

C B G
M E B



Collegedag 8 juni 2011
workshops ronde 2, #9 (beam)

**Verrijkte geneesmiddelen hebben
de toekomst**

WELKOM

Participanten

- Prof.mr. Marie-Hélène Schutjens (UU, Utrecht)
- Dr. Rogier Bos (CBG-MEB, Bilthoven)
- Prof.Dr. Martina Cornel, arts (VUMC, Amsterdam)
- Dr. Monique op ten Berg, arts (Roche, Woerden)
- Prof.Dr. Kees Kluit (CHDR, Leiden)

Opzet van de workshop

- Intro + peiling (Bos)
- Context (10)
 - Schutjens
- Experts (3x15)
 - Cornel
 - Op ten Berg
 - Kluft
- Forumdiscussie (allen)
- Wrap up (+ peiling)

Geschiedenis

- Verrijking meestal in combinatie met voeding
- Bekende voorbeelden:
 - Broodbesluit 1942 (Jodium in bakkerszout)
 - Fluorideringsarrest 1973 (Fluoride in drinkwater)
- Jaren 90 “tsunami” aan verrijkte voedingswaren
- Nieuw: combinatie geneesmiddelen met geneesmiddelen (of zoals we vandaag gaan leren ook andere combinaties)

De polypil, een casus

- Combinatie van 3 of 4 actieve stoffen
 - Bloedverdunner
 - Cholesterolverlager
 - Bloeddrukverlager
 - Ontstekingsremmer
- Beoogd effect: 50% verminderd risico op hartfalen.
- Doelgroep: 50+
- 15 – 35 € pppj

Perspectieven ☹️

- Industrie: lage marges
- Beoordelaar: complexe risicoafweging
- Betaler (VWS) 150M€ extra kosten per jaar
- Voorschrijver overmedicatie
- Patiënt uitgesteld effect (wat heb ik er aan?)

Perspectieven 😊

- Industrie hoog volume product
 - Beoordelaar individueel goed bekende stoffen
 - Betaler (VWS) reductie uitgaven AWBZ
 - Voorschrijver betere zorg: helpt de laag-risico groep
 - Patiënt beter mee verleggen, dan om verleggen
-
- Nu **GEEN** discussie: komt straks....

De Stelling

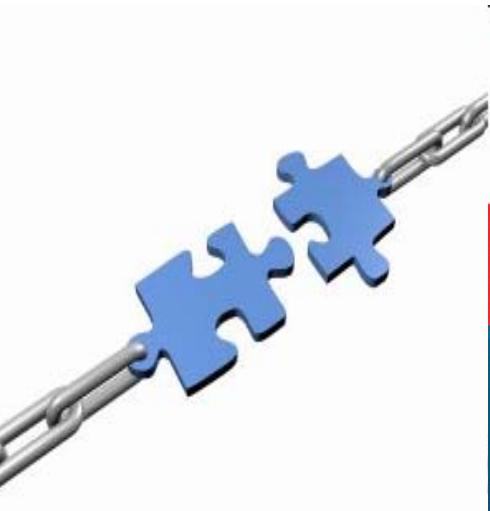
Verrijkte geneesmiddelen hebben een belangrijke toegevoegde waarde in het zorgpakket.

- **EENS = GROEN**
- **ONEENS = ROOD**

Geef nu graag woord aan:

- Marie-Hélène Schutjens
 - Farmaceutisch recht, RU Utrecht
- Martina Cornel, arts
 - Klinische Genetica en Antropogenetica, VU Amsterdam
- Monique op ten Berg, arts
 - Medical Director, Roche Nederland BV, Woerden
- Kees Kluit
 - Hemostasis expert, Gaubius TNO, Leiden
 - Biomarker specialist, CHDR, Leiden
- Forumdiscussie

Wat is verrijking?



Verschillende manieren tot verrijking te komen

Verrijking van het geneesmiddelenarsenaal zelf

1. Geneesmiddelen voor *neglected diseases*

– Priority medicines

2. Geneesmiddelen voor bepaalde groepen

– Weesgeneesmiddelen

– Geneesmiddelen voor kinderen

3. Nieuwe indicaties




The screenshot shows the WHO website interface. At the top is the WHO logo and 'World Health Organization'. Below it is a navigation menu with 'Statistics', 'Media centre', 'Publications', 'Countries', 'Programmes and projects', and 'About'. A search bar is present. The main content area is titled 'Essential medicines for children' and features a sub-section 'Priority medicines for mothers and children'. Below this is a thumbnail for a document titled 'Priority medicines for mothers and children 2011'.

Priority medicines are medicines with potential to save lives and should be available in all health systems. The priority medicines list for mothers and children helps countries select and make available the most important medicines.

Major causes of death in mothers and children could be prevented or treated with access to simple and affordable medicines. However, many medicines are not available in countries.

In order to improve access, priority medicines should be:

- Manufactured according to quality standards
- Available for use by regulatory authorities


Verrijking van farmaceutische zorg

4. Nieuwe toedieningsvormen
 - Gebruiksgemak
 - bevordering compliance (retardvormen, ...)

5. Verrijking van de farmaceutische zorg (op niveau apotheker)
 - Informatie
 - Sms-services
 - Complianceprogramma's (GGG: **g**oed **g**eneesmiddelen **g**ebruik)
 - Weekdoseersystemen
 -



6. Verrijking van de informatie voor de patiënt



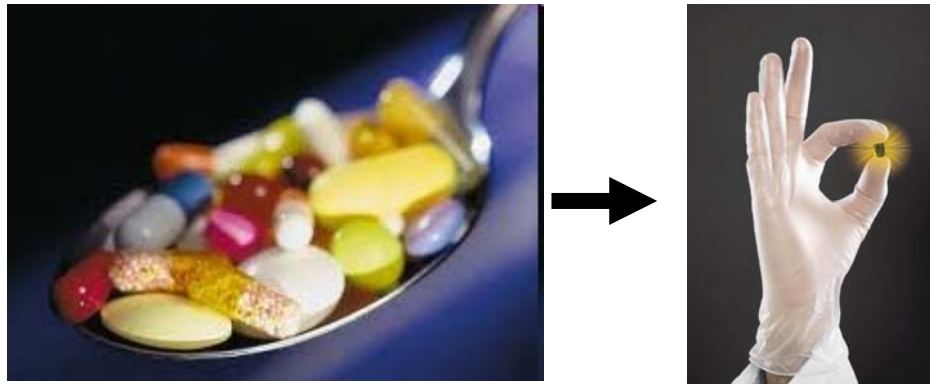
The screenshot shows the TED website interface. At the top left is the TED logo with the tagline 'Ideas worth spreading'. To the right are navigation links for Themes, Speakers, Talks, and Translations. Below this is the title of the talk: 'TALKS | TED PARTNER SERIES Thomas Goetz: It's time to redesign medical data'. The main content is a video player for 'TEDMED 2010, Filmed Oct 2010; Posted Jan 2011'. The video shows a man (Thomas Goetz) on a stage with a large 'MED' logo in the background. The video player includes a play button, a progress bar showing 00:45 / 10:33, and 'Share' and 'Rate' buttons. Below the video player, there is a social media sharing section with a 'Tweet this talk' button and icons for Facebook, MySpace, LinkedIn, YouTube, and others.

- Meer duiding van de informatie naar de patiënt
- Meer begrip bij de patiënt
- *Personalised information*
 - Labwaarden met duiding
 - Bijsluiter 'op maat'

http://www.ted.com/talks/thomas_goetz_it_s_time_to_redesign_medical_data.html?utm_source=newsletter_weekly_2011-01-25&utm_campaign=newsletter_weekly&utm_medium=email

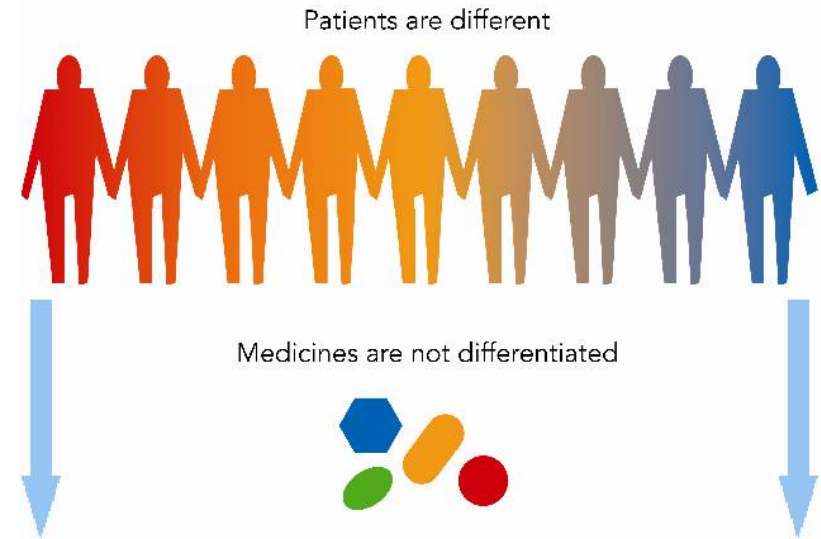
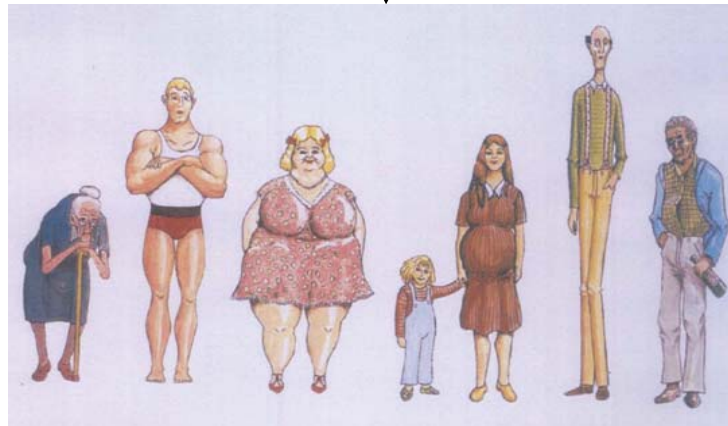
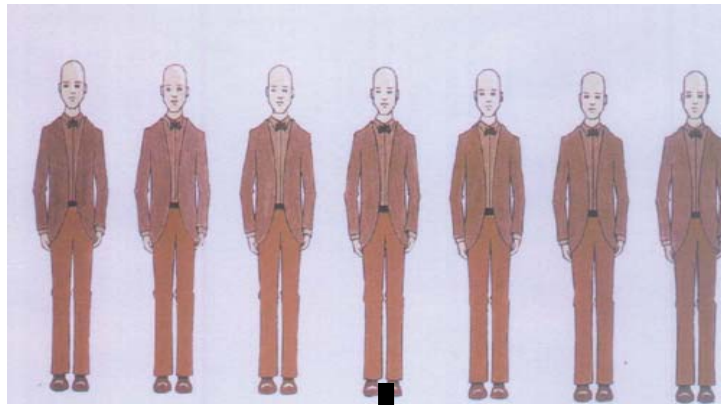
7. Verrijking van het geneesmiddel zelf

- Polypil ($\rightarrow 1+1=3?$)



- Prof.Dr. Martina Cornel

8. Verrijking door directe combinatie geneesmiddel en test



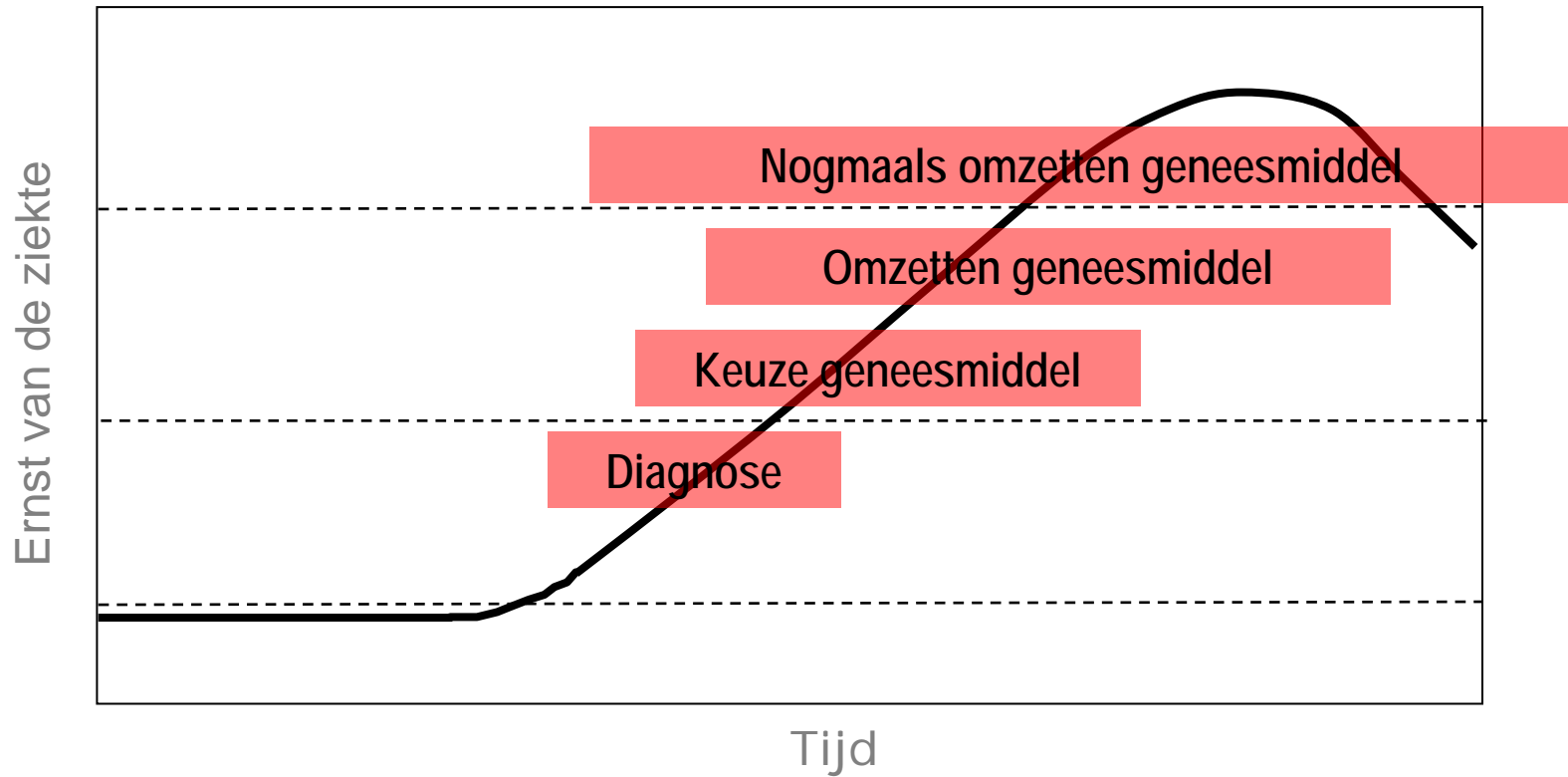
~ 30% of patients do not benefit from medicines¹
(100,000 deaths and 2.2 million nonfatal events from ADR in the US in 1994)

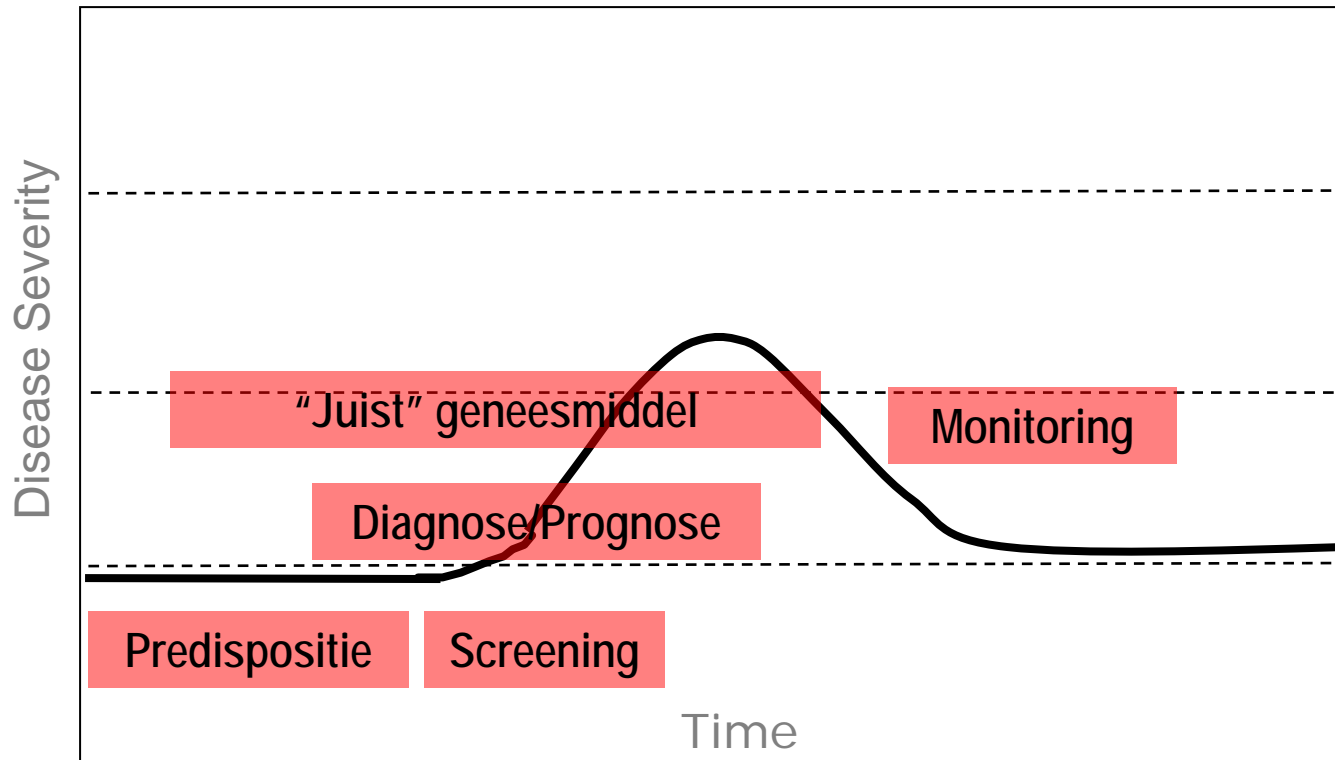
¹JAMA 1998, 279: 1200

Source: Bayer HealthCare Diagnostics and Burrill & Company

Dr Monique op ten Berg

Paradigma-shift: van trial and error naar betere diagnose en dus zorg op maat





Personalised medicine/theranostiek

Concept → combinatie test en geneesmiddel (selectieproces)

- Verzamelen gegevens (moleculaire processen, erfelijke eigenschappen) d.m.v. een test
- Levert informatie op over het gen-, eiwit- en/of metaboliseringsprofiel
- Zorg op maat door medische zorg specifiek toe te spitsen op de individuele behoefte van een patiënt door
 1. stratificeren ziekte in subtypen
 2. bepalen effectiviteit bepaalde behandeling bij individu
 3. bepalen optimale dosis van een medicijn (verminderen bijwerkingen/ effectiviteit verhogen)
 4. preventieve maatregelen op maat



Perspective
JULY 22, 2010

The Path to Personalized Medicine

Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.

Major investments in basic science have created an opportunity for significant progress in clinical medicine. Researchers have discovered hundreds of genes that harbor variations contributing to human illness, identified genetic suitability in patients' responses to doses of treatment, and begun to target the molecular causes of some diseases. In addition, scientists are developing and using diagnostic tests based on genetics to better predict patients' responses to targeted therapies.

The challenge is to deliver the benefits of this work to patients, as the leaders of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA), we have a shared vision of personalized medicine and the scientific and regulatory structure needed to support its growth. Together, we have been

the NIH and the FDA will invest in advancing translational and regulatory science, better define regulatory pathways for modification of approved or orphaned diagnostics and therapeutics, develop risk-based approaches for appropriate review of diagnostics to more accurately assess their safety and clinical utility, and make information about tests readily available.

Moving from concepts to clinical use requires basic, translational, and regulatory science. On the basic-science front, studies are identifying many genetic variations underlying the risks of both rare and common diseases. These newly discovered genes, proteins, and pathways can represent potential new drug targets, but currently there is insufficient evidence of a downstream marker to make the private sector to explore some of them. To fill that void, the NIH and the FDA will

Budesonide	IBD Serology 7	Inflammatory bowel disease: Identifies subset of patients who will benefit from budesonide.
Gleevec® (imatinib mesylate)	<i>BCR-ABL</i>	Leukemia: "Gleevec® (imatinib mesylate) is indicated for the treatment of newly diagnosed adult and pediatric patients with Philadelphia chromosome positive [indicated by presence of <i>BCR-ABL</i>] chronic myeloid leukemia (CML) in chronic phase."
Dasatinib	Philadelphia Chromosome	Leukemia: "Dasatinib is indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy"
Busulfan	Philadelphia Chromosome	Leukemia: "Busulfan is clearly less effective in patients with chronic myelogenous leukemia who lack the Philadelphia (Ph1) chromosome."
Purinethol® (mercaptopurine) Thioguanine Azathioprine	TPMT	Leukemia: Guides adjustment of dose in treatment of acute lymphoblastic leukemia: "Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe Purinethol toxicity from conventional doses..."
Tarceva® (erlotinib)	<i>EGFR</i> expression	Lung cancer: The test determines patients most likely to respond.
Capecitabine	DPD	Multiple cancers: "Rarely, unexpected severe toxicity (e.g., stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity."
Pharmaceutical and surgical treatment options and surveillance	<i>MLH1, MSH2, MSH6</i>	Multiple cancers: Guides surveillance and preventive treatment based on susceptibility risk for colon and other cancers.
Chemotherapy	CupPrint™	Multiple cancers: Determines cancer classification for tumors of unknown primary origin.
Chemotherapy	Aviara CancerTYPE ID®	Multiple cancers: Classifies 39 tumor types from tumors of unknown primary origin, using a gene expression profile.
Elitek® (rasburicase)	G6PD deficiency	Multiple cancers: "Rasburicase administered to patients with glucose- phosphate dehydrogenase (G6PD) deficiency can cause severe hemolysis. ... It is recommended that patients at higher risk for G6PD deficiency ... be screened prior to starting ELITEK therapy."
Drugs metabolized by CYP P450	Amplichip® <i>CYP2D6/CYP2C19</i>	Multiple diseases: FDA classification 21 CFR 862.3360: "This device is used as an aid in determining treatment choice and individualizing treatment dose for therapeutics that are metabolized primarily by the specific enzyme about which the system provides genotypic information."
2C9 Celecoxib, Codeine, Diazepam, Esomeprazole, Nefazodone, Omeprazole, Pantoprazole, Rabeprazole, Venlafaxine		
2D6 Acetaminophen, Aniprisazole, Atomoxetine, Clavulidol, Cevimeline hydrochloride, Clozapine, Fluoxetine HCl, Fluoxetine HCL and Olanzapine, Meprobrolol, Propafenolol, Propafenone, Promethazine HCL, Risperidone, Tamoxifen, Terfenadine, Thioridazine, Timolol maleate, Tiotropium bromide inhalation, Tolterodine, Tramadol, Venlafaxine		
Rifampin Isoniazid Pyrazinamide	NAT	Multiple diseases: N-acetyltransferase slow and fast acetylators and toxicity: "slow acetylation may lead to higher blood levels of the drug, and thus, an increase in toxic reactions."
Rituximab	PGx Predict™; Rituximab	Non-Hodgkin's lymphoma: Detects CD-20 variant (polymorphism in the IgG Fc receptor gene <i>FcγRIIIa</i>) to predict response to cancer drug rituximab.
Celebrex® (celecoxib)	<i>CYP2C9</i>	Pain: "Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance."
Risperdal® (risperidone) Zyprexa® (olanzapine)	PhyziType PIMS	Psychiatric disorders: Predicts risk of psychotropic-induced metabolic syndrome, based on a patient's combinatorial genotype for 50 genes.
Gleevec® (imatinib mesylate)	<i>c-KIT</i>	Stomach cancer: "Gleevec® is also indicated for the treatment of patients with <i>Ki1 (CD117)</i> positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)."

* This list is not intended to be comprehensive but reflects commonly used or available products as of March 2009. Some products, for which the FDA recommends or requires pharmacogenomic testing or which have pharmacogenomic information in their label, are listed at the FDA's Web site (http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm). Other listed products that are novel, and/or that address large populations, have been identified via websites and public announcements.

Indications in quotes are taken from the therapeutic product label.

BCR-ABL = breakpoint cluster region - Abelson
 BRCA 1,2 = breast cancer susceptibility gene 1 or 2
 c-KIT = tyrosine kinase receptor
 CYP = cytochrome P450 enzyme
 DPD = dihydropyrimidine dehydrogenase
 G6PD = glucose 6 phosphate dehydrogenase
 HER2 = human epidermal growth factor receptor 2
 NAT = N-acetyltransferase
 TOP1 = topoisomerase 1
 TPMT = thiopurine S-methyltransferase
 TS = thymidylate synthase
 UGT7AT = UDP-glucosyltransferase 1A1

Table 1: Selected Personalized Medicine Drugs, Treatments, and Diagnostics as of March 2009*

Therapeutic product label contains pharmacogenomic information as:

- Information only
- Recommended
- Required

THERAPY	BIOMARKER/TEST	INDICATION
Herceptin® (trastuzumab) Tykerb® (lapatinib)	HER-2/neu receptor	Breast cancer: "...for the treatment of patients with metastatic breast cancer whose tumors over-express the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease."
Pharmaceutical and surgical prevention options and surveillance	<i>BRCA 1,2</i>	Breast cancer: Guides surveillance and preventive treatment based on susceptibility risk for breast and ovarian cancer.
Tamoxifen	Aviara Breast Cancer Index™ (<i>HOXB13, IL17BR</i>)	Breast cancer: Calculates a combined risk analysis for recurrence after tamoxifen treatment for ER-positive, node-negative breast cancer.
Chemotherapy	Mammostrat®	Breast cancer: Prognostic immunohistochemistry (IHC) test used for postmenopausal, node negative, estrogen receptor expressing breast cancer patients who will receive hormonal therapy and are considering adjuvant chemotherapy.
Chemotherapy	MammaPrint®	Breast cancer: Assesses risk of distant metastasis in a 70 gene expression profile.
Coumadin® (warfarin)	<i>CYP2C9</i>	Cardiovascular disease: "an increased bleeding risk for patients carrying either the <i>CYP2C9*2</i> or <i>CYP2C9*3</i> alleles."
Coumadin® (warfarin)	<i>VKORC1</i>	Cardiovascular disease: "Certain single nucleotide polymorphisms in the <i>VKORC1</i> gene (especially the -1639G>A allele) have been associated with lower dose requirements for warfarin."
Coumadin® (warfarin)	PGx Predict™; Warfarin	Cardiovascular disease: Determines <i>CYP2C9</i> and <i>VKORC1</i> genotypes to predict likelihood of adverse events with warfarin therapy.
Coumadin® (warfarin)	Protein C deficiencies	Cardiovascular disease: Hereditary or acquired deficiencies of protein C or its cofactor, protein S, has been associated with tissue necrosis following warfarin administration.
Pharmaceutical and lifestyle prevention options	Family® 5-gene profile	Cardiovascular disease: Guides prevention and drug selection for patients with inherited cardiac channelopathies such as Long QT Syndrome (LQTS), which can lead to cardiac rhythm abnormalities.
Statins	PhyziType SINM	Cardiovascular disease: Predicts risk of statin-induced neuro-miopathy, based on a patient's combinatorial genotype for 50 genes.
Atorvastatin	<i>LDLR</i>	Cardiovascular disease: "Doses should be individualized according to the recommended goal of therapy. Homozygous Familial Hypercholesteremia (10-80mg/day)and heterozygous (10-20mg/day)."
Camptosar® (irinotecan)	<i>UGT1A1</i>	Colon cancer: "Variations in the <i>UGT1A1</i> gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects."
Erbix® (cetuximab) Gefitinib Vectibix® (panitumab)	<i>EGFR</i> expression	Colon cancer: "Patients enrolled in the clinical studies were required to have...evidence of positive <i>EGFR</i> expression using the DakoCytomation <i>EGFR</i> pharmDx™ test kit." <i>EGFR</i> positive individuals are more likely to respond to the drug than those with reduced <i>EGFR</i> expression.
Erbix® (cetuximab) Gefitinib Vectibix® (panitumab)	<i>KRAS</i>	Colon cancer: Certain <i>KRAS</i> mutations lead to unresponsiveness to the drug.
Erbix® (cetuximab) and Vectibix® (panitumab) Fluorouracil Camptosar® (irinotecan)	Target GI™	Colon cancer: Provides information of the expression of key molecular targets— <i>KRAS, TS, and TOP1</i> —to guide therapy.
Tegretol (carbamazepine)	<i>HLA-B*1502</i>	Epilepsy and bipolar disorder: Serious dermatologic reactions are associated with the <i>HLA-B*1502</i> allele in patients treated with carbamazepine. "Prior to initiating Tegretol therapy, testing for <i>HLA-B*1502</i> should be performed in patients with ancestry in populations in which <i>HLA-B*1502</i> may be present."
Immunosuppressive drugs	AlloMap® gene profile	Heart transplantation: Monitors patient's immune response to heart transplant to guide immunosuppressive therapy.
Ziagen® (abacavir)	<i>HLA-B*5701</i>	HIV: "Patients who carry the <i>HLA-B*5701</i> allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the <i>HLA-B*5701</i> allele is recommended."
Selzentry® (maraviroc)	CCR5 receptor (1)	HIV: "Selzentry, in combination with other antiretroviral agents, is indicated for treatment experienced adult patients infected with only CCR5-tropic HIV-1 detectable..."

9. Verrijking door aanpassing lifestyle

- Gezondheidszorg erg gericht op symptoombestrijders
- Moet er niet meer worden gekeken naar
 - preventieve zorg (medicatie)
 - ontwikkeling van meer primaire, causale behandelingen
 - Leefstijlaanpassing

- Prof. Kees Kluit



C B G

M E B



Universiteit Utrecht

Geef nu graag woord aan:

- Marie-Hélène Schutjens
 - Farmaceutisch recht, RU Utrecht
- Martina Cornel, arts
 - Klinische Genetica en Antropogenetica, VU Amsterdam
- Monique op ten Berg, arts
 - Medical Director, Roche Nederland BV, Woerden
- Kees Kluft
 - Hemostasis expert, Gaubius TNO, Leiden
 - Biomarker specialist, CHDR, Leiden
- Forumdiscussie

C B G

M E B



Universiteit Utrecht

Nogmaals : de Stelling

Verrijkte geneesmiddelen hebben een belangrijke toegevoegde waarde in het zorgpakket.

- **EENS = GROEN**
- **ONEENS = ROOD**

Dank voor uw bijdrage !!!

C B G

M E B

