
The greater part of medicinal products with pharmacogenomic testing mentioned in the SPC are indicated for oncological diseases. These include medicinal products for which testing is required as well as those for which testing is optional. In the case of required testing, tests are almost exclusively performed in order to ascertain whether the medicinal product is indicated for the patient in question. Where testing is optional, the information may be used for other purposes, such as dose adjustment and monitoring. The SPC states the genetic biomarker that must be tested for before start of treatment but it seldom provides information on a specific test, testing device or testing principle. Sometimes it states that a validated method should be used; most often it does not provide any information on testing at all. As well as in SPCs, information on pharmacogenomic testing of medicinal products is provided in Dutch clinical practice guidelines. The information on pharmacogenomic tests, testing principles and biomarkers to be tested for is not always concordant between SPCs and clinical guidelines. However, in case of personalised medicine products where testing is required, the information in the SPC and clinical guidelines is generally concordant.

For the genetic biomarkers mentioned in the SPCs of the medicinal products, CE-marked testing devices (IVDs) are available. The research into CE-marked IVDs for this report showed that for some biomarkers that must be tested for before treatment with the medicinal product, several CE-marked IVDs were on the market. In some cases, the testing principle of the CE-marked IVDs did not

match the testing principle of the IVD used in the clinical trials of the medicinal product. The medicinal product for which the companion diagnostic was intended was not always specified in the instructions for use of the IVD.

Medicinal products and IVDs (including pharmacogenomic tests and companion diagnostics) are regulated by different legislative frameworks. In personalised medicine, these two components are linked [16]. The combination may have implications for the safe use of personalised medicine products. Regarding SPCs and the clinical guidelines that are provided with personalised medicine products, potential hazards for patients may be limited by providing comprehensive information on pharmacogenomic tests in these documents. Also, concordance between these documents must be ensured. Similarly, instructions for the use of companion diagnostics should state the medicinal product for which their use is intended. However, for some biomarkers to be tested for in advance of using a personalised medicine product, multiple CE-marked companion diagnostics are on the market, including IVDs and/or testing principles that are different from those used in the clinical trials of the medicinal product. Furthermore, in-house tests may be used. In these cases, patient safety may be at stake; results may vary between these tests and the one used in the clinical trial, risking the stratification of different populations and leading to a shift in benefit–risk balance. Comparison of the results of alternative tests, testing principles with those obtained by the IVD used in the clinical trial may help to minimise this risk.

Step 2: semi-structured interviewing of healthcare professionals
Healthcare professionals practising personalised medicine on a daily basis were interviewed to identify whether they had experienced or foresaw patient safety issues with the use of personalised medicine products. In all phases leading up to the treatment decision, risks to patient safety can be expected – namely, during diagnosis and consideration of treatment options, when choosing and performing a pharmacogenomic test and in the interpretation of the test results – as well as in the resulting treatment choice itself. An important potential hazard mentioned in the interviews was the current lack of knowledge of personalised medicine and pharmacogenomic tests among healthcare professionals nationwide. This may negatively influence the treatment options that are considered; for example, not deciding to do a pharmacogenomic test. When it is decided to perform a pharmacogenomic test as part of the treatment but knowledge is lacking on how it should be performed, unreliable results may be the consequence. To control this hazard, the information gap on tests and test performance should be covered by educating healthcare professionals on personalised medicine. The need for training of healthcare professionals in personalised medicine was also recognised in a European workshop on the opportunities and challenges of personalised medicine for European healthcare [5].

Another potential hazard mentioned is the lack of information on the relationship between biomarkers and medicinal products and on pharmacogenomic test performance. We therefore suggest that studies investigating biomarker–medicinal product relationship are needed and that the results should be communicated to healthcare professionals through SPCs and guidelines even if evidence is weak or lacking.

As identified by us in step 1 of this report, the interviewed healthcare professionals identified the variety of pharmacogenomic testing devices and/or testing principles that are available on the market or that can be used in house

as an important hazard, potentially leading to different results from those obtained in the clinical trials of the medicinal product. The healthcare professional must be aware of which specific test, device or testing principle provides the right stratification, comparable to, or better than, that obtained in the clinical trials of the medicinal product. It should be assessed whether other tests, devices or testing principles provide similar or different results. If this is not known, studies should be performed to fill this information gap.

Step 3: review of legislation
In the current regulatory frameworks for medicinal products (Directive 2001/83/EC) and IVDs (Directive 98/79/EC), there is no specific mention of personalised medicine or any reference to the use of IVDs in combination with medicinal products. This gap is addressed by a proposal for an IVD Regulation, replacing the IVDD, which was published in September 2012 by the European Commission. This proposal aims to strengthen the current legislation for IVDs, and to assure a more uniform implementation of legislation by making it a Regulation rather than a Directive. It also proposes to extend the scope of the legislation by explicitly mentioning genetic tests and companion diagnostics. Other changes concerning companion diagnostics include the requirement that the notified body consult a medicinal product-competent authority regarding the suitability of an IVD in relation to the medicinal product concerned and more detailed and stringent requirements for post-market-approval follow-up (by the manufacturer), market surveillance and vigilance.

In pre-market-approval activities, some imperfections in the legislation are identified, including unclear rules for cases where a new medicinal product and a new IVD are simultaneously developed. For medicinal products, clinical trials need to be performed to assure clinical performance. For IVDs, analytical performance, i.e. the ability of a device to correctly detect or measure a particular analyte, needs to be assured. In addition, in the new proposal for IVD regulation, the clinical performance of IVDs is addressed. For IVDs, clinical performance means the ability of a device to yield results that are correlated with a particular clinical condition or a physiological state in accordance with the target population and intended user. The need to perform clinical trials of medicinal products as well as of IVDs to test clinical performance may lead to a duplication of effort. In this report, we propose adaptation of the legislation on medicinal products to that on IVDs or, in cases where a personalised medicine product and an IVD are developed simultaneously, ‘soft legislation’ to reduce the number of clinical trials required to assess their performance. A proposal has also been made for standardised interactions with agencies for the co-development of medicinal products and IVDs [3]. It is proposed that joint meetings with pharmaceutical and diagnostics industry and therapeutic and diagnostics regulatory authorities should be scheduled right from the early phases of medicinal product development. For example, four-party pre-clinical, pivotal and pre-submission meetings would cover the process from initial trials up to market approval and stimulate concordance [3].

The regulatory frameworks for medicinal products and IVDs do not adequately control the risks involved in the use of personalised medicine products, specifically during the phase following the market approval of medicine products, with potential adverse consequences for patient safety. The main hazard in this regard, which was also identified in steps 1 and 2 in this report, is the lack of information in the SPCs of medicinal products or the discrepancies between that information and the instructions for use of the related IVDs. To restrict this hazard, there must be uniformity between information in the SPCs of medicinal

products and in the instructions for use of IVDs, in particular in the case of companion diagnostics, i.e. tests that must be carried out before the medicinal products may be administered. It is also imperative for comprehensive information to be provided in SPCs as to which IVD(s) to use and for this information to be updated regularly.

Another hazard identified in steps 1 and 2 is the variety of IVDs (CE-marked or developed in house) that may be available for one biomarker. An IVD may also be used with a medicinal product for which it was not developed ('off-label' use). As mentioned in step 2, studies comparing the results of different tests should be performed, for example those of an alternative or new IVD and the IVD that was used in the clinical trial. The names of the IVDs that correctly stratify the treatment group, together with the test results, may then be added to the SPC. In current legislation on medicinal products and IVDs, vigilance activities are insufficiently linked; therefore, hazards may exist. Problems with medicinal products may be due to a lack of sensitivity of or incorrect stratification by the IVD. Currently, only problems with medicinal products must be reported to the Netherlands Vigilance Center Lareb. Greater insight into the effectiveness of vigilance activities related to personalised medicine may be achieved if problems with *both* personalised medicine products *and* companion diagnostics had to be submitted.

A final hazard has been demonstrated by reports from the FDA of recalls of IVDs [17]: it is the possibility that an IVD is recalled or otherwise withdrawn from the market after the relevant medicinal product has been approved.

Without exception, all the potential hazards of personalised medicine that are due to the different regulatory frameworks of its two components indicate that legislation must apply consistently to both medicinal products and the corresponding IVDs. If this consistency is achieved, the risks of personalised medicine products may be adequately controlled within the regulatory framework.

5 Conclusion

The adequacy of the regulatory framework to control the risks of personalised medicine products was evaluated. In step 1, information contained in the SPCs of personalised medicine products, clinical guidelines and instructions for the use of CE-marked IVDs were researched and compared. In step 2, healthcare professionals practising personalised medicine on a daily basis were interviewed. In step 3, the legislation on medicinal products and IVDs was reviewed. The main findings were that:

- The lack of information in SPCs, clinical guidelines and instructions for the use of CE-marked companion diagnostics and discordance between information provided in these documents are a potential hazard for patient safety. Concordance between documents should be achieved to provide unambiguous guidance to healthcare professionals in selecting the appropriate medicinal product and IVD combination;
- In both SPCs and clinical guidelines, recommendations are needed on which specific pharmacogenomic test(s) or testing principle(s) to use. It may not be necessary to recommend exactly the same test that was used in the clinical trial of the medicinal product; either commercial or in-house tests may be used. However, the results of alternative tests should be compared with those of the test used in the clinical trials to assure the adequate stratification of patients;
- Given that different regulatory frameworks exist for medicinal products and IVDs in personalised medicine, the September 2012 proposal for a Regulation on IVDs is an improvement, since it more specifically addresses companion diagnostics, although not in much detail.

In conclusion, this report indicates that a strong system for personalised medicine can only be obtained if the regulation of medicinal products is linked to that of the relevant IVDs. This will control some of the risks involved and support the safe use of personalised medicine.

6 Recommendations

To control the risks of personalised medicine within the regulatory framework, we propose the following:

1. That the summary of product characteristics (SPC) of a personalised medicine should include information on:
   - the biomarker tested for in the pivotal clinical trials of the medicinal product;
   - the companion diagnostic testing principle(s) used in the pivotal clinical trials of the medicinal product, including information on the analytical performance (e.g. sensitivity, specificity, accuracy, reproducibility) and clinical performance (e.g. sensitivity, specificity) characteristics;
   - the influence of pharmacogenomics on the clinical outcome (even when there is no influence or when evidence of influence is not conclusive);
   - clear advice on the action to be taken on the basis of the companion diagnostics test results (e.g. dosing, monitoring);
   - post-market activities: any new testing principle(s) that have been proven to result in an acceptable stratification.
   → *All these issues could be dealt with in a future revision of the Guideline on SPCs (current version: Revision 2, September 2009).*

2. That the instructions for the use of an IVD should include information on:
   - the (type of) medicinal product(s) for which the IVD has been proven to be suitable.
   → *This issue could be dealt with in the (revised) proposal for a Regulation on IVDs.*

3. In order to guarantee accurate and correct stratification, that guidance is needed on how to prove the equivalence or non-inferiority of new testing principles in companion diagnostics to the principle(s) used in clinical trials of the medicinal product. This guidance should be applicable to CE-marked IVDs as well as to lab-developed devices.
   → *This issue could be dealt with in a guidance document developed jointly by the EMA and IVD-Technical Group (IVD-TG) of the European Commission.*

4. That guidance on clinical performance studies for companion diagnostics should be developed and aligned with guidance on clinical trials for medicinal products.
   → *This issue could be dealt with in guidance document(s) developed jointly by the EMA and IVD-TG.*

5. That any incidents, safety issues, safety corrective actions and recalls related to companion diagnostics should be communicated to medicinal product agencies, with a notification as to which (type of) medicinal product(s) the information is relevant to. If needed, SPCs should be revised accordingly.
   → *This issue could be dealt with in the (revised) proposal for a Regulation on IVDs.*

6. That any incidents, safety issues, safety corrective actions and recalls related to medicinal products should be communicated to the notified bodies, with a notification as to which (type of) companion diagnostics the information is relevant to. If needed, product information should be revised accordingly.
   → This issue could be dealt with in the (revised) proposal for a Regulation on IVDs.

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List of abbreviations

BRAF	betatype receptor activation factor
BRC-ABL	breakpoint cluster region-Abelson
CCR	C-C chemokine receptor
CISH	chromogenic in situ hybridisation
CYP	cytochrome P450
DPD	dihydropyrimidine dehydrogenase
EGFR	epidermal growth factor receptor
EM	extensive metaboliser
EMA	European Medicines Agency
ER	estrogen receptor
EU	European Union
FISH	fluorescent in situ hybridisation
G6PD	glucose-6-phosphate dehydrogenase
HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IHC	immunohistochemistry
IL	interleukine
IM	intermediate metaboliser
IVD	*in vitro* diagnostic medical device
IVD-TG	*in vitro* diagnostic medical device-technical group
KNMP	Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie
KRAS	Kirsten rat sarcoma
LDL	low density lipoprotein
LDLR	low density lipoprotein receptor
MAF	minor allele frequency
PCR	polymerase chain reaction
PDGFR	platelet derived growth factor receptor
PGx	pharmacogenomics
PM	poor metaboliser
PML/RAR	promyelocytic leukemia/retinoic acid receptor
SISH	silver stain in situ hybridisation
SPC	summary of product characteristics
TPMT	thiopurine S-methyltransferase
UGT	uridine glucuronosyltransferase
UM	ultra-rapid metaboliser

Annexes

Annex 1 List of websites visited to search for Dutch clinical practice guidelines

CBO	http://www.artsennet.nl/Richtlijnen/Per-organisatie/richtlijnen_CBO.htm
Oncoline	http://www.oncoline.nl/index.php?pagina=/site/pagina.php&id=54321
NHG	https://www.nhg.org/nhg-standaarden
NVKG	http://www.nvkg.nl/artsen/richtlijnen
NVVP	http://www.nvvp.net/publicaties/richtlijnen/
HOVON	http://www.hovon.nl/behandeladvies.html
VIKC	http://www.pallialine.nl/index.php?pagina=/site/pagina.php&id=54343&regio_filter=5&regtoe_filter=VIKC

Annex 2 List of interviewees

Interviewee	Profession	Institute
Prof. J.H. van Krieken	Pathologist	Nijmegen Centre for Molecular Life Sciences (NCMLS)
I. Stap	Director of European Distribution Channels	Agendia NV, Amsterdam
Dr J. van der Weide	Clinical chemist	St Jansdal hospital, Harderwijk
Dr J.J. Swen	Hospital pharmacist	Leiden University Medical Centre (LUMC)
Dr J.G. Gregoor	Psychiatrist	Rembrandthof, Hilversum
Dr R.H.J. Mathijssen	Medical oncologist/ clinical pharmacologist	Erasmus MC, Rotterdam
Dr V.H.M. Deneer	Hospital pharmacist/ clinical pharmacologist	St Antonius hospital, Nieuwegein

Annex 3 List of questions asked during interviews

Color code:
Black: question relevant to all interviewees
Blue: question only relevant to medical specialist
Green: question only relevant to clinical chemist

Diagnosis and treatment options

Treatment guidelines		
Key question	Which information sources do you use when considering all treatment options?	
	What is your opinion on completeness and uniformity of information on pharmacogenomic tests in these sources / guidelines?	
	What do you consider as risks or hindrances of national as well as local guidelines regarding the use of personalised medicine?	Think of: completeness and uniformity in guidelines
Other questions	Does your institution make use of local guidelines? If this is the case, what kind of information is included in these guidelines?	

Testing devices

Choice for a testing device		
Key questions	What reasons do you have to use a pharmacogenomic test in case such as test is not obligatory for the medicinal product at issue?	Think of: agreements made in guidelines
	What are your considerations regarding testing device choice when you receive a request to measure a specific biomarker?	Think of: - choice for testing principle - choice of using a commercial or in house test
	How do you keep yourself up to date regarding the pharmacogenomic tests available on the market?	Think of: innovation, availability
	What do you consider as risks or hindrances for the use a medicinal product when choosing a testing device?	Think of: availability, costs, reimbursement, interchangeability, reliability
Other questions	What are your considerations when buying a commercially available testing device?	Think of: utilization, costs, agreements, influence of medical representatives, testing principles
	What is your opinion on interchangeability of pharmacogenomic tests, taking into consideration differences in testing principles as well as developing laboratories?	
Utilization of testing devices		
Key questions	What are your considerations when choosing to perform a pharmacogenomic test in your own laboratory or to	

	outsource the testing?	
	What arrangements are in place regarding ensuring test validity and quality assurance during executing a pharmacogenomics test?	Think of: guidelines, standard operating procedures, sensitivity and specificity of tests
	What do you consider as risks or hindrances for the use a medicinal product when executing a test?	Think of: - time needed to perform the test - testing in your own laboratory or outsourcing
Interpretation of testing results		
Key questions	Which information sources do you use when interpreting testing results?	
	What is your opinion or experience on the uniformity of interpretation when more than one person interprets the testing results?	Think of: interindividual variability between practitioner, clinical chemist, hospital pharmacist, or outsourcing facility
	What do you consider as risks or hindrances for the use a medicinal product when interpreting testing results?	Think of: - uniformity of interpretation - tuning the interpretation of the test with the treatment decision

Treatment options

Key questions	Which information sources do you use when making a final treatment choice based on device testing results?	
	To what extent do you trust the treatment choices made based on device testing results?	Think of: false positive and false negative testing results
	What do you consider as risks or hindrances for the use of personalised medicine when using the available information sources?	Think of: - uniformity - completeness - effect on final treatment decision

Final questions

Key questions	What role do you foresee for the application of personalised medicine in the future?	Think of: availability of genetic information for other practitioners, pharmacists or assurance companies
	What do you consider as risks or hindrances for the future of personalised medicine?	Think of: implementation, storage and use of genetic information of patients
	What are your expectations regarding interference of governmental parties in order to eliminate hindrances for the implementation of personalised medicine?	

Annex 4 Characteristics of medicines with pharmacogenomic information in the SPC

Active substance	Therapeutic area	Year autho-rised	Registration procedure; authorisa-tion number	Biomarker(s)	Clinical effect related to the biomarker	Pharmacogenomic test information	Test mandatory	Type of action prescribed	Description of action	Other information
Abacavir	Antivirals	1999	Centralised procedure; EU/1/04/298/002	HLA-B*5701	Carriers of HLA-B*5701 have a significantly higher risk of Abacavir hypersensitivity reaction.	Skin patch test is mentioned, which was used in the PREDICT1-study but is not suitable for use in clinical practice according to the manufacturer	Test is required for prescribing	Usage warning	Testing each HIV patient, even if re-initiation is applied in patients who previously tolerated Abacavir with unknown HLA-B*5701 status. Do not prescribe Abacavir for HLA-B*5701-positive patients except where no other therapeutical options exist. (SPC section 4.1)	-
Arsenic trioxide	Oncology	2005	Centralised procedure; EU/1/02/204/001	PML/RARα	Arsenic trioxide is indicated in patients with the PML/RARα fusion protein and/or translocation of t(15;17)	No information in SPC	Test is required for prescribing	Indication	No action described	-

Atomoxetine	Psychiatry	2008	Mutual recognition procedure; RVG 100392	CYP2D6	CYP2D6 poor metabolisers have a significantly higher risk of developing adverse events	No information in SPC	PGx info for information only	Dose adjustment	Lower starting dose and up-titration in known CYP2D6 poor metabolisers (SPC section 4.2)	-
Atorvastatin	Metabolic and Endocrinology	1997	Mutual recognition procedure; RVG 108984	LDL-receptor	In homozygote familial hypercholesterolemia higher dose and as adjunct to other lipid-lowering treatments	No information in SPC	PGx info for information only	Dose adjustment	In homozygote familial hypercholesterol-emia higher dose and as adjunct to other lipid-lowering treatments (SPC section 4.2).	-
Azathioprine	Rheumatology	1963	Mutual recognition procedure; RVG 107495	TPMT	Patients with poor TPMT status have a higher risk of developing excessive drug toxicity (myelosuppression and opportunistic infections)	No information in SPC	PGx info for information only	No action	-	-

Boceprevir	Antivirals	2011	Centralised procedure; EU/1/11/704/001	IL28B	The genetic variation IL28B rs12979860 is a strong predictor of drug response	No information in SPC	PGx info for information only	No action	-	Effect is seen in SPRINT-2 and RESPOND-2 study. The manufacturer has to provide information before May 2014 about this topic (SPC section 5.2)
Capecitabine	Oncology	2001	Centralised procedure; EU/1/00/163/001	DPD	DPD deficiency can lead to extreme toxicity	No information in SPC	PGx info for information only	Contra-indication	Contra-indicated in patients with known DPD deficiency (SPC section 4.3).	-

Carbamazepine	Neurology	1964	Mutual recognition procedure; RVG 25069	HLA-B*1502	Presence of the HLA-B*1502 allele is a strong predictor for the Stevens-Johnson syndrome	No information in SPC	Test recommend-ded for a certain group of patients before prescribing.	Usage warning	Before treatment initiation Han Chinese or Thais patients should be tested for the HLA-B*1502 allele. Carbamazepine should not be prescribed in patients who are positive, except where no other alternatives exist. (SPC section 4.2, 4.4)	-
Celecoxib	Analgesics	1998	Centralised procedure; RVG 25054	CYP2C9	Slow CYP2C9 metabolisers need caution with Celecoxib because the risk of dosage-dependant adverse events is increased	No information in SPC	PGx info for information only	Dose adjustment	Reconsider reduction to 50% of Celecoxib dosage in known or expected CYP2C9 poor metabolisers. (SPC section 4.2, 4.4, 4.5)	-

Cetuximab	Oncology	2004	Centralised procedure; EU/1/04/281/001	EGFR and KRAS	Cetuximab is indicated in EGFR expressing and KRAS wild-type metastatic colorectal cancer	Validated test method by an experienced laboratory.	Tests are required for prescribing	Indication	Do not use Cetuximab in KRAS mutations or unknown KRAS status because of a negative benefit–risk balance. (SPC section 4.1)	-
Citalopram	Psychiatry	1995	Mutual recognition procedure; RVG 107819	CYP2C19 and CYP2D6	Citalopram is mainly metabolised by CYP2C19. Therefore, poor activity of CYP2C19 will result in higher plasma levels and more adverse events	No information in SPC	PGx info for information only	Dose adjustment	For known poor CYP2C19 metaboliser start regime 10mg/day for the first two weeks. Depending on clinical result increase dosage to 20mg/day.* (4.2)	According to KNMP database no action is recommended. No information about CYP2D6 because the role of CYP2C19 in the metabolism is greater
Clopidogrel	Cardiovascular	1998	Centralised procedure; EU/1/10/649	CYP2C19	CYP2C19 PM status is associated with diminished response to clopidogrel	Tests are available but no mention of which to use	PGx info for information only	No action	No dosage regimes are available. The optimal dosage regime has yet to be determined (SPC section 4.2, 4.4, 5.2)	According to the KNMP database an alternative should be considered (e.g. Prasugrel)

Dapsone	Dermatology and Dental	1992	National procedure (CBG); RVG 24184 =52476	G6PD	More side-effects (haemolysis) in seriously G6PD-deficient patients	No information in SPC	PGx info for information only. Testing for liver function is recommend-ded	Contra-indication	If patient is slightly to moderately seriously G6PD-deficient, the drug must be given with caution. In seriously G6PD-deficient patients Dapsone is contra-indicated. (SPC section 4.3, 4.4, 4.8, 4.9)	-
Dextromethor-phan	Neurology	1953	National procedure (CBG); RVG 28949	CYP2D6	CYP2D6 PM and EM patients have different first-pass effect	No information in SPC	Pgx info for information use only	No action	-	-
Dasatinib	Oncology	2006	Centralised procedure; EU/1/06/363/011	BCR-ABL gene (Philadelphia Chromosome)	Dasatinib is effective only in Philadelphia chromosome-positive patients	No information in SPC	Test is required for prescribing	Indication	No actions are mentioned but indication is obvious (SPC section 4.1, 4.2)	-
Erlotinib	Oncology	2004	Centralised procedure; EU/1/05/311/003	EGFR	Erlotinib is effective only on EGFR-positive tumours	Use robust and validated method that can exclude false negative/positive results	Test is required for prescribing	Indication	EGFR testing prior to treatment initiation. Do not prescribe for EGFR-negative patients (SPC section 4.1, 4.2, 4.4, 5.1)	-

Escitalopram	Psychiatry	2004	Mutual recognition procedure; RVG 35339	CYP2C19	CYP2C9 PM has a two-fold higher plasma level of Escitalopram than EM	No information in SPC	PGx info for information only	Dose adjustment	CYP2C19 PM patients should be given a start dose of 50% of the normal dose during the first two weeks. Thereafter the dosage can be increased to normal dose if tolerated (SPC section 4.2)	It is stated that a difference in plasma levels between PM and EM has no significant effect to the exposure. However, a dosage adjustment is given
Esomeprazole	Gastroentero-logy	2000	Mutual recognition procedure; RVG 108869	CYP2C19	CYP2C19 PMs have a higher pharmacokinetic profile than EMs. The altered pharmacokinetic profile of CYP2C19 PM patients has no effect on the dosage	No information in SPC	PGx info for information only	No action	-	-
Fluorouracil	Oncology	1962	Mutual recognition procedure; RVG 06292	DPD	DPD deficiency results in 5-FU toxicity	No information in SPC	Test is recommended in patients with known and expected toxicity.	Close monitoring	Known DPD-deficient patients should be closely monitored for toxicity (SPC section 4.4)	-

Fulvestrant	Oncology	2002	Centralised procedure; EU/1/03/269/001	ER receptor	Fulvestrant is indicated for oestrogen receptor-positive cancer	No information in SPC	Test is required for prescribing.	Indication	No action is mentioned but indication is obvious (SPC section 4.1)	-
Galantamine	Neurology	1991	Mutual recognition procedure; RVG 108105	CYP2D6	Differences in CYP2D6 status are not clinically significant	No information in SPC	PGx info for information only	No action	-	-
Gefitinib	Oncology	2002	Centralised procedure; EU/1/09/526/001	EGFR and CYP2D6	Gefitinib has no clinically relevant activity in EGFR mutation-negative tumours. CYP2D6 PMs have a greater risk of developing adverse events	For the EGFR mutation: the test should be validated and robust in order to avoid false negative/positive results	EGFR: test is required for prescribing CYP2D6: PGx info for information only	Indication Close monitoring	EGFR: No action is mentioned but indication is obvious (SPC section 4.1) CYP2D6: No dose adjustment for CYP2D6 status but close monitoring (SPC section 4.2)	-
Imatinib	Oncology	2001	Centralised procedure; EU/1/01/198/013	C-kit, BCR-ABL gene (Philadelphia Chromosome), PDGFR and FIP1L1-PDGFRα	Imatinib is indicated in one or a combination of the displayed biomarkers.	No information in SPC	Test is required for prescribing	Indication	No action is mentioned but indication is obvious (SPC section 4.1)	-

Irinotecan	Oncology	1997	Mutual recognition procedure; RVG 103670	UGT1A1	Homozygous UGT1A1*28 patients have a higher risk of developing hematological toxicity at regular and high irinotecan doses (>150mg/m2)	No information available in EU SPC/EPAR	PGx info for information only	Close monitoring	In known homozygous UGT1A1*28 patients start at regular dose but close monitoring is indicated. If toxicity occurs, lower the dose (SPC section 4.4)	No lower starting dose is advised because of possible risk of under-treatment.
Lansoprazole	Gastroentero-logy	1992	Mutual recognition procedure; RVG 105431	CYP2C19	Exposure to Lansoprazole is much higher in CYP2C19 PM than EM	No information in SPC	PGx info for information only	No action	-	The KNMP database states that no action has to be taken, because higher Lansoprazole exposure results in higher efficacy without adverse events
Lapatinib	Oncology	2007	Centralised procedure ; EU/1/07/440/ 001	Her2/neu	Lapatinib is effective in tumours over expressing Her2	Defined by IHC3+, or IHC2+ with gene amplification, or gene amplification alone. Methods used to determine should be accurate and validated	Test is required for prescribing	Indication	No actions mentioned but indication is obvious (SPC section 4.1, 4.2)	-

Lenalidomide	Haematology	2005	Centralised procedure; EU/1/07/391/004	Chromosome 5q	Lenalidomide is especially effective in patients with a deletion on chromosome 5	No information in SPC	PGx info for information only	No action	-	-
Maraviroc	Antivirals	2007	Centralised procedure; EU/1/07/418/006-010	CCR5	Maraviroc is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable	Use adequate and validated method on new-drawn blood samples	Test is required for prescribing	Indication	Before treatment only the CCR5-tropic HIV-1 must be detectable (SPC section 4.2)	-
Mercaptopurine	Oncology	1953	National procedure (CBG); RVG 00859	TPMT	TPMT-deficient patients are likely to develop severe toxicity	No information in SPC	PGx info for information only	Close monitoring	Testing for TPMT is not mandatory because patients without TPMT deficiency can also develop toxicity. Therefore, close monitoring is required for all patients (SPC section 4.4)	-

Moclobemide	Psychiatry	1991	Mutual recognition procedure; RVG 30006	CYP2C19	CYP2C19 PMs could have a decreased metabolism	No information in SPC	PGx info for information only	No action	-	According to the database no action has to be taken. There is no evidence of a relation between plasma concentration and side-effects
Nelfinavir	Antivirals	1997	Centralised procedure; EU/1/97/054/001	CYP2C19	It is expected that in CYP2C19 PM patients or in patients receiving concomitantly strong CYP2C19 inhibitors, Nelfinavir plasma levels will be elevated whereas levels of tert-butyl hydroxyl nelfinavir will be negligible or non-measurable	No information in SPC	PGx info for information only	No action	-	-
Nilotinib	Oncology	2007	Centralised procedure; EU/1/07/422/0006	BCR-ABL gene (Philadelphia Chromosome)	Nilotinib is indicated in newly diagnosed Philadelphia chromosome-positive patients	No information in SPC	Test is required for prescribing	Indication	Action not mentioned but indication is obvious (SPC section 4.1)	-

Omeprazole	Gastroentero-logy	1988	Mutual recognition procedure; RVG 110810	CYP2C19	CYP2C19 PMs have different pharmacokinetic values	No information in SPC	PGx info for information only	No action. These differences have no implications on the dosage (SPC section 5.2)	-	
Panitumumab	Oncology	2006	Centralised procedure; EU/1/07/423/003	EGFR and KRAS	Indicated for patients with the wild type KRAS protein	Test should be performed according to a validated method by an experienced laboratory	Test is required for prescribing	Indication	No actions are mentioned for EGFR but indication is obvious (SPC section 4.1) KRAS status has to be determined before treatment initiation. Panitumumab should not be prescribed for patients with mutations in KRAS (SPC section 4.2)	There are no anti-tumour effects seen in EGFR-negative patients

Phenytoin	Neurology	1938	Mutual recognition procedure; RVG 08051	HLA-B*1502	HLA-B*1502 is possibly correlated with SJS in Han Chinese and Thai patients	No information in SPC	PGx info for information only	Usage warning	The use of phenytoin in patients with known HLA-B*1502 is acceptable only where a positive benefit–risk ratio exists (SPC section 4.4)	The MAF in Caucasian and Japanese patients is extremely low, with the result that no clear conclusion can be made about the risk
Rasburicase	Oncology	2001	Centralised procedure; EU/1/00/170/002	G6PD	Rasburicase causes haemolytic anaemia in G6PD-deficient patients	No information in SPC	PGx info for information only	Contra-indication	No action is mentioned.	-
Sertraline	Psychiatry	1990	Mutual recognition procedure; RVG 106062	CYP2C19	CYP2C19 PMs have 50% higher plasma concentrations than EMs.	No information in SPC	PGx info for information only	Close monitoring	Treat patient according to clinical response. Be aware of adverse events in this patient	-

Tamoxifen	Oncology	1973	Mutual recognition procedure; RVG 32447	ER receptor CYP2D6	Tamoxifen is indicated in hormone-dependenttumours. CYP2D6 PM may have lower response to Tamoxifen because of lower levels of Endoxifen	No information in SPC No information in SPC	Test is required for prescribing PGx info for information only	Indication No action	No action is mentioned but indication is obvious (SPC section 4.1) The effect of CYP2D6 PM status on response has not been fully explored (SPC section 4.4, 5.1)	Tamoxifen is also to a certain extent effective in ER-negative tumours, suggesting that there may be another mechanism of action that is not yet known
Tegafur	Oncology	2001	Centralised procedure; EU/1/11/669/002	DPD	Tegafur is contra-indicated for DPD PM patients	No information in SPC	PGx info for information only	Contra-indication	No action mentioned	According to the KNMP database an alternative should be given

Thioguanine	Oncology	1966	National procedure (CBG); RVG 07070	TPMT	TPMT-deficient patients are likely to develop severe toxicity	No information in SPC	PGx info for information only	Close monitoring	No action mentioned	Testing for TPMT status is not mandatory because patients without TPMT deficiency can also develop toxicity. Therefore, close monitoring is required for all patients

Trastuzumab	Oncology	1998	Centralised procedure; EU/1/00/145/001	Her2/neu	Herceptin should be used only in patients with Her2 over-expression or Her2 gene amplification.	Her2 over-expressing: immunohistochemistry (IHC) Her2 gene amplification: fluorescence *in situ* hybridisation (FISH) or chromogenic *in situ* hybridisation (CISH) Patients are eligible for Herceptin treatment if they show strong HER2 over-expression as indicated by a IHC 3+ score or a positive FISH or CISH result	Test is required for prescribing	Indication	Her2 testing before treatment initiation. Herceptin should be prescribed only in patients with Her2-positive tumours (SPC section 4.1, 4.2, 4.4, 5.1)	The SPC of Trastuzumab (unlike that of other medicines in this table) has detailed information about Her2 detection

Venlafaxine	Psychiatry	1993	Mutual recognition procedure; RVG 108592	CYP2D6	CYP2D6 PM patients have higher venlafaxine plasma levels than UM patients. Considering the fact that the exposure is the same in both patient groups no different dosages for these groups have to be applied	No information in SPC	PGx info for information only	No action	-	According to the KNMP database CYP2D6 UM/ PM patients should be switched to an alternative or have an increased/ decreased dose.
Voriconazole	Antifungals	2004	Centralised procedure; EU/1/02/212/ 026	CYP2C19	CYP2C19 PMs have a 4-fold higher exposure (AUC) to Voriconazole than EMs. CYP2C19 IMs have a 2-fold higher exposure.	No information in SPC	PGx info for information only	No action	-	According to the KNMP database CYP2C19 PM patients should be monitored on their plasma concentration

Annex 5 Characteristics of CE-marked *in vitro* diagnostic devices

Device name	Biomarker(s)	Year of CE marking	Manufacturer	Intended use	Used in clinical trials according to (E)PAR	Testing principle	Instructions related to interpretation of results	Other relevant information
Asuragen® BCR-ABL mbcr FusionQuant ™ Test	BCR-ABL1 (Philadelphia chromosome)	2010	Asuragen	Assessment of complete cytogenetic response (CCyR), MMR, MRD and relapse. No (specific) medicines are mentioned	No (specific) test mentioned in EPAR	RT-PCR[5]		Product bulletin available from: http://www.asuragen.com/pdfs/Dx/2500-0166_BCR_ABL_Whitepaper.pdf
Vysis BCR/ABL1/ASS1 Tri-Color DF FISH Probe Kit	BCR-ABL1 (Philadelphia chromosome)	unknown	Abbott Molecular	Detection of the t(9;22)(q34;q11.2) reciprocal translocation involving the BCR and ABL1 gene regions. No (specific) medicines are mentioned	No (specific) test mentioned in EPAR	FISH	No instructions for use found on manufacturer's website	
BCR-ABL Mbcr IS-MMR Kits	BCR-ABL1 (Philadelphia chromosome)	2010	Ipsogen	Disease monitoring under TKI therapy. It is intended to detect the t(9;22)(q34;q11.2) reciprocal translocation involving the BCR and ABL1 gene regions	No (specific) test mentioned in EPAR	RT-Quantitative PCR	No instructions for use found on manufacturer's website	Brochure available from: http://www.ipsogen.com/uploads/media/IPSOGEN_EHA2011_Web.pdf
c-Kit PharmDx™	C-kit	unknown	DAKO	Differential diagnosis of gastrointestinal stromal tumours (GIST). After diagnosis of GIST, results from c-Kit PharmDx may be used as an aid to identifying patients eligible for treatment with Gleevec™/Glivec® (Imatinib mesylate)	No (specific) test mentioned in EPAR	ICH		Instructions for use available from: http://www.dako.com/nl/08070_ckit_interpret_manual.pdf

AID RDB 2075e	CYP2C9	2006	Autoimmun Diagnostika GmbH	Determination of the predisposing alleles for Wafarin hypersensitivity R144C and I359L and the polymorphism C1173T in the human VKORC1 gene		PCR	Some guidance offered on the website. Manual for the test not available	
AmpliChip CYP450 Test	CYP2C19 and CYP2D6	2004	Roche Molecular Diagnostics	Detection of 29 CYP2D6 polymorphisms, including CYP2D6 duplication and deletion, as well as of 2 CYP2C19 polymorphisms. The test also gives the predictive phenotype and is applied in order to aid physicians in their therapy strategy with drugs that are metabolised by CYP2D6 or CYP2C19	Not applicable	DNA-Microarray	No instructions for use found on manufacturer's website	
INFINITI™ CYP450 2C19+ Assay	CYP2C19	unknown	AutoGenomics	Detection of 10 CYP2C19 polymorphisms. Test applied to aid physicians in therapy strategy with drugs that are metabolised by CYP2C19	Not applicable	DNA-Microarray	No instructions for use found on manufacturer's website	
Spartan RX	CYP2C19	2011	Spartan Bioscience, Inc.	Determination whether the patient carries the CYP2C19*2 allele (none, one, two)	Not applicable	PCR	Manual available	Information is provided on interfering substances and cross-contamination of the sample
xTAG® CYP2D6 Kit	CYP2D6	unknown	Luminex Molecular Diagnostics	Detection of several mutations (including the deletion (*5) and the duplication) in CYP2D6 in order to aid physicians in therapy strategy with drugs that are metabolised by CYP2D6. This test is not indicated for stand-alone diagnostic purposes	Not applicable	Multiplex PCR, followed by multiplex allele specific primer extension for genotyping, hybridised to multiplexed fluorescing	No instructions for use found on manufacturer's website	Brochure available from: http://www.luminexcorp.com/Products/Assays/ClinicalDiagnostics/xTAGCYP2D6/index.htm

						microparticles, detected by flow cytometry		
Therascreen EGFR PCR Kit	EGFR	2007	Qiagen	Detection of 28 mutations in the EGFR gene in order to select non-small cellular lung carcinoma patients for the treatment with TKIs[4] (Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib and Nilotinib)	No. In the clinical trials the EGFR pharmDx™ Kit (DAKO) was used	RT-PCR[5]	Instructions for use available from: http://www.qiagen.com/products/therascreenegfrpcrkit.aspx#Tabs=t2	
Therascreen EGFR RGQ PCR Kit	EGFR	2010	Qiagen	Detection of 29 mutations in the EGFR gene in order to select non-small cellular lung carcinoma patients for the treatment with TKIs[4] (Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib and Nilotinib), including the resistance mutation T790M	No. In the clinical trials the EGFR pharmDx™ Kit (DAKO) was used	RT-PCR[5]	Instructions for use available from: http://www.qiagen.com/products/therascreenegfrrgqpcrkit.aspx#Tabs=t2	
Therascreen EGFR Pyro Kit	EGFR	2010	Qiagen	Quantitative detection of mutations in exon 18, 19, 20 and 21 of the EFGR gene, in order to select cancer patients for the treatment with anti-EGFR agents (Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib and Nilotinib)	No. In the clinical trials the EGFR pharmDx™ Kit (DAKO) was used	DNA sequencing	Instructions for use available from: http://www.qiagen.com/products/therascreenegfrpyrokit.aspx#Tabs=t2	
EGFR pharmDx™ Kit (Manual Use or Dako Autostainer)	EGFR	unknown	DAKO	Identification of EGFR in normal and neoplastic tissue in order to select patients that would benefit from Cetuximab and Panitumumab	Yes	Qualitative ICH	Instructions for use available from: http://www.dako.com/nl/ar39/p222342/prod_products.htm	A detailed working procedure is available from: http://www.dako.com/nl/ar39/p222342/prod_products.htm

Cobas® EGFR mutation test	EGFR	2011	Roche Molecular Diagnostics	Detection of 41 mutations in the EGFR gene in order to select non-small cellular lung carcinoma patients for the treatment with TKIs[4] (Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib and Nilotinib)	No. In the clinical trials the EGFR pharmDx™ Kit (DAKO) was used	RT-PCR[5] (using multiplex chemistry)	No instructions for use found on manufacturer's website	
OncotypeDX ®:Breast®	ER-receptor	2007	Genomic Health	Test provides DCIS patients with an individualised prediction of the ten-year risk of local recurrence (DCIS or invasive carcinoma) to help guide treatment decision making for women with ductal carcinoma in situ treated by local excision, with or without adjuvant Tamoxifen therapy	No EPAR available	RT-PCR[5]		Information is available on the manufacturer's website: http://www.oncotypedx.com/en-US/Breast/HealthcareProfessional/DCIS.aspx#f2
ER/PR pharmDx™ Kits	ER-receptor	unknown	DAKO	Kit indicated as an aid in identifying patients eligible for treatment with anti-hormonal (Tamoxifen) or aromatase inhibitor therapies as well as in the prognosis and management of breast cancer	No EPAR available	Semi-quantitative ICH	Instructions for use available from: http://www.dako.com/nl/download.pdf?objectid=117052001	
PathVysion® HER-2 DNA Probe Kit	HER-2	2003	Abbott Molecular	Trastuzumab therapy selection	The commercial test Hercep Test® is mentioned in EPAR. During the pivotal clinical study HER-2 over-expression was determined with in-house investigational test	FISH[1]		A detailed working procedure is available from: http://www.abotmolecular.com

HER2 FISH pharmDx™ Kit	HER-2	unknown	DAKO (The Netherlands)	Trastuzumab therapy selection	The commercial test Hercep Test® is mentioned in EPAR. During the pivotal clinical study HER-2 over-expression was determined with in-house investigational test	FISH[1]. The advantage over the above-mentioned test is a ready-to-use FISH probe mix	Instructions for use available from: http://www.dako.com/nl/ar39/p119420/prod_products.htm	
HER2 CISH pharmDx™ Kit	HER-2	2010	DAKO (The Netherlands)	Trastuzumab therapy selection	The commercial test Hercep Test® is mentioned in EPAR. During the pivotal clinical study HER-2 over-expression was determined with in-house investigational test	CISH[2]	Instructions for use available from: http://www.dako.com/nl/ar39/p235615/prod_products.htm	
DAKO DuoCISH™	HER-2	unknown	DAKO (The Netherlands)	Trastuzumab therapy selection	The commercial test Hercep Test® is mentioned in EPAR. During the pivotal clinical study HER-2 over-expression was determined with in-house investigational test	CISH[2]	Instructions for use available from: http://www.dako.com/nl/ar42/p235375/prod_products.htm	
SPoT-Light® HER2 CISH Kit	HER-2	2004	Invitrogen™/Zytomed	Trastuzumab therapy selection	The commercial test Hercep Test® is mentioned in EPAR.	CISH[2]	Instructions for use available from: www.invitrogen.com	

					During the pivotal clinical study HER-2 over-expression was determined with in-house investigational test		/etc/medialib/en/filelibrary/pdf.Par.7249.../84-0146	
INFORM HER2 Dual ISH DNA Probe Cocktail	HER-2	2010	Ventana Medical Systems	Trastuzumab therapy selection	The commercial test Hercep Test® is mentioned in EPAR. During the pivotal clinical study HER-2 over-expression was determined with in-house investigational assays	SISH[3]	No instructions for use found on manufacturer's website	Brochure available from: http://www.ventana.com/documents/INFORM_HER2_Dual_ISH_F&B_brochure.pdf
Hercep Test™	HER-2	unknown	DAKO	Trastuzumab therapy selection	Yes	Semi-quantitative ICH		A detailed working procedure is available from: http://www.dako.com/nl/28630_19feb10_herceptest_interpretation_manual-breast_ihc_final.pdf
PG1502 DNA Detection Kit	HLA-B*1502	unknown	Pharmigene	Carbamazepine toxicity		RT-PCR[5]		A detailed working procedure is available from: http://www.hkdnachips.com/kitManual/Clinical/C02-01-1155.pdf
Olerup SSP® HLA-B*5701 Kit	HLA-B*5701	2008	Qiagen	Abacavir therapy selection	No (specific) test mentioned in EPAR	PCR (Kit contains ready-to-use PCR wells with primers and	No instructions for use available	

						reagents)		
COBAS® AmpliPrep / COBAS® TaqMan® HLA-B*5701 Screening Test	HLA-B*5701	2011	Roche Molecular Diagnostics	Abacavir therapy selection	No (specific) test mentioned in EPAR	RT-PCR[5]	No instructions for use available	
G6PD Deficiency Screen Reagent Set	G6PD	unknown	Pointe Scientific Inc.	Qualitative, visual, colorimetric determination of G6PD deficiency in red blood cells		Qualitative colorimetric	Instructions for use available from: http://www.pointescientific.com/products/PI/G7583.pdf	
Glucose-6-phosphate dehydrogenase deficiency	G6PDH	2011	Trinity Biotech Plc	Glucose-6-Phosphate Dehydrogenase reagents are for the quantitative, ultraviolet, kinetic determination of G-6-PDH in blood at 340 nm.		Quantitative photospectrometric	Instructions for use available from: http://www.trinitybiotech.com/Product%20Documents/345-29%20EN.pdf	
TheraScreen®: K-RAS Mutation Kit	KRAS	2009	DxS	Detection of seven somatic mutations in the KRAS gene in order to select colorectal cancer patients most likely to benefit from EGFR therapy (Cetuximab and Panitumumab)	No (specific) test mentioned in EPAR. The applicant has guaranteed the availability of KRAS test kit	RT-PCR[5]		A detailed working procedure is available from: http://www.oem-info.com/roche/handbooks/data/DU001g_KRAS_TheraScreen_ENGLISH.pdf
Therascreen *KRAS Pyro Kit*	KRAS	2009	Qiagen	Detection of mutations in codon 12, 13, and 16 of the human KRAS gene in order to select colorectal cancer patients most likely to benefit from EGFR therapy (Cetuximab and	No (specific) test mentioned in EPAR. The applicant has guaranteed the availability of KRAS test	DNA-sequencing		A detailed working procedure is available from: http://www.qiagen.com/products/therascreenkraspyrokit.aspx#Tabs=t2

				Panitumumab)	kit			
Therascreen KRAS RGQ PCR Kit	KRAS	2011	Qiagen	Detection of seven somatic mutations in the KRAS gene in order to select colorectal cancer patients most likely to benefit from EGFR therapy (Cetuximab and Panitumumab)	No (specific) test mentioned in EPAR. The applicant has guaranteed the availability of KRAS test kit	RT-PCR[5]		A detailed working procedure is available from: http://www.qiagen.com/products/therascreenkrasrgqpcrkit.aspx#Tabs=t2
SURVEYOR® Scan K-RAS Kit	KRAS	2010	Transgenomic	Detection of mutations in exon 2 and codon 12/13 (other assay) in order to select colorectal cancer patients most likely to benefit from EGFR therapy (Cetuximab and Panitumumab)	No (specific) test mentioned in EPAR. The applicant has guaranteed the availability of KRAS test kit	DNA-sequencing		A detailed working procedure is available from: http://www.transgenomic.com/lib/ug/English.pdf
PNAClamp™ K-ras Mutation Detection Kit	KRAS	unknown	PANAGENE (Korea)	Not stated.	No (specific) test mentioned in EPAR. The applicant has guaranteed the availability of KRAS test kit	RT-PCR[5]		
AmoyDx's™ KRAS Seven Mutation Detection Kit	KRAS	2011	Amoy Diagnostics (China)	Detection of the seven most common somatic mutations in codons 12 and 13 in order to select colorectal cancer patients most likely to benefit from EGFR therapy (Cetuximab and Panitumumab)	No (specific) test mentioned in EPAR. The applicant has guaranteed the availability of KRAS test kit	RT-PCR[5]		A detailed working procedure is available from: http://www.amoydx.com/down/KRAS_Instructions_Pre-loaded.2011.12.06.pdf
K-ras Strip Assay®	KRAS	unknown	ViennaLab	Detection of ten mutations in codons 12 and 13 in order to select colorectal cancer patients most likely	No (specific) test mentioned in EPAR. The applicant has	DNA isolation, PCR and reverse		A detailed working procedure is available from: http://www.viennalab.com/gene

				to benefit from EGFR therapy (Cetuximab and Panitumumab)	guaranteed the availability of KRAS test kit	hybridisation.		tic-mutation-treatment-syndrome-prevention-molecular-biology/medicines-drugs-therapy-chemotherapy/egfr-cetuximab-panitumumab-kras-wildtype-mutated-tumour-remission?showAll=1
Cobas® KRAS mutation test	KRAS	2011	Roche	Detection of all reported mutations in codons 12, 13 and 61 in order to select colorectal cancer patients most likely to benefit from anti-EGFR therapy	No (specific) test mentioned in EPAR. The applicant has guaranteed the availability of KRAS test kit	RT-PCR[5]	No instructions for use found on manufacturer's website	
KRAS – BRAF StripAssay®	KRAS and BRAF	unknown	Viennalab	Detection of ten mutations in codons 12 and 13 of the KRAS gene and 1 mutation of the BRAF gene in order to select colorectal cancer patients most likely to benefit from EGFR therapy (Cetuximab and Panitumumab)	No (specific) test mentioned in EPAR. The applicant has guaranteed the availability of KRAS test kit	DNA isolation, PCR and reverse hybridisation		A detailed working procedure is available from: http://www.viennalab.com/genetic-mutation-treatment-syndrome-prevention-molecular-biology/medicines-drugs-therapy-chemotherapy/therapies-target-egfr-metastatic-colorectal-cancer-monoclonal-antibody-therapies-cetubimax-panitumumab?showAll=1
K-Ras/B-Raf Mutation Analysis kit	KRAS and BRAF		EntroGen	Detection of all reported mutations in codons 12, 13 and 61 of the KRAS gene and mutation V600E of the BRAF gene in order to select colorectal cancer patients most likely	No (specific) test mentioned in EPAR. The applicant has guaranteed the availability of KRAS test	PCR	No instructions for use found on manufacturer's website	

				to benefit from anti-EGFR therapy (e.g. Cetuximab, Panitumumab and Erlotinib)	kit			
PDGFR, alpha	PDGFR, alpha	2011	Lab Vision Corp.	Qualitative immunohistochemistry with normal and neoplastic formalin-fixed, paraffin-embedded tissue sections, to be viewed by light microscopy		Immunohistology	Brief instructions are available from: http://www.labvision.com/pdf/ivd/9027%20(ivd).pdf	Reference is made to 'General Protocol' instructions
PML-RARa FusionQuant® kit	PML/RARα	unknown	Ipsogen	Quantification of specific PML-RARa fusion gene transcripts (bcr1, bcr2 or bcr3) relative to ABL control gene. For these patients arsenic trioxide has led to dramatic improvements in outcomes	No commercial test is mentioned in the EPAR. However, the following methods are advised: conventional/molecular cytogenetic testing, RT-PCR and FISH. This latter test method is also standardised in the Europe Against Cancer programme	RT-Quantitative PCR	No instructions for use found on manufacturer's website	Brochure available from: http://www.ipsogen.com/uploads/media/PML-RARa_IPSOGEN_Products_1110_ROW.pdf
Vysis PML/RARA Dual Color Translocation Probe Kit	PML/RARα	unknown	Abbott Molecular	Detection of the t(15;17)(q22;q21.1) reciprocal translocation involving the PML and RARA gene regions. The PML/RARA fusion is associated with a good response to all-trans retinoic acid therapy	No commercial test is mentioned in the EPAR. However the following types of methods are advised: conventional/molecular cytogenetic testing, RT-PCR and FISH.	FISH[1]	No instructions for use found on manufacturer's website	
PGX-TPMT StripAssay®	TPMT	unknown	ViennaLab	Detection of three mutations (238 G>C, 460 G>A, 719 A>G) of the TPMT gene in order to identify	No EPAR available	DNA isolation, PCR and reverse		A detailed working procedure is available from: http://www.amplitech.net/PDF/V

				patients' response to thiopurine.		hybridisation		IENNALAB/4740-Description%202010-03.pdf
Artus TPMT LC PCR Kit	TPMT	unknown	Qiagen	Detection of the three most common mutations in the TPMT gene that lead to a deficient enzyme. Carriers of these mutations can be given an alternative or dosage can be adjusted for Thioguanine, Mercaptopurine or Azathioprine	No EPAR available	RT-PCR[5]		A detailed working procedure is available from: http://www.qiagen.com/literature/handbooks/literature.aspx?id=1000920
AccuPower® TPMT genotyping Kit	TPMT	unknown	Bioneer (Korea)	Detection of three mutations (G239C, G460A and A719G) of the TPMT gene prior to treatment with thiopurine drugs	No EPAR available	RT-PCR[5]	No instructions for use found on manufacturer's website	
INFINITI® UGT1A1 Assay	UGT1A1	unknown	AutoGenomics	Detection of the UGT1A1 *1, *28, *36, *37, alleles in order to assist physicians in determining the specific dosage of Irinotecan (reducing toxicity)	No EPAR available	Microarray	No instructions for use found on manufacturer's website	

1. Fluorescence in situ hybridisation (FISH): fluorescently labelled single-stranded DNA anneals to a complementary DNA sequence. Hybridisation of the probe to the target DNA is visualised under a fluorescent microscope.
2. Chromogenic In Situ Hybridisation (CISH): fluorescently labelled single-stranded DNA or RNA anneals to a complementary DNA or RNA in a tissue specimen. Determines gene amplification, gene deletion, chromosome translocation or chromosome number.
3. Silver-enhanced in situ hybridisation (SISH) is a rapid fully automated assay providing permanently stained slides that are interpreted by conventional bright field microscopy, which enables pathologists to evaluate slides within the context of tissue morphology.
4. Tyrosine Kinase Inhibitors.
5. Real Time Polymerase Chain Reaction (RT-PCR).

Annex 6 Clinical practice guidelines

Subject of guideline	Year of adoption	Organisation	Personalised medicine (active substance)	Pharmacogenetic test information	Test mandatory or not	Type of action taken by healthcare professional	Description of action	Additional information
Recommendations on the treatment of chronic myeloid leukemia 2011	2011	HOVON leukemiewerk-groep	Dasatinib	BCR-ABL1-mRNA using RQ-PCR	Yes	Indication	The presence of Philadelphia chromosome and/or BCR-ABL1-translocation is necessary for the diagnosis of CML. BCR-ABL1-mRNA should be monitored every three months using RQ-PCR. In the case of major molecular response, monitoring can be restricted to every four months	Molecular response to treatment is defined in nlog reduction BCR-ABL1-mRNA (qPCR)
Recommendations on the treatment of chronic myeloid leukemia 2011	2011	HOVON leukemiewerk-groep	Imatinib	BCR-ABL1-mRNA using RQ-PCR	Yes	Indication	The presence of Philadelphia chromosome and/or BCR-ABL1-translocation is necessary for the diagnosis of CML. BCR-ABL1-mRNA should be monitored every three months using RQ-PCR. In the case of major molecular response, monitoring can be	Molecular response to treatment is defined in nlog reduction BCR-ABL1-mRNA (qPCR)

Subject of guideline	Year of adoption	Organisation	Personalised medicine (active substance)	Pharmacogenetic test information	Test mandatory or not	Type of action taken by healthcare professional	Description of action	Additional information
							restricted to every four months	
Recommendations on the treatment of chronic myeloid leukemia 2011	2011	HOVON leukemiewerk-groep	Nilotinib	BCR-ABL1-mRNA using RQ-PCR	Yes	Indication	The presence of Philadelphia chromosome and/or BCR-ABL1-translocation is necessary for the diagnosis of CML. BCR-ABL1-mRNA should be monitored every three months using RQ-PCR. In the case of major molecular response, monitoring can be restricted to every four months	Molecular response to treatment is defined in nlog reduction BCR-ABL1-mRNA (qPCR)
Colon carcinoma	2008	Integraal Kankercentrum Nederland	Capecitabine	No	-	-	-	No mention of DPD deficiency in guideline
Colon carcinoma	2008	Integraal Kankercentrum Nederland	Fluorouracil	No	-	-	-	No mention of DPD deficiency in guideline

Subject of guideline	Year of adoption	Organisation	Personalised medicine (active substance)	Pharmacogenetic test information	Test mandatory or not	Type of action taken by healthcare professional	Description of action	Additional information
Colon carcinoma	2008	Integraal Kankercentrum Nederland	Irinotecan	No	-	-	-	No mention of UGT1A1 deficiency in guideline
Colorectal liver metastasis	2006	Integraal Kankercentrum Nederland	Fluorouracil	No	-	-	-	No mention of DPD deficiency in guideline
Colorectal liver metastasis	2006	Integraal Kankercentrum Nederland	Irinotecan	No	-	-	-	No mention of UGT1A1 deficiency in guideline
Diagnostics and treatment of rheumatoid arthritis	2009	Nederlandse Vereniging voor Reumatologie	Azathioprine	No	-	-	-	No mention of measuring TPMT activity or dosing recommendations in guideline
Diagnostics and treatment of rheumatoid arthritis	2009	Nederlandse Vereniging voor Reumatologie	Celecoxib	No	-	-	-	No mention of CYP2C9 genetic variations in guideline
Epilepsy - guideline for diagnosis and treatment	2006	Nederlandse Vereniging voor Neurologie (NVvN)	Carbamazepine	No	-	-	-	No mention of increased risk of SJS. HLA-B*1502 does not appear to be associated with SJS in the Caucasian population [13]
Epilepsy - guideline for diagnosis and treatment	2006	Nederlandse Vereniging voor Neurologie (NVvN)	Phenytoin	No	-	-	-	No mention of increased risk of SJS. HLA-B*1502 does not appear to be associated with SJS in the

Subject of guideline	Year of adoption	Organisation	Personalised medicine (active substance)	Pharmacogenetic test information	Test mandatory or not	Type of action taken by healthcare professional	Description of action	Additional information
								Caucasian population [13]
Guidelines for the management of APL	2009	European LeukemiaNet	Arsenic trioxide	Quantification of PML-RARa fusion gene transcripts. PML-RARA positive APL, identified by karotyping, FISH, reverse transcriptase PCR, or immunostaining with anti-PML monoclonal antibodies	Yes	Indication	Diagnosis should be confirmed by molecular detection of PML-RARA fusion. Treatment with arsenic trioxide should be restricted to cases confirmed to be PML/RARA-positive	APL: 10–15% of AML. PML-RARa associated with >90% of APL long (L or bcr1): 55%; variant (V or bcr2): 5%; short (S or bcr3: 40%. [2]
Hypopharynx carcinoma	2010	Integraal Kankercentrum Nederland	Cetuximab	No	-	-	-	Testing is only indicated for patients with EGFR expressing, KRAS wild type metastatic colorectal cancer. ICH detection for EGFR expression is not performed for squamous cell cancer of the head and neck, since more than 90% of these

Subject of guideline	Year of adoption	Organisation	Personalised medicine (active substance)	Pharmacogenetic test information	Test mandatory or not	Type of action taken by healthcare professional	Description of action	Additional information
								patients have tumours that express EGFR. There is still little place for cetuximab in the colorectal cancer guidelines for the treatment of metastases; no information on PGx testing in guideline
Small-cell lung carcinoma	2011	vereniging integrale kankercentra (VIKC)	Irinotecan	No	-	-	-	No mention of UGT1A1
Stomach carcinoma	2009	Integraal Kankercentrum Nederland	Fluorouracil	No	-	-	-	No mention of DPD deficiency in guideline
Stomach carcinoma	2009	Integraal Kankercentrum Nederland	Irinotecan	No	-	-	-	No mention of UGT1A1 deficiency in guideline

Subject of guideline	Year of adoption	Organisation	Personalised medicine (active substance)	Pharmacogenetic test information	Test mandatory or not	Type of action taken by healthcare professional	Description of action	Additional information
Mamma carcinoma	2012	Integraal Kankercentrum Nederland	Fulvestrant	ER and PR testing using IHC. A standardised receptor test should be used. A representative section of the tumour should be used, fixated in formalin and embedded in paraffin. External audits are required (e.g. SKML, NordiQC, UK-Negas) to verify quality of techniques used	Yes	Indication	Should only be used in patients with metastatic ER+ and/or PR+ breast cancer	The details of specific requirements the test should comply with (regarding pre-analytical, analytical and post-analytical factors) to determine the ER and PR status are outside the scope of the guideline

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Mamma carcinoma	2012	Integraal Kankercentrum Nederland	Tamoxifen	ER and PR testing using IHC. A standardised receptor test should be used. A representative section of the tumour should be used, fixated in formalin and embedded in paraffin. External audits are required (e.g. SKML, NordiQC, UK-Negas) to verify quality of techniques used	Yes	Indication	Should only be used in patients with metastatic ER+ and/or PR+ breast cancer	The details of specific requirements the test should comply with (regarding pre-analytical, analytical and post-analytical factors) to determine the ER and PR status are outside the scope of the guideline
Mamma carcinoma	2012	Integraal Kankercentrum Nederland	Lapatinib	HER2 using IHC and amplification (in-situ hybridisation is possible first; however, false-positive results occur as often as	Yes	Indication	Should only be used in patients with HER2 over-expression	-

Subject of guideline	Year of adoption	Organisation	Personalised medicine (active substance)	Pharmacogenetic test information	Test mandatory or not	Type of action taken by healthcare professional	Description of action	Additional information
				with IHC). In the case of 2+ colour score with IHC, an amplification test should be carried out using FISH, CISH or SISH. A standardised receptor test should be used. A representative section of the tumour should be used, fixated in formalin and embedded in paraffin. External audits are required (e.g. SKML, NordiQC, UK-Negas) to verify quality of techniques used				

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Mamma carcinoma	2012	Integraal Kankercentrum Nederland	Trastuzumab	HER2 using IHC and amplification (in-situ hybridisation is possible first; however, false-positive results occur as often as with IHC). In the case of 2+ colour score with IHC, an amplification test should be carried out using FISH, CISH or SISH. A standardised receptor test should be used. A representative section of the tumour should be used, fixated in formalin and embedded in paraffin. External audits are required	Yes	Indication	Should only be used in patients with HER2 over-expression	-

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				(e.g. SKML, NordiQC, UK-Negas) to verify quality of techniques used				
Mamma carcinoma	2012	Integraal Kankercentrum Nederland	Capecitabine	No	-	-	-	No mention of DPD deficiency in guideline
Mamma carcinoma	2012	Integraal Kankercentrum Nederland	Fluorouracil	No	-	-	-	No mention of DPD deficiency in guideline
Mamma carcinoma	2012	Integraal Kankercentrum Nederland	Tamoxifen	No	No	No action	-	There is not enough evidence on the influence of CYP2D6 genotype variations on the activity of tamoxifen. Determining the CYP2D6

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								genotype is therefore not recommended
Multidisciplinary guideline on ADHD	2005	CBO	Atomoxetine	No	-	-	-	No mention of CYP2D6 genotypes or recommendations on starting dose
Multidisciplinary guideline on anxiety disorders (first revision)	2010	Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ / Trimbos-instituut	Venlafaxine	No	-	-	-	No mention of CYP2D6 genetic variations in guideline
Multidisciplinary guideline on gastric disorders	2004	Nederlands Huisartsen Genootschap (NHG)	Esomeprazol	No	-	-	-	No mention of CYP2C19 genotypes
Multidisciplinary guideline on disorders related to alcohol use	2009	Nederlandse Vereniging voor Psychiatry (NVvP)	Carbamazepine	No	-	-	-	No mention of increased risk of SJS. HLA-B*1502 does not appear to be associated with SJS in the Caucasian population [13]

Subject of guideline	Year of adoption	Organisation	Personalised medicine (active substance)	Pharmacogenetic test information	Test mandatory or not	Type of action taken by healthcare professional	Description of action	Additional information
NHG guideline M78 Acute cough	2011	Nederlands Huisartsen Genootschap (NHG)	Dextromethorphan	No	-	-	-	No mention of CYP2D6 genetic variations in guideline
NHG guidelines M83 treatment policy after cardiac failure; M81 CVA; M86 deep venous thrombosis; M13 peripheral arterial blood vessel disorders; M43 stable angina pectoris; M45 TIA		Nederlands Huisartsen Genootschap (NHG)	Clopidogrel	No	-	-	-	No mention of CYP2C19 genetic variations in guidelines
Non-small-cell lung carcinoma	2011	vereniging integrale kankercentra (VIKC)	Erlotinib	Determining EGFR mutation status is preferable to determining EGFR expression, EGFR gene copy numbers and/or KRAS mutations	Yes	Indication	For patients with stage IV NSCLC the diagnosis should be confirmed with additional EGFR mutation analysis in order to establish the optimal first-line treatment	EGFR mutations, EGFR gene copy number and EGFR expression (using ICH) have a predictive value for treatment response to EGFR-TKIs. EGFR mutation analysis has the best test characteristics. Patients with EGFR activating mutations should be treated with an EGFR-TKI as initial treatment. There is no place for a first-line treatment with an EGFR-TKI for patients with no

Subject of guideline	Year of adoption	Organisation	Personalised medicine (active substance)	Pharmacogenetic test information	Test mandatory or not	Type of action taken by healthcare professional	Description of action	Additional information
								EGFR mutation or when mutation status is unknown. However, patients without EGFR activating mutations can be treated with an EGFR-TKI in the second- or third-line treatment
Non-small-cell lung carcinoma	2011	vereniging integrale kankercentra (VIKC)	Gefotinib	Determining EGFR mutation status is preferable to determining EGFR expression, EGFR gene copy numbers and/or KRAS mutations	Yes	Indication	For patients with stage IV NSCLC the diagnosis should be confirmed with additional EGFR mutation analysis in order to establish the optimal first line treatment	EGFR mutations, EGFR gene copy number and EGFR expression (using ICH) have a predictive value for treatment response to EGFR-TKIs. EGFR mutation analysis has the best test characteristics. Patients with EGFR activating mutations should be treated with an EGFR-TKI as initial treatment. There is no place for a first-line treatment with an EGFR-

Subject of guideline	Year of adoption	Organisation	Personalised medicine (active substance)	Pharmacogenetic test information	Test mandatory or not	Type of action taken by healthcare professional	Description of action	Additional information
								TKI for patients with no EGFR mutation or when mutation status is unknown. However, patients without EGFR activating mutations can be treated with an EGFR-TKI in the second- or third-line treatment
Non-small-cell lung carcinoma	2011	vereniging integrale kankercentra (VIKC)	Gefotinib	No	-	-	-	No mention of CYP2D6 genetic variations in guideline
Pancreas carcinoma	2011	Integraal Kankercentrum Nederland	Erlotinib	No	-	-	-	No mention of EGFR testing in guideline
Pancreas carcinoma	2011	Integraal Kankercentrum Nederland	Fluorouracil	No	-	-	-	No mention of DPD deficiency in guideline
Rectal carcinoma	2008	Integraal Kankercentrum Nederland	Capecitabine	No	-	-	-	No mention of DPD deficiency in guideline

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Rectal carcinoma	2008	Integraal Kankercentrum Nederland	Fluorouracil	No	-	-	-	No mention of DPD deficiency in guideline
Rectal carcinoma	2008	Integraal Kankercentrum Nederland	Irinotecan	No	-	-	-	No mention of UGT1A1 deficiency in guideline
Guideline on bipolar disorders	2008	Nederlandse Vereniging voor Psychiatry (NVvP)	Carbamazepine	No	-	-	-	No mention of increased risk of SJS. HLA-B*1502 does not appear to be associated with SJS in the Caucasian population [13]
Guideline on coeliakie and dermatitis herpetiformis	2008	Nederlandse Vereniging van Maag-Darm-Leverartsen	Dapsone	No	Yes	Contra-indication	Before initiating treatment with dapsone, G6PD deficiency should be ruled out	G6PD deficiency is a relative contra-indication. Patients with this deficiency can be treated with dapsone. However, they should be frequently monitored for the development of hemolysis and a dose adjustment may be necessary. In the case of a contra-indication or unacceptable side-effects, sulfapyridine can be used

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								instead
Guideline on constitutional eczema	2006	Nederlandse Vereniging voor Dermatologie en Venereologie	Azathioprine	No	No	Active monitoring	No TPMT activity measurement or intermediate activity (2-37,5 nmol/g.Hb/uur) lab measurements every other week for the first eight weeks. Low TPMT activity: do not prescribe azathioprine	
Guideline on cryopreservation of ovarian tissue	2007	Nederlandse Vereniging voor Obstetrie en Gynaecologie	Fluorouracil	No	-	-	-	No mention of DPD deficiency in guideline
Guideline on diagnostics and treatment of inflammatory bowel disease in adults	2008	Nederlandse Vereniging van Maag-Darm-Leverartsen	Azathioprine	No	No	Dose adjustment	Intermediate TPMT activity (IM): reduce dose to 50%. Low TPMT activity (PM): reduce dose to 10%	Cost-effectiveness not proven. TPMT genotyping before initiating treatment does not make TDM unnecessary. Genotyping can be

Subject of guideline	Year of adoption	Organisation	Personalised medicine (active substance)	Pharmacogenetic test information	Test mandatory or not	Type of action taken by healthcare professional	Description of action	Additional information
								performed for patients with previous leukopenia after thiopurine if it is available
Guideline on diagnostics and treatment of inflammatory bowel disease in adults	2008	Nederlandse Vereniging van Maag-Darm-Leverartsen	Mercaptopurine	No	No	Dose adjustment	Intermediate TPMT activity (IM): reduce dose to 50%. Low TPMT activity (PM): reduce dose to 10%	Cost-effectiveness not proven. TPMT genotyping before initiating treatment does not make TDM unnecessary. Genotyping can be performed for patients with previous leukopenia after thiopurine if it is available
Guideline on the diagnostics and pharmacotherapy of dementia	2005	Nederlandse Vereniging voor Klinische Geriatrie	Galantamine	No	-	-	-	No mention of CYP2D6 genotypes
Guideline on gastro-esophageal reflux	2010	Nederlandse Vereniging van Maag-Darm-Leverartsen	Esomeprazol	No	-	-	-	No mention of CYP2C19 genotypes

Subject of guideline	Year of adoption	Organisation	Personalised medicine (active substance)	Pharmacogenetic test information	Test mandatory or not	Type of action taken by healthcare professional	Description of action	Additional information
Guideline on HIV [3] / Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents	2011	Nederlandse Vereniging van HIV behandelaren (NVHB) / AIDSinfo (service of the U.S. Department of Health and Human Services (HSS))	Maraviroc	Coreceptor tropism assay: Trofile, Monogram Biosciences, Inc., South San Francisco, CA, was used to screen patients who were participating in studies that formed the basis of approval for maraviroc. Other assays are under development and are currently used primarily for research purposes or in clinical situations in which the Trofile assay is not readily available	Yes	Indication	Coreceptor tropism assay should be performed whenever the use of a CCR5 inhibitor is being considered	-

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Guideline on HIV [3] / Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents	2011	Nederlandse Vereniging van HIV behandelaren (NVHB) / AIDSinfo (service of the U.S. Department of Health and Human Services (HSS))	Abacavir	No	Recommended	Usage warning	Screening for HLA-B*5701 before starting patients on an abacavir-containing regimen is recommended to reduce the risk of hypersensitivity reaction. HLA-B*5701-positive patients should not be prescribed abacavir	The positive status should be recorded as an ABC allergy in the patient's medical record. When HLA-B*5701 screening is not readily available, it remains reasonable to initiate abacavir with appropriate clinical counselling and monitoring for any signs of hypersensitivity reactions
Guideline on HIV [3] / Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents	2011	Nederlandse Vereniging van HIV behandelaren (NVHB) / AIDSinfo (service of the U.S. Department of Health and Human Services (HSS))	Nelfinavir	No	-	-	-	No mention of CYP2C19 genetic variations

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Guideline on NSAID use and gastric protection	2003	Kwaliteitsinstituut voor de Gezondheidszorg CBO	Esomeprazol	No	-	-	-	No mention of CYP2C19 genotypes
Guideline on the diagnostics and treatment of Ankyloetic Spondylitis	2009	Nederlandse Vereniging Reumatologie (NVR)	Celecoxib	No	-	-	-	No mention of CYP2C9 genetic variations in guideline
Guideline on the diagnostics and treatment of chronic myeloid leukemia	2002	Integraal Kankercentrum Nederland	Thioguanine	No	-	-	-	No mention of TPMT deficiency in guideline
Guideline on plasma cell disorders 2010	2010	Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON)	Lenalidomide	No	-	-	-	No mention of variations on chromosome 5
Revision of the multidisciplinary guideline on depression	2009	Nederlandse Vereniging voor Psychiatry (NVvP)	Citalopram	No	-	-	-	No mention of CYP2C19 genetic variations in guideline
Revision of the multidisciplinary guideline on depression	2009	Nederlandse Vereniging voor Psychiatry (NVvP)	Venlafaxine	No	-	-	-	No mention of CYP2D6 genetic variations in guideline
SWAB-guideline for the treatment of invasive fungal infection	2008	Stichting Werkgroep Antibioticabeleid (SWAB)	Voriconazole	No	-	-	-	No mention of CYP2C19 genetic variations

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Soft tissue tumours	2011	Integraal Kankercentrum Nederland	Imatinib	Mutation analysis can select GIST variants less sensitive to imatinib	Recommen-ded	Indication	Mutation analysis can play a role in determining whether to start neoadjuvant treatment with imatinib or not and prevent unnecessary postponing of surgery for unresponsive disease. Patients with imatinib-resistant tumours are not eligible for treatment with imatinib	-

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De zorg voor morgen begint vandaag