cBG MEB

Universiteit Utrecht

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

Verrijkte geneesmiddelen hebben de toekomst

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 Kluft (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 verlegen, dan om verlegen

- 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 Nederand BV, Woerden
- Kees Kluft
  - Hemostasis expert, Gaubius TNO, Leiden
  - Biomarker specialist, CHDR, Leiden

- Forumdiscussie

Wat is verrijking?

Verschillende manieren tot verrijking te komen

Verrijking van het geneesmiddelenarsenaal zelf

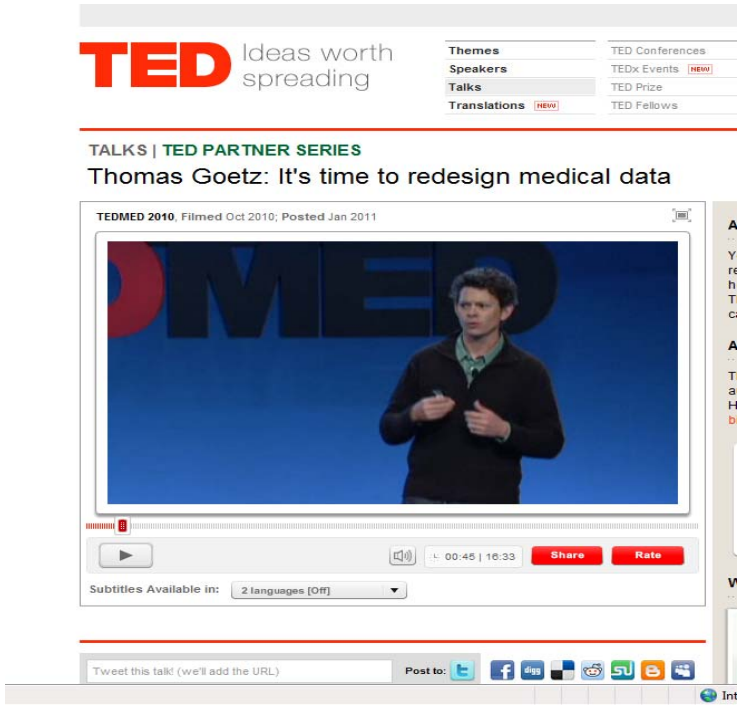
1. Geneesmiddelen voor *neglected diseases*
   - –Priority medicines
2. Geneesmiddelen voor bepaalde groepen
   - –Weesgeneesmiddelen
   - –Geneesmiddelen voor kinderen
3. Nieuwe indicaties

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



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

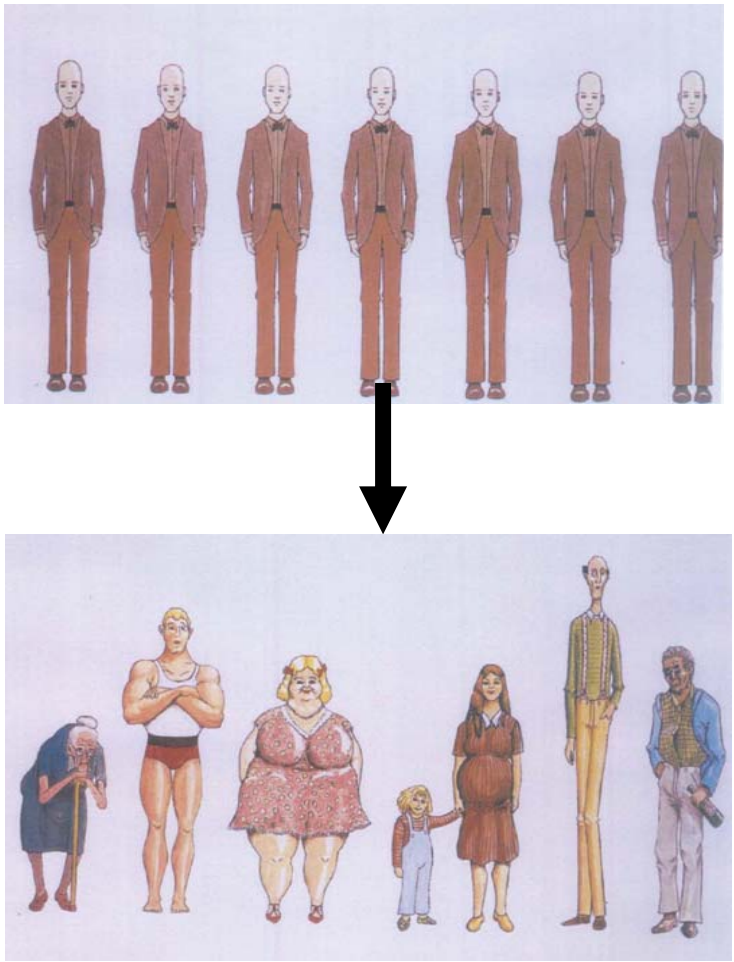
http://www.ted.com/talks/thomas_goetz_it_s_time_to_redesign_medical_data.html?utm_source=newsletter_weekly_2011-01-25&utm_campaign=newsletter_weekly&utm_medium=email

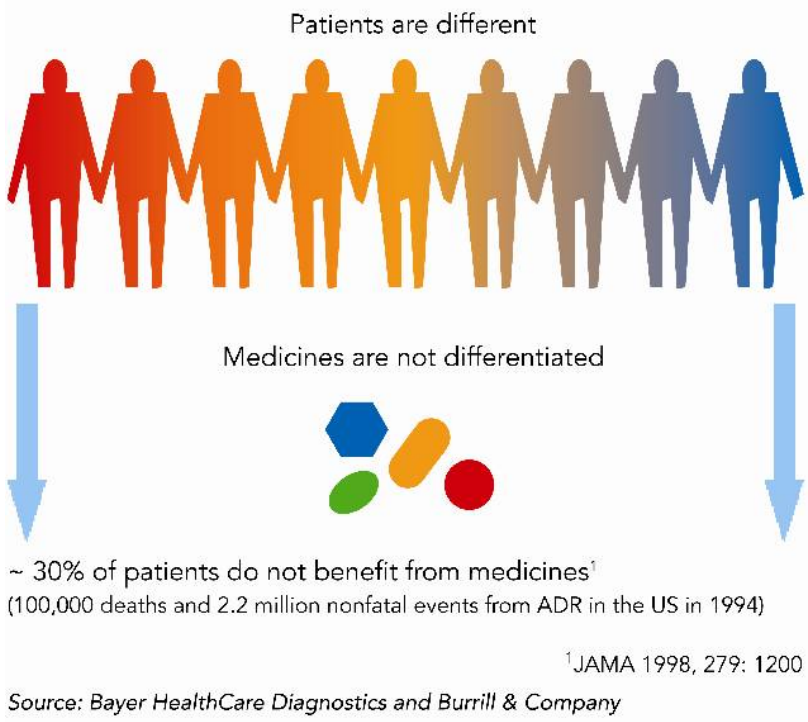
7. Verrijking van het geneesmiddel zelf

- Polypil (→ 1+1=3?)

- Prof.Dr. Martina Cornel

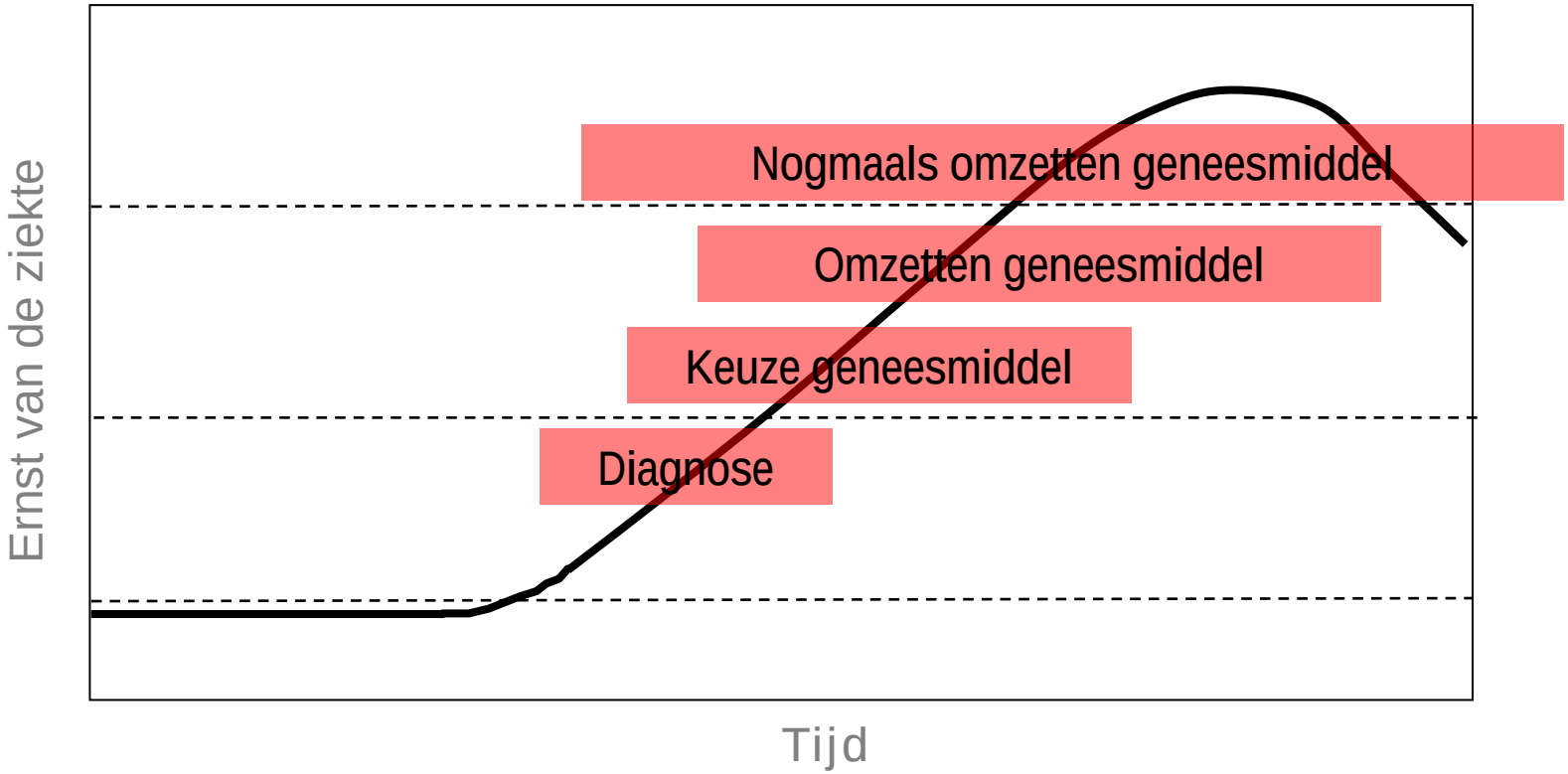
8. Verrijking door directe combinatie geneesmiddel en test

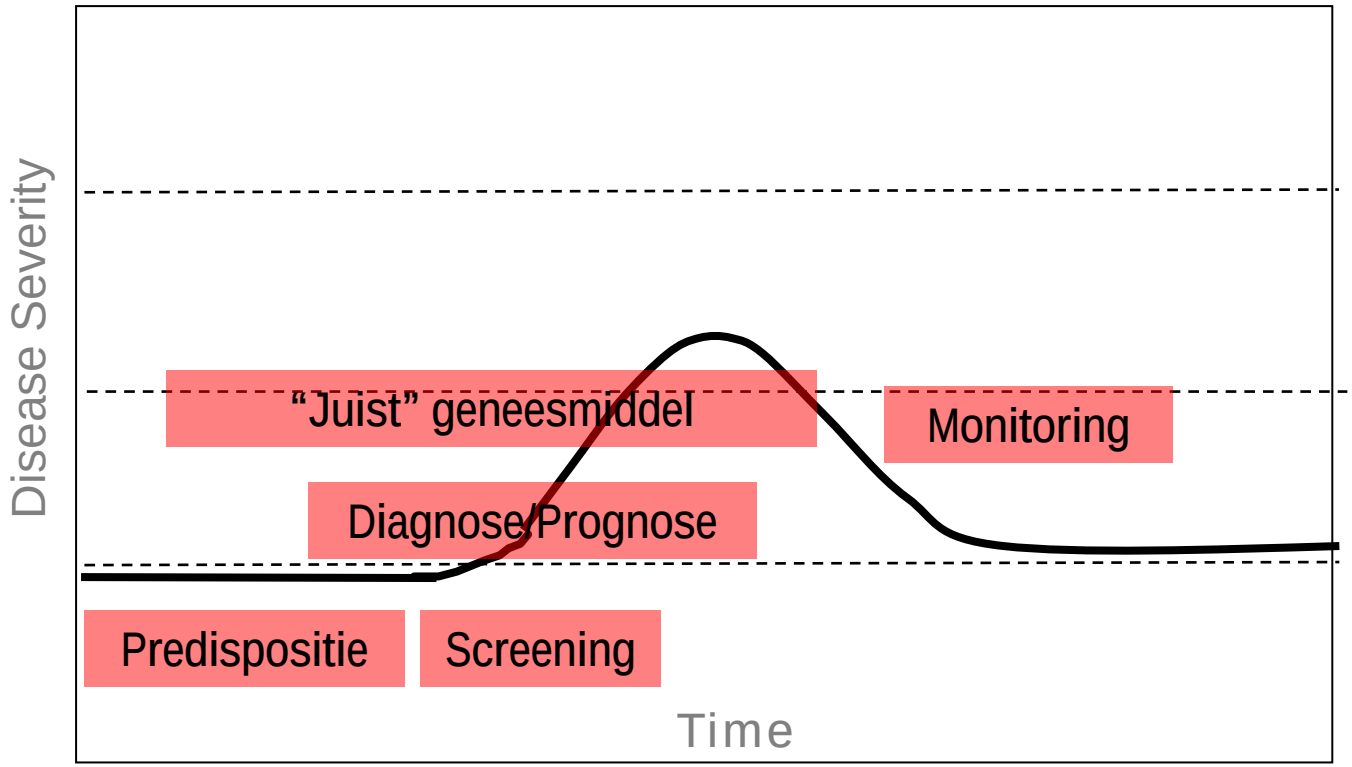




Dr Monique op ten Berg

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




Disease Severity
"Juist" geneesmiddel
Monitoring
Diagnose/Prognose
Predispositie
Screening
Time

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


The NEW ENGLAND JOURNAL of MEDICINE

Perspective
JULY 22, 2010

The Path to Personalized Medicine

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

Budesonide	IBD Serology 7	**Inflammatory bowel disease:** Identifies subset of patients who will benefit from budesonide.
Gleevec® (imatinib mesylate)	*BCR-ABL*	**Leukemia:** "Gleevec® (imatinib mesylate) is indicated for the treatment of newly diagnosed adult and pediatric patients with Philadelphia chromosome positive [indicated by presence of *BCR-ABL*] 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)	*EGFR* 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	*MLH1, MSH2, MSH6*	**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 **2C19**: Celecoxib, Codeine, Diazepam, Esomeprazole, Nelfinavir, Omeprazole, Pantoprazole, Rabeprazole, Voriconazole **2D6**: Acetaminophen, Aripiprazole, Atomoxetine, Carvedilol, Cevimeline hydrochloride, Clozapine, Fluoxetine HCl, Fluoxetine HCL and Olanzapine, Metoprolol, Propranolol, Propafenone, Protriptyline HCl, Risperidone, Tamoxifen, Terbinafine, Thioridazine, Timolol maleate, Tiotropium bromide inhalation, Tolterodine, Tramadol, Venlafaxine	Amplichip® *CYP2D6/CYP2C19*	**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."
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 *FcgRIIIa*) to predict response to cancer drug rituximab.
Celebrex® (celecoxib)	*CYP2C9*	**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® (resperidone) Zyprexa® (olanzapine)	PhyzioType PIMS	**Psychiatric disorders:** Predicts risk of psychotropic-induced metabolic syndrome, based on a patient's combinatorial genotype for 50 genes.
Gleevec® (imatinib mesylate)	*c-KIT*	**Stomach cancer:** "Gleevec® is also indicated for the treatment of patients with Kit (*CD117*) 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
TOPO1 = topoisomerase 1
TPMT = thiopurine S-methyltransferase
TS = thymidylate synthase
UGT1A1 = UDP-glucuronosyltransferase 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 overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease."
Pharmaceutical and surgical prevention options and surveillance	*BRCA 1,2*	**Breast cancer:** Guides surveillance and preventive treatment based on susceptibility risk for breast and ovarian cancer.
Tamoxifen	Aviara Breast Cancer Index℠ (*HOXB13, IL17BR*)	**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)	*CYP2C9*	**Cardiovascular disease:** "an increased bleeding risk for patients carrying either the *CYP2C9*2* or *CYP2C9*3* alleles."
Coumadin® (warfarin)	*VKORC1*	**Cardiovascular disease:** "Certain single nucleotide polymorphisms in the *VKORC1* gene (especially the -1639G>A allele) have been associated with lower dose requirements for warfarin."
Coumadin® (warfarin)	PGx Predict™: Warfarin	**Cardiovascular disease:** Determines *CYP2C9* and *VKORC1* 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	Familion® 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	PhyzioType SINM	**Cardiovascular disease:** Predicts risk of statin-induced neuro-myopathy, based on a patient's combinatorial genotype for 50 genes.
Atorvastatin	*LDLR*	**Cardiovascular disease:** "Doses should be individualized according to the recommended goal of therapy. Homozygous Familial Hypercholestremia (10-80mg/day)and heterozygous (10-20mg/day)."
Camptosar® (irinotecan)	*UGT1A1*	**Colon cancer:** "Variations in the *UGT1A1* 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."
Erbitux® (cetuximab) Gefitinib Vectibix® (panitumab)	*EGFR* expression	**Colon cancer:** "Patients enrolled in the clinical studies were required to have…evidence of positive *EGFR* expression using the DakoCytomation *EGFR* pharmDx™ test kit." *EGFR* positive individuals are more likely to respond to the drug than those with reduced *EGFR* expression.
Erbitux® (cetuximab) Gefitinib Vectibix® (panitumab)	*KRAS*	**Colon cancer:** Certain *KRAS* mutations lead to unresponsiveness to the drug.
Erbitux® (cetuximab) and Vectibix® (panitumab) Fluorouracil Camptosar® (irinotecan)	Target GI™	**Colon cancer:** Provides information of the expression of key molecular targets—*KRAS*, *TS*, and *TOPO1*—to guide therapy.
Tegretol (carbamazepine)	*HLA-B*1502*	**Epilepsy and bipolar disorder:** Serious dermatologic reactions are associated with the *HLA-B*1502* allele in patients treated with carbamazepine. "Prior to initiating Tegretol therapy, testing for *HLA-B*1502* should be performed in patients with ancestry in populations in which *HLA-B*1502* may be present."
Immunosuppressive drugs	AlloMap® gene profile	**Heart transplantation:** Monitors patient's immune response to heart transplant to guide immunosuppressive therapy.
Ziagen® (abacavir)	*HLA-B*5701*	**HIV:** "Patients who carry the *HLA-B*5701* allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the *HLA-B*5701* 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 Kluft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Geef nu graag woord aan:

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- Forumdiscussie


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Nogmaals : de Stelling

Verrijkte geneesmiddelen hebben een belangrijke toegevoegde waarde in het zorgpakket.

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

Dank voor uw bijdrage !!!

CBG MEB