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

Application of personalized medicine

Opportunities and challenges for policy

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Colophon

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Synopsis

Application of personalized medicine
Opportunities and challenges

Pharmacotherapy based on individual patient characteristics, such as genetic makeup, offers opportunities towards more effective treatment of disease, but also faces a lot of challenges. Genetic characteristics are notably only part of the puzzle to treat a disease effectively with medicines. Also other factors play a role, such as age, genus, eating habit, other concomitant disease and the use of various medicines simultaneously. This is the outcome of RIVM research into the opportunities and challenges of personalised medicine, performed by the order of the Dutch Ministry of Health, Welfare and Sport.

Personalised medicine (PM), treatment based on the patient's unique characteristics, is relatively new in medical society. PM is strongly developing because the influence of individual characteristics on the development of disease and the efficacy of medicines is becoming more evident. Some people have, due to their genetic makeup, a higher risk of severe side effects when using specific medicines. Others are more sensitive to the efficacy of medicines and need a different dose than generally recommended. Also the genetic characteristics of tumours in cancer may differ per patient, which offers opportunities to tune the therapy based on tumour characteristics.

One of the challenges is to optimally utilize all available data and patients' characteristics for research. The same is true for the translation of research results into clinical practice. Also, the education of doctors and pharmacists must prepare for all developments in PM. In addition, consideration must be given to privacy and ownership of patient data as well as to the suitability of the health care system in the Netherlands to fruitfully implement PM.

Keywords: medicinal products, personalized medicine, genetic characteristics

Publiekssamenvatting

Toepassing van personalized medicine
Kansen en uitdagingen

De behandeling met medicijnen op basis van individuele kenmerken van een patiënt, zoals erfelijke eigenschappen, biedt veel kansen om therapieën per patiënt effectiever te maken maar staat ook nog voor veel uitdagingen. Zo vormt erfelijke informatie van een persoon bijvoorbeeld maar een deel van de puzzel om een ziekte effectief te behandelen met medicijnen. Ook andere factoren kunnen een rol spelen, zoals leeftijd, geslacht, eetgewoonten, aanwezigheid van andere ziekten en het gebruik van meerdere medicijnen tegelijk. Dit blijkt uit onderzoek van het RIVM, uitgevoerd in opdracht van het ministerie van VWS, naar de kansen en uitdagingen van *personalized medicine*.

Personalized medicine (PM), de behandeling van de patiënt op basis van zijn unieke kenmerken, is een relatief nieuw begrip in de medische wereld. PM is sterk in opkomst nu het steeds duidelijker wordt welke invloed individuele eigenschappen kunnen hebben op het ontstaan van ziekten en op de werking van medicijnen. Sommige mensen hebben door hun erfelijke eigenschappen een grotere kans op ernstige bijwerkingen bij gebruik van bepaalde medicijnen. Anderen zijn veel gevoeliger voor een medicijn en hebben daardoor een andere dosis nodig. Ook genetische eigenschappen van tumoren bij kanker kunnen per patiënt verschillen en dat biedt mogelijkheden om beter op het individu afgestemde behandelingen aan te bieden.

Een van de uitdagingen is om alle beschikbare gegevens en eigenschappen van patiënten optimaal voor onderzoek te benutten. Dit geldt ook voor de vertaling van onderzoeksresultaten naar de behandeling in de praktijk. Daarnaast zal de opleiding van artsen en apothekers afgestemd moeten worden op de ontwikkelingen rondom PM. Ook moet goed worden nagedacht over privacy en beheer van patiëntgegevens en of de wijze waarop de zorg nu in Nederland is geregeld wel geschikt is voor PM.

Kernwoorden: geneesmiddelen, personalized medicine, erfelijke eigenschappen

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Samenvatting

Toepassing van 'personalized medicine'
Context
Personalized medicine (PM) is een relatief nieuw 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. PM is een term die voor verschillende invalshoeken wordt gebruikt. In de volle breedte betreft PM een integrale benadering waarbij genetische kenmerken, leefstijlfactoren, sociale factoren en omgevingsfactoren van een individu worden gebruikt voor preventie, diagnostiek en therapie. Een smallere invalshoek betreft farmacotherapie op basis van genetische of andere kenmerken van de patiënt. Vooral de smallere invalshoek wordt momenteel in de praktijk toegepast.

Sinds de doorbraak van het Human Genome Project in 2001 bestaan er hoge verwachtingen van het gebruik van genetische kenmerken van personen voor de gezondheidszorg. Het wordt echter steeds duidelijker dat voor begrip van complexe aandoeningen en effectieve toepassing van de kennis van genetische kenmerken, meer gegevens van personen nodig zijn om de invloed van genen op gezondheid te kunnen voorspellen. Er is in de afgelopen jaren een toename in het aantal biobanken van patiëntenweefsels, het gebruik van elektronische patiëntendossiers, de hoeveelheid data die zijn verkregen met beeldvormende technieken en elektronische beschikbaarheid van laboratoriumuitslagen. Samen met de technologische vooruitgang in de opslag van data en de rekenkracht van computers, creëert het integreren van al deze vormen van klinische gegevens enorme kansen voor betere klinische besluitvorming per individu, zorg op maat, en daarmee uiteindelijk voor effectievere zorg.

Momenteel wordt PM vooral toegepast bij de farmacotherapeutische behandeling van kanker, maar ook bij andere specialismen is PM in opkomst (zoals de psychiatrie). Ook wordt steeds duidelijker dat PM voor specifieke groepen potentieel tot betere farmacotherapeutische keuzes kan leiden. Vrouwen kunnen bijvoorbeeld anders op geneesmiddelen reageren dan mannen; uitbreiding van kennis op dit vlak kan leiden tot geslachtsgerelateerde farmacotherapeutische keuzes. De verwachting is dat de toepassing van PM niet alleen in frequentie, maar ook in de breedte verder zal toenemen. Dat kan beleidsconsequenties hebben voor het ministerie van VWS. Een overzicht met de stand van zaken en de verwachtingen ten aanzien van toekomstige ontwikkelingen kan inzichtelijk maken wat de belangrijkste beleidsthema´s zijn en richting geven aan onderwerpen die met voorrang aandacht vergen van VWS.

Doelstelling
Met dit rapport is beoogd een overzicht te schetsen van de huidige praktijk van PM, de ontwikkelingen die zich voordoen, en vooral ook de uitdagingen voor de komende 5 tot 10 jaar, met het oog op het benutten van kansen.

Dit rapport beperkt zich tot *personalized genomics*, omdat op dat terrein de meeste farmacotherapeutische toepassingen worden toegepast. Binnen *personalized genomics* onderscheiden we twee categorieën van farmacotherapie, te weten gebruik van geneesmiddelen op basis van 'gene-drug interactions' en gebruik van geneesmiddelen gericht op 'gene-based drug targeting' (samen genaamd *pharmacogenomics* of farmacogenetica; PGx). Bij 'gene-drug interactions' gaat het om de invloed van genetische kenmerken op de werking en/of bijwerkingen van het geneesmiddel, terwijl bij 'gene-based drug targeting' het geneesmiddel aangrijpt op genen/genetische kenmerken. Beide categorieën hebben optimalisatie van de keuze van de farmacotherapeutische behandeling als focus, ofwel gericht op het individu (*precision medicine* genoemd), ofwel op subgroepen van de populatie (*stratified medicine* genoemd). Met dit kader richten we ons op de meest actuele ontwikkelingen en vraagstukken binnen PM.

Methoden
Allereerst is er een **overzicht** gemaakt van de **geneesmiddelen** waarvan bekend is dat genetische kenmerken van invloed (kunnen) zijn op de werking en/of bijwerkingen of waarvan bekend is dat deze aangrijpen op een genetisch kenmerk. Dit is gedaan door raadpleging van diverse websites en databases met informatie over geneesmiddelen die tot de markt zijn toegelaten. Op basis van de samenvatting van de productkenmerken van de geregistreerde geneesmiddelen met PGx-informatie zijn er gegevens verzameld over de farmacotherapeutische gebieden en indicaties, de (te meten) biomarkers en het genetische kenmerk dat hieraan ten grondslag ligt, het klinisch effect gerelateerd aan de biomarker, en in welke setting (eerstelijns- of tweedelijnszorg) het geneesmiddel wordt gebruikt. Daarnaast is een **literatuuronderzoek** uitgevoerd naar de ontwikkelingen die zich momenteel voordoen. Op basis van overzichtsartikelen gepubliceerd in de periode 2008-2015 is geïnventariseerd binnen welke ziektegebieden PGx in ontwikkeling is en wat de stand van zaken daarin is. Het literatuuronderzoek is gecomplementeerd met **interviews** met negen wetenschappelijke experts uit verschillende vakgebieden. Aan hen is gevraagd aan te geven wat de huidige toepassingen behelzen en wat de toekomstige verwachtingen en kansen zijn, inclusief belemmerende factoren. Hieruit hebben we de belangrijkste kansen en uitdagingen voor PGx gedestilleerd en **aanbevelingen** voor beleid beschreven.

Toepassingen van PGx
Gene-drug interactions
Het aantal geneesmiddelen dat geregistreerd is met genetische informatie die van invloed kan zijn op de werking en/of bijwerkingen van het geneesmiddel, wordt per therapeutisch gebied weergegeven in Figuur a. Het totale aantal geneesmiddelen binnen deze categorie is 42. Voor 24 van deze geneesmiddelen geldt dat de afbraak in het lichaam wordt beïnvloed door variaties in genen voor leverenzymen. In de samenvatting

voor de productkenmerken zijn voor deze geneesmiddelen echter over het algemeen geen aanwijzingen opgenomen over bijvoorbeeld aanpassing van de dosering. Wél heeft de KNMP Werkgroep Farmacogenetica sinds 2014 een richtlijn voor het voorschrijven van tachtig medicijnen waarvan bekend is wat de invloed is van genetische variatie. In de richtlijn staan therapeutische doseringsadviezen beschreven die kunnen worden opgevolgd als het genetische profiel van de patiënt bekend is. Desondanks is in de klinische praktijk de toepassing van PGx voor deze geneesmiddelen nog beperkt.

Bij vier andere geneesmiddelen zijn waarschuwingen opgenomen in de samenvatting voor de productkenmerken vanwege overgevoeligheidsreacties ten gevolge van genetische variatie in bepaalde eiwitten. PGx wordt voor deze geneesmiddelen wél in de praktijk toegepast en is soms zelfs noodzakelijk om zeer ernstige bijwerkingen te voorkomen. Een voorbeeld daarvan is Abacavir dat wordt toegepast bij patiënten met hiv/aids.
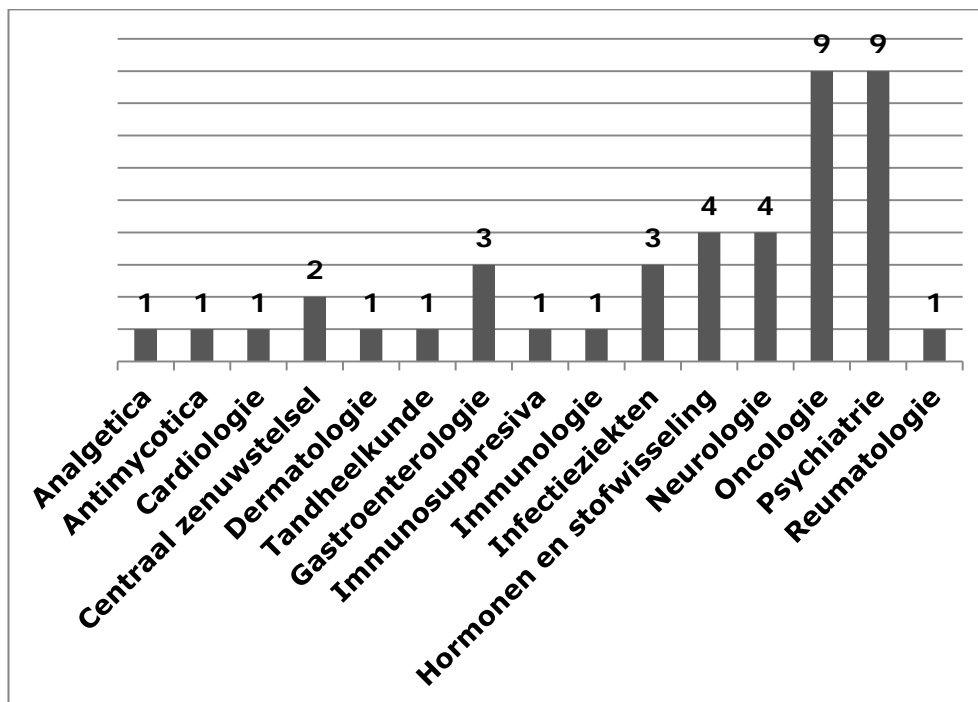
Figuur a Aantal geregistreerde geneesmiddelen, per farmacotherapeutische groep, met PGx informatie in de samenvatting van de productkenmerken; geneesmiddelen die beïnvloed worden door een genetisch kenmerk

Gene-based drug targeting
Het aantal geneesmiddelen dat geregistreerd is met als doel in te grijpen op een genetisch kenmerk, wordt per therapeutisch gebied weergegeven in Figuur b. Het totale aantal geneesmiddelen binnen deze categorie is 39. Veruit de grootste groep geneesmiddelen wordt gebruikt in de oncologie en grijpt daarbij aan op genetische kenmerken van de tumor. In de samenvatting van de productkenmerken wordt over het algemeen duidelijk aangegeven in welke patiënten (met specifieke genetische kenmerken van de tumor) het geneesmiddel kan worden

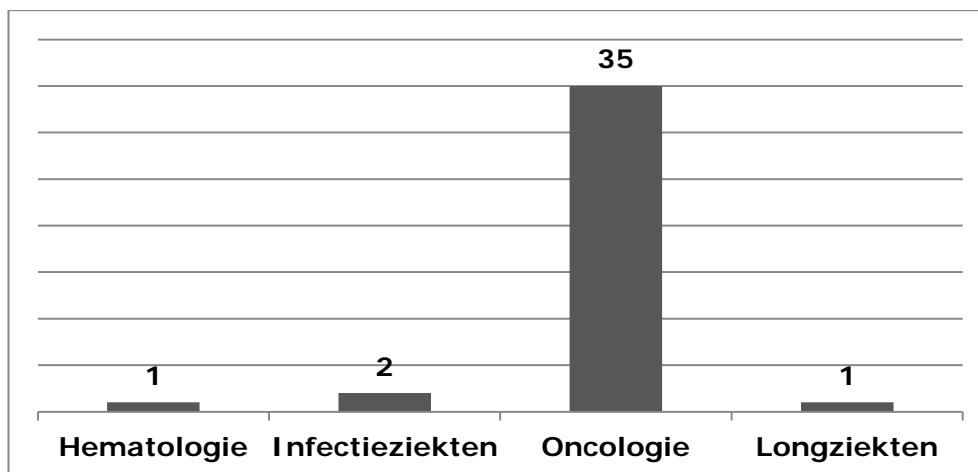toegepast. Het gebruik van PGx in deze categorie producten is gemeengoed.

Figuur b Aantal geregistreerde geneesmiddelen, per farmacotherapeutische groep, met PGx-informatie in de samenvatting van de productkenmerken; geneesmiddelen die aangrijpen op een genetisch kenmerk

Ontwikkelingen in PGx
Gene-drug interactions
Dat er genetische variatie bestaat in genen die een rol spelen bij de afbraak van geneesmiddelen in het lichaam en dat dit van invloed kan zijn op de gevoeligheid voor een geneesmiddel, is algemeen bekend. Een bepaalde genetische variatie kan ervoor zorgen dat iemand een geneesmiddel sneller of juist langzamer afbreekt, wat de effectiviteit en/of gevoeligheid voor bijwerkingen sterk kan beïnvloeden. Samen met andere factoren, zoals nierfunctie, wordt in de literatuur gesuggereerd dat de variatie in respons op een geneesmiddel kan variëren in orde van grootte van 25-60%. Het is echter voor het grootste deel van de populatie niet bekend welke genetische varianten men heeft, omdat dit niet is getest. Het is nog geen gangbare praktijk om het genetische profiel van een patiënt te bepalen zonder dat daar directe aanleiding voor is. Door problemen in de bewijsvoering van het klinische nut is de toepassing van PGx momenteel slechts voor een klein aantal geneesmiddelen verplicht, bijvoorbeeld het screenen voor HLA-varianten voor de behandeling van hiv/aids-patiënten met Abacavir. Wél is van circa 15% van de door de FDA en de EMA goedgekeurde geneesmiddelen PGx-informatie opgenomen in de bijsluiter.

Naar verwachting zal het gebruik van PGx langzamerhand toenemen in ziekenhuizen en dan verder uitbreiden naar de eerstelijnszorg. Hoe de adoptie verloopt en in hoeverre de toepassing daadwerkelijk leidt tot klinische meerwaarde is afhankelijk van de mogelijkheden tot het wegnemen van een reeks belemmeringen die verderop staat beschreven. De invoering van deze categorie PGx zal met name klinisch relevant zijn voor patiënten waarbij snelle en effectieve behandeling nodig is om verergering van de aandoening te voorkomen en er geen tijd is om de optimale dosis via *trial-en-error* te bepalen, zoals bijvoorbeeld bij ernstige pijn. Ook daar waar medicatie tot ernstige of zelfs fatale bijwerkingen kan leiden zal deze vorm van PGx zeer relevant

zijn, zoals bij het gebruik van Abacavir bij hiv/aids. Ten slotte kan deze categorie behulpzaam zijn in gevallen waarbij de respons op farmacotherapie moeilijk of pas zeer laat na aanvang van de behandeling te voorspellen is, zoals bijvoorbeeld bij reuma.

Onderzoek in dit veld richt zich op invoering van PGx in de eerstelijnszorg, op veelvoorkomende ziekten zoals COPD/astma, diabetes, hart- en vaatziekten, en op ziekten waarbij vroeg ingrijpen van groot belang is voor optimaal herstel, zoals bij infectieziekten.

Gene-based drug targeting
Gene-based drug targeting betreft het gebruik van geneesmiddelen die speciaal gericht zijn op genetische defecten. Hiervoor is kennis van de genetische achtergrond van een ziekte nodig. Deze categorie heeft daarom alleen betrekking op ziekten die een (bekende) genetische oorzaak hebben, zoals kanker en (andere) erfelijke aandoeningen. Er zijn vele ontwikkelingen gaande op internationaal niveau. Een groot aantal internationale samenwerkingsverbanden, zowel binnen de Europese Unie (EU) als tussen de EU en de Verenigde Staten (VS), is opgestart om genetische profielen van tumoren van kankerpatiënten te verzamelen. Dit moet inzicht geven in de genetische achtergrond van kanker en daaropvolgend de ontwikkeling van betere klinische beslismodellen van op de patiënt afgestemde behandelingen. Een voorbeeld hiervan is het GENIE-project, gecoördineerd door de VS, waarin ook Nederland deelneemt. Los daarvan heeft een aantal landen zich gecommitteerd om onderzoek naar PM te steunen door van grote aantallen patiënten het erfelijk materiaal in kaart te brengen. In de VS heeft president Obama in 2015 het *Precision Medicine Initiative* opgestart waarin genetische profielen van 1 miljoen Amerikanen zullen worden verzameld. In het Verenigd Koninkrijk verzamelt het *100,000 Genomes Project* sinds 2013 genetische profielen en combineert deze met data uit elektronische patiëntendossiers. In Nederland verzamelt het Center for Personalized Cancer Treatment (CPCT) genoomprofielen van kankerpatiënten met uitzaaiingen. Hierbij wordt niet het hele genoom bepaald, maar alleen mutaties in tweeduizend kanker-gerelateerde genen.

Hoewel deze ontwikkelingen veel kennis zullen opleveren is inmiddels ook duidelijk dat genetische informatie slechts een deel van de puzzel is om een ziekte aan te kunnen pakken. Onderzoek naar andere –omics technologieën, zoals *transcriptomics*, *epigenomics*, *proteomics*, *metabolomics* en *microbiomics*, lopen parallel aan *genomics* en zullen bijdragen aan betere typering van ziekten zoals kanker. Daarnaast is de nieuwe organoïdentechnologie een veelbelovende nieuwe speler in het veld met de potentie om een grote bijdrage te leveren aan PM. Met behulp van deze technologie kan de werkzaamheid van geneesmiddelen worden getest op levend weefsel van een individuele patiënt, dat tot een mini-orgaan is opgekweekt in het laboratorium. Er is echter nog veel onderzoek nodig voordat deze technologie routinematig in de kliniek kan worden toegepast.

Uitdagingen
Uit literatuuronderzoek en interviews met experts is een aantal
belemmeringen naar boven gekomen voor de toepassing van PGx.
Sommige hiervan betreft algemene/internationale aspecten, terwijl
andere zich meer op nationaal niveau bevinden.

Implementatie in de klinische praktijk
Of PGx in de klinische praktijk toegepast zou moeten worden, hangt
nauw samen met de analytische validiteit, klinische validiteit, het
klinisch nut van de genetische/biomarker test en van ethische,
juridische en sociale aspecten. De analytische validiteit betreft de
juistheid en precisie waarmee een genetische variant kan worden
gedetecteerd. Die wordt momenteel nog beperkt door het ontbreken van
(internationale) standaarden met betrekking tot (onder andere) het type
te gebruiken test, de wijze van monstername, de data-analyse, de data-
interpretatie en het ontbreken van cross-validatie tussen laboratoria.

De klinische validiteit betreft de juistheid en precisie waarmee een
genetische test in staat is om patiënten te onderscheiden die wel of
geen baat hebben bij gebruik van een specifiek geneesmiddel. Deze
validiteit is lang niet altijd goed aan te tonen, onder meer omdat er vaak
meerdere genen invloed hebben op het geneesmiddeleffect. Ook spelen
vele andere factoren een rol (bijvoorbeeld nierfunctie, leeftijd, geslacht,
ziektestadium, multimorbiditeit, polyfarmacie, therapietrouw, voeding,
roken). Ook de heterogeniteit, wat betreft genetische eigenschappen
van tumorcellen, binnen een tumor en tussen de primaire tumor en de
uitzaaiingen is een beperkende factor in de effectiviteit van de therapie.
Daarnaast is het lastig om de klinische validiteit aan te tonen wanneer
er sprake is van kleine patiëntpopulaties en er geen gerandomiseerd
gecontroleerd klinisch onderzoek met voldoende onderscheidend
vermogen mogelijk is.

Het klinisch nut betreft de mate waarin een test nuttig is om toe te
passen in de praktijk, met andere woorden in hoeverre deze tot
verbeterde klinische uitkomsten leidt. Dit nut hangt onder meer af van
de ernst van de aandoening, de beschikbaarheid van alternatieven, de
mate waarin een bepaalde genetische variant voorkomt en de kosten-
effectiviteit. Er is momenteel nog geen (internationale) consensus welke
mate van bewijs nodig is om het klinisch nut aannemelijk te maken.
Voor de ethische, juridische en sociale aspecten: zie verderop.

Adoptie in de klinische praktijk
In welke mate PGx door de beroepsbeoefenaren in de klinische praktijk
wordt opgenomen als onderdeel van de zorg die zij leveren, hangt onder
meer af van de aanwezigheid van beroepsrichtlijnen, (na)scholing,
bekendheid bij patiënten en het klinische nut van een test.

Kosten en vergoeding
De kosten voor genotypering zijn in de afgelopen tien jaar dramatisch
gedaald. Desalniettemin is het lastig om de kosteneffectiviteit van
genetische tests te bepalen, omdat die mede afhangt van het volume
aan monsters dat door een laboratorium wordt bepaald en of er een

DNA-paspoort[1] beschikbaar is op het moment van therapiekeuze (of dat er een test moet worden gedaan voor het voorschrijven van een specifiek geneesmiddel). Een test op voorhand, zonder specifieke noodzaak op dat moment, wordt niet (altijd) vergoed. Bovendien is er discussie in het veld of toepassing van PM in de praktijk altijd kostenbesparend is (vooral als de kosten voor de test relatief hoog zijn).

Data-infrastructuur
Data zijn cruciaal om PGx, en PM in het algemeen, naar een hoger plan te krijgen. Er spelen echter veel zaken rondom data-infrastructuur die nadere aandacht vergen vanuit het veld en de overheid: de opkomst van commerciële testfaciliteiten, opslag van ruwe data, opslag van bewerkte/geïnterpreteerde data, beheer van databases, het delen van data, eigendomsrecht, privacy, standaardisering van opgeslagen gegevens, koppeling van databases en het vervagen van grenzen tussen onderzoek en diagnostiek. Dit laatste heeft bijvoorbeeld gevolgen voor de financiering van beide domeinen. Ook het inzichtelijk maken van data voor beroepsbeoefenaren en patiënten, zodat zij gezamenlijk klinische besluiten kunnen nemen, is een uitdaging.

Markttoelating
Het markttoelatingsproces voor geneesmiddelen kent vooral uitdagingen op het terrein van klinische bewijsvoering in geval van PGx; het is soms lastig om een goede baten/risico-afweging te maken, omdat er vaak sprake is van kleine patiëntenpopulaties waarvoor een 'randomized controlled trial' niet altijd mogelijk is. Daarnaast is er een toenemende maatschappelijke druk op snelle toegankelijkheid van innovatieve geneesmiddelen. Voor discussie over de houdbaarheid van het markttoelatingssysteem en de aansluiting van geneesmiddelenwetgeving op wetgeving voor medische hulpmiddelen wordt verwezen naar twee eerder gepubliceerde RIVM-rapporten: *Minds open: Sustainability of the European regulatory system for medicinal products* en *Personalized medicine products: evaluation of the regulatory framework*.

Onderzoek en ontwikkeling
De ontwikkeling van nieuwe geneesmiddelen op basis van PGx neemt toe, maar concentreert zich met name op de oncologie. Er wordt nauwelijks geïnvesteerd in het vergroten van de PGx-kennis voor bestaande geneesmiddelen die uit patent zijn. De financiering van dergelijk onderzoek is een uitdaging, waarbij met name klinische validiteit en klinisch nut aandacht vergen.

Ethische, juridische en sociale aspecten
Er zijn diverse ethische, juridische en sociale aspecten die spelen rondom PM. Deze zijn echter niet specifiek voor PGx en zijn ook, of juist, aan de orde bij screening en preventie op basis van genetica. Enkele voorbeelden van uitdagingen zijn privacy, het ontbreken (of juist beschikbaar komen) van handelingsperspectieven, het recht op 'niet weten', het delen van data en de vervagende grenzen tussen basaal wetenschappelijk onderzoek, klinische studies, diagnostiek en screening.

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[1] Een DNA-paspoort bevat de gehele genetische code van een persoon of een selectie van genen waarvan bekend is dat deze bepalen of iemand afwijkend op een medicijn of behandeling reageert.

Conclusie
Er zijn diverse ontwikkelingen en uitdagingen waar het veld, inclusief overheid/beleid, voor staat op het terrein van PGx. De uitdagingen zijn verbonden aan het principe van PM en maken aandacht noodzakelijk voor de huidige wijze waarop de gezondheidszorg en het markttoelatingssysteem zijn ingericht. Denk hierbij bijvoorbeeld aan de huidige wijze waarop klinische studies worden vereist en uitgevoerd voor markttoelating, kosteneffectiviteitsvraagstukken en zaken die spelen rondom data-infrastructuur. Beleidsmakers zullen deze fundamentele vraagstukken moeten adresseren in hun beleid teneinde de voordelen te benutten die de toepassing van PM kan hebben.

Aanbevelingen voor beleid
Gegeven de huidige praktijk van PGx, de ontwikkelingen die gaande zijn en de uitdagingen en belemmeringen waar het veld voor staat, biedt dit rapport enkele aanbevelingen voor nationaal beleid om hierop te anticiperen voor de toekomst.

Onderzoeksfinanciering
1. Prioriteer de inzet van onderzoeksgelden ten behoeve van *Personalized Medicine* op basis van het potentiële klinische nut van de toepassing van *Personalized Medicine*. Focus daarbij op (bestaande) geneesmiddelen en de ontwikkeling van geschikte diagnostische technieken om deze geneesmiddelen effectief in te kunnen zetten. Geef daarbij prioriteit aan:
- ziekten waarbij de effectiviteit van geneesmiddelen zeer variabel is, waardoor er tussen personen (onacceptabel) veel variabiliteit in ziektelast is;
- geneesmiddelen met ernstige bijwerkingen die mogelijk voorkomen kunnen worden door het toepassen van *Personalized Medicine*;
- geneesmiddelen waarvoor de tijd benodigd voor evaluatie van het klinisch effect relatief lang is, terwijl de ziekte een progressief karakter heeft;
- geneesmiddelgroepen met een grote impact op het gezondheidszorgbudget (door hoge prijs en/of groot volume).

Stel prioritaire gebieden (ziekten/geneesmiddelen/diagnostische tests) vast in samenspraak met patiëntenverenigingen, beroepsgroepen in de zorg en andere experts. Spreek daarbij financieel belanghebbende partijen aan op hun (maatschappelijke) rol als co-financier.

2. Start een traject om (de financiering van) onderzoek en de klinische praktijk meer met elkaar te verweven, zodat gegevens uit de klinische praktijk eenvoudiger kunnen worden ingezet ten behoeve van onderzoek en onderzoeksresultaten sneller kunnen worden gebruikt in de klinische praktijk. Breng voorafgaand aan dit traject in kaart welke belemmeringen en kansen er in deze verweving liggen.

Data-infrastructuur
3. Stel duidelijke (wettelijke) kaders rondom patiëntengegevens die in het kader van *Personalized Medicines* worden gegenereerd en opgeslagen. Denk daarbij aan het (laten) opstellen van richtlijnen voor opslag, eigendomsrecht en mogelijkheden tot databasekoppelingen. Zet in op het opheffen en/of voorkomen van versnippering van initiatieven op het gebied van dataverzameling en ga na wat nodig is voor goed beheer van data ten behoeve van onderzoek, implementatie in de klinische praktijk en financiering/vergoeding.

Regulatoire systemen
4. Onderzoek welke gevolgen veranderingen in de hoeveelheid en de aard van klinische data hebben voor de systemen van markttoelating, vergoeding en financiering van zorg. Ga daarbij na of er belemmeringen zijn die uiteindelijk de toepassing van *Personalized Medicine* kunnen verhinderen of vertragen.

5. Zet via het European Medicines Agency en de Heads of Medicines Agencies in op uitbreiding van de Summary of Product Characteristics (SmPCs) van bestaande geneesmiddelen met informatie over de handelingsperspectieven in geval van genetische variaties, voor zover deze bekend zijn en onderbouwd op basis van wetenschappelijk bewijs. Ga daarbij tevens na hoe de SmPCs steeds up-to-date kunnen blijven, aangezien de kennis op dit vlak zich snel vermeerdert en verandert.

Implementatie in de klinische praktijk
6. Beleg bij het Zorginstituut Nederland de regie om in samenspraak met het College ter Beoordeling van Geneesmiddelen, andere belanghebbenden en experts te komen tot aanbevelingen over het type data dat nodig is om het klinisch nut en de kosteneffectiviteit van de toepassing van farmacogenetica in te kunnen schatten. Neem daarbij Europese en internationale ontwikkelingen mee in de aanbevelingen.

7. Aanbevolen wordt om het bewustzijn en begrip bij het publiek ten aanzien van de mogelijkheden en beperkingen van genetische testen te vergroten. Ook kunnen patiënten beter worden toegerust om geïnformeerde beslissingen te nemen over het al dan niet laten testen van genetische eigenschappen ten behoeve van Personalized Medicine.

8. Stimuleer het opstellen van standaarden voor het verzamelen genetische informatie en andere gegevens die voor *Personalized Medicines* van belang kunnen zijn. Deze standaardisatie zou ten minste moeten meenemen:
 - klinische monstername;
 - analytische tests;
 - data-analyse;
 - data-interpretatie;
 - data-opslag;
 - data-uitwisseling;
 - data-visualisatie voor gebruik door behandelaren en patiënten.

9. Stimuleer de opname van *Personalized Medicines* in beroepsrichtlijnen van behandelaren, zodat toepassing in de praktijk wordt bevorderd. Daarbij dient het klinisch nut meegewogen te worden.

Educatie
10. Behandelaren, apothekers en verpleegkundigen moeten
(uitgebreider) opgeleid worden om farmacogenetische data (en
andere -omics-data) te genereren, te interpreteren en om te zetten in
behandelingsbeslissingen. Ook is opleiding gewenst om de voor- en
nadelen van genetische tests te bediscussiëren met patiënten.

11. Zet in op het opleiden van bio-informatici om interpretatie van grote
datasets mogelijk te maken.

Summary

Context
Ever since the Human Genome Project in 2001, there have been high expectations of genomics and other –omics technologies (such as transcriptomics, proteomics, metabolomics and epigenetics) in health care. Parallel to this, biobanks with growing collections of tissue samples have evolved and electronic medical records (EMRs), including imaging data, are being implemented in health care systems globally that integrate all types of patient data in one system. Linking all these new domains of clinical data together creates a huge potential for better clinical decision-making and medicine that is more effective.

Using genomics in clinical practice has been common for several decennia now. Because of the technological advancements in (bio)informatics and the rise of biobanks and genetic banks, a huge area of new possibilities has come about that could change the health care system tremendously. Next to that, a diversity of questions have arisen concerning the use of genetics and other individualized -omics technologies, such as ethical and privacy issues. To facilitate this transition, to accelerate the translation of (bio)medical research into better clinical care and to ensure a safeguarded and equal society, policy is needed.

Aim
In this report we have aimed to provide a helicopter view of the current state of practice in personalized medicine (PM), to describe future perspectives and to determine the opportunities and challenges that lie ahead in the coming 5 to 10 years. For the sake of scoping, we have focused mainly on genomics, and within genomics mainly on gene-drug interactions and gene-based drug targeting (together called 'pharmacogenomics/pharmacogenetics', PGx in short). Both categories focus on treatment optimization, some to the extent of the individual patient (unique treatment, precision medicine) and others to stratified (sub)groups of the human population (stratification). In this way, we have aimed to focus on the most recent developments and issues in PM.

Methods
To begin, we created an overview of current applications in the Netherlands. We then searched for relevant scientific literature. In tandem with this, we interviewed nine experts in different (bio)medical fields to complement the literature search on current developments and future perspectives, as well as on the challenges that lie ahead.

Results
In optimizing drug response based on gene-drug interactions, research has, for various medicinal products, led to usage warnings, monitoring requirements or contra-indications in the SmPC owing to potentially severe side effects. Yet, for the majority of products with PGx information in the SmPC, no action is mentioned or considered necessary when tests are performed. This lack of information has been partly overcome through guidance provided to health care professionals. Yet clinical utility is still debated and may be one of the factors

hampering reimbursement and adoption in clinical practice. The research in this area of optimizing drug response focuses on the implementation of PGx in first-line health care, on specific disease areas with large numbers of patients, such as COPD/asthma and diabetes, and on areas in which early effective treatment will make a difference, such as inflammatory diseases.

In the last few years, substantial progress has been made in the development and market approval of new medicinal products aimed at the gene-based targeting of a disease, especially in cancer treatment. Yet opinions differ as to whether this progress currently contributes, to any large extent, to overall cancer survival. A consistent genetic defect allows for the development of a drug that specifically targets this defect. But most cancers / diseases are quite complex with regard to genomics. Research into the gene-based targeting of a disease focuses on oncology, rare diseases and organoid technology. Organoids present an opportunity to bridge the current experimental gap between sequencing efforts in cancer and patient outcome. They have great potential, yet more research is needed to see whether organoid technology truly lives up to expectations.

There are still many challenges for the implementation of PM in health care. This starts with (the funding of) research and development. But amendments to the marketing authorization system and the system for reimbursement may also be necessary due to changes in the amount and nature of clinical (evidence) data that becomes available. Specific attention should furthermore be paid to clinical utility: the determination of whether the use of a genetic test leads to improved health outcomes. It is not yet clear what kind of data is necessary to assess clinical utility. And finally, another element that is important to address is data infrastructure, as well as the ethical, legal and social issues related to this.

Recommendations for Dutch policy
Given the current clinical application, the developments, future directives and challenges, this report concludes by giving some recommendations for Dutch policy in order to anticipate the developments in personalized medicine. Directions are given on the topics of research funding, the regulatory system, implementation in clinical practice, and data infrastructure. In addition to that, general recommendations for the whole field of personalized medicine are briefly described within the topics of standardization, guidelines and education.

1   Introduction

Personalized medicine (PM) is a relatively new medical model for classifying, understanding, treating and preventing disease based on data and information on individual biological and environmental differences. PM stretches from prevention to screening and therapy, and refers to 'P4 medicine': predictive, preventive, personalized and participatory medicine. There is no universally accepted definition of PM (see various terms in Figure 1).
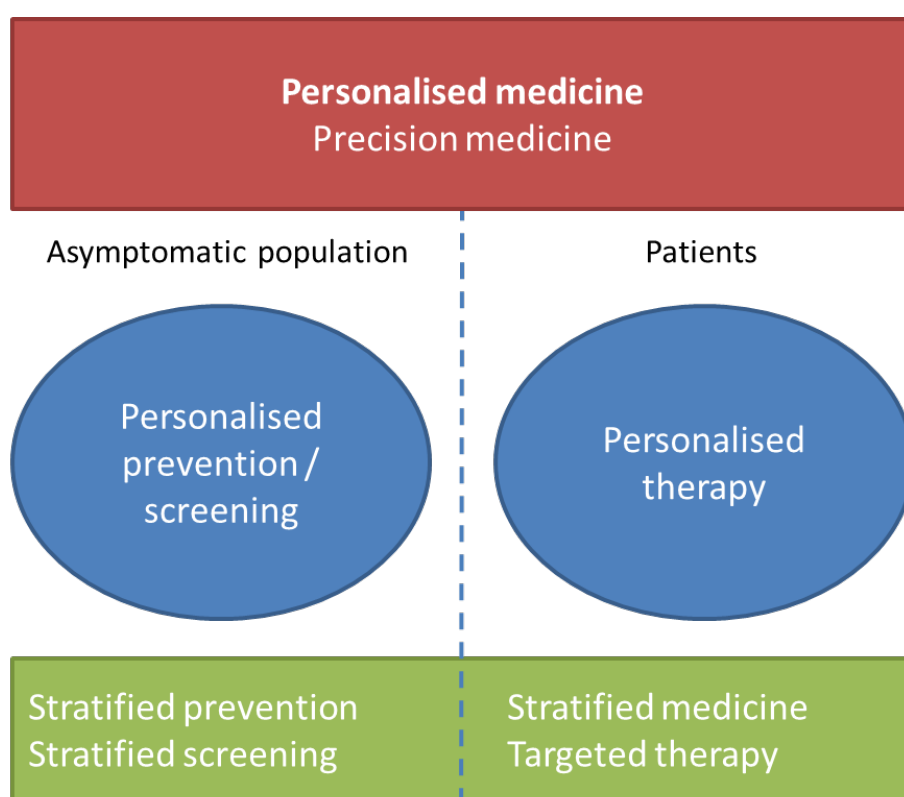
Figure 1. Various terms used for PM

The Horizon 2020 Advisory Group of the European Commission defines PM as "*a medical model using characterization of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention*". This report focuses on therapy with medicinal products and does not address screening and prevention.

For many years, the prescription of medicines has followed a "one-size-fits-all" principle, usually starting with standard doses and adjusting the doses or drugs by a "trial and error" process. Yet human physiology is complex. The data collected on a patient is often incomplete, hindering a fully informed decision about either the diagnosis or the intervention and thus reducing the effectiveness of medicine. Awareness has grown of the fact that genetics is one of the contributors to the complexity of a

patient's response to a medicinal product. With the Human Genome Project, a huge step forward has been taken towards an increase of knowledge. And with data technology advancements, a new era of insight into human physiology has begun.

Genetic variants can be determined using targeted genotyping (i.e. sequencing a single or a pre-determined set of genes) or by using next-generation sequencing (NGS, sequencing larger parts of the DNA), whole exome sequencing (i.e. all known protein-coding genes) or whole genome sequencing. Subsequently, the implications of these variants must be determined for each clinical indication. Finally, to optimize clinical decision-making, our understanding of genetics must be considered in conjunction with other clinical data (Aronson and Rehm 2015). Genetics can be a crucial element to understanding disease. But the significance of genetic make-up for the required treatment differs in medicine. Also, the epigenome, the proteome, the transcriptome and the metabolome can be of crucial importance to proper diagnosis and in treatment (see text box on "Omics technologies"). A whole new dimension altogether is the organoid technology, which is more of an advanced form of phenotypical analysis. Parallel to sequencing, biobanks with growing collections of tissue samples have evolved. And electronic medical records (EMRs), including imaging data, are being implemented in health care systems globally that integrate all types of patient data in one system. Linking all these new domains of clinical data creates a huge potential for better clinical decision-making and more effective health care.

Because of the technological advancements and the need for patient samples in research from which to learn, research disciplines and clinical practice are becoming intertwined in order to build a foundation of knowledge that can better guide individualized patient care (Aronson and Rehm 2015). This transition has a large impact on the health care system, making it a subject of (inter)national policy. In addition to this, a diversity of other questions arise concerning the use of genetics and other individualized -omics technologies, such as ethical and privacy issues. To facilitate this transition, to accelerate the translation of (bio)medical research to better clinical care and to ensure a safeguarded and equal society, policy is needed.

In this report, we focus mainly on genomics, as this field is the most developed of the –omics fields as yet.

-Omics technologies
-Omics technologies share the principle of massive quantification of biological processes as seen from a certain type of building block. The building block can be DNA, RNA, the epigenetic structure, a protein, gastrointestinal bacteria, etc. The goal is the better phenotyping of a biological state, for example a disease.

Epigenetics is a relatively new field that focuses on environmentally driven, inheritable variations in the DNA structure, i.e. the way the string of DNA bases is folded. The structure of DNA is highly dynamic and regulates gene expression.

Transcriptomics investigates the transcriptome, the RNA transcripts produced by the genome, and the regulation of that process. In order to translate genetic information into proteins, DNA needs to be transcribed into RNA. Subsequently, these RNA molecules can be used to produce proteins.

Proteomics assesses the regulation and production of all the proteins in a cell. An alteration in the genome or transcriptome does not necessarily correlate with an alteration in a functional protein; therefore, proteomic profiling may sometimes be more accurate in predicting treatment response. However, genetic information is static, whereas proteomic information is a reflection of a snapshot in time, rendering the information more difficult to interpret.

Metabonomics (or metabolomics) assesses the effect of a systematic change in the metabolic system caused by the intake of something, such as nutrition or a drug. A promising field within this area is the gut microbiome, which appears to have a major influence on metabolic reactions and subsequently the impact on the biological state, disease development and drug reactions.

Genomics studies genes and their functions. It addresses all genes and their interrelationships in order to identify their combined influence on the growth and development of the organism.
(WHO:http://www.who.int/genomics/geneticsVSgenomics/en/).

Source: (Vijverberg 2013)

1.1 Aim of this study

In this report, we aim to provide a helicopter view of the current state of practice in personalized medicine (PM), to describe future perspectives and to determine the opportunities and challenges that lie ahead in the coming 5 to 10 years. In this way, we aim to support policymakers in prioritizing actions in the field of PM.

1.2 Definitions and scope

Focusing on genomics, we have identified three categories that grasp the nature of the different directions in genomics:

1. *Optimizing drug response: gene-drug interactions*
   A person's genetic constitution can be determined in order to address gene-drug interactions. The aim is to optimize drug efficacy and to minimize adverse events from drug treatment ("the right drug, at the right dose, at the right time, given to the right person"). Applications include genetics-based and genomics-based tests that commonly target medicines that are administered to populations with a specific gene variant. Such tests typically aim to stratify patient populations into subgroups on the basis of clinical effectiveness (response) or safety (avoidance of adverse events) (Shabaruddin, Fleeman et al. 2015). In gene-drug interactions, the focus is directed to either metabolism genes or genes related to the immune system:
   a) Metabolism: There are a number of general metabolism genes that show genetic variants in the population. These gene variants can generate differences in the kinetics of drug metabolism (pharmacokinetics). Multiple studies have shown that genetic variation in genes that play a role in the transport and metabolism of certain medicines can result in underdosage or overdosage (Swen and Houwink 2015). The effects of these variants result in four phenotypes; ultra-rapid, extensive, intermediate or poor metabolizers. Research has focused on the discovery of metabolism gene variants and the medicines for which accurate dosing is sensitive to either severe side effects or treatment survival (effectiveness and timespan), for example the CYP2D6 gene variants.
   b) Immune system: Variants in HLA-genes relate to hypersensitivity reactions to various medicines, such as Flucloxacilline, Carbamazepine and Abacavir. The role of HLA-genes in hypersensitivity reactions was discovered when Abacavir appeared to cause severe side effects in 5% of the HIV-population treated. The molecular mechanisms are still unknown.

2. *Gene-based drug targeting*
   Another area of individualization is the development of molecular-mechanism-specific treatment, also called gene-based drug targeting. Most research efforts are seen in the field of oncology (somatic variations) and increasing attention is being paid to genetically based diseases (germline variations), such as Cystic Fibrosis. Apart from this, many research efforts are undertaken in disease areas in which there is a significant genetic association with the disease, as is the case with the VKORC1 gene in thrombosis patients. Applications include;
   a) Genetics-based and genomics-based companion diagnostic tests that target treatment in terms of clinical response,
   b) Mechanism-based targeted agents, and
   c) Advanced therapeutic medicinal products (ATMP's): medicinal products based on individual genes (gene therapy, gene editing), cells (cell therapy) or tissues (tissue engineering).

3. *Prediction and diagnosis*
   Lastly, individualization efforts are undertaken to:
   a) diagnose more accurately (detailed disease characterization / diagnosis of hereditary diseases that are not well-understood yet.),

b) predict disease vulnerability (i.e. risk of disease), and
c) predict disease prognosis.
These efforts provide greater insight into a patient's constitution, contributing to a better diagnosis. The results can imply preventive treatment, the start of an otherwise unwarranted intervention or, in the case of fertility clinics, selection of viable embryos.

Except for the prediction of disease and disease prognosis, all categories focus on treatment optimization, some to the extent of the individual patient (unique treatment, precision medicine) and others to stratified groups/subgroups of the human population (stratification).
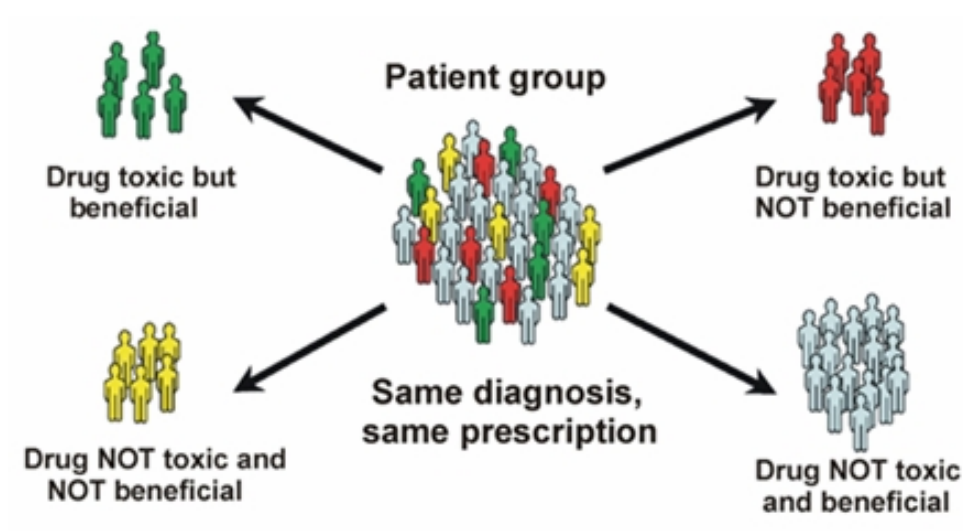
Figure 2. Concept of stratified medicine. Biomarkers will enable us to target treatment specifically to subpopulations of patients that are more likely to benefit from a particular treatment. Source: (Vijverberg 2013)

Genetic research in the first two categories is called pharmacogenetics/ pharmacogenomics (PGx). In this report, both are referred to as PGx. For the sake of scoping, we focus on PGx in this report, in which we follow Swen et al's definition of PGx as "the individualization of drug therapy through medication selection or dose adjustment based upon direct (e.g. genotyping) or indirect (e.g. phenotyping) assessment of a person's genetic constitution for drug response." This definition includes tests that operate at protein, metabolite or other biomarker levels whenever these factors are affected by genetic variation (i.e. single nucleotide polymorphisms, insertions, deletions, microsatellites, variance in copy number, etc.). Both germline (i.e. heritable mutations) and somatic mutations (i.e. non-heritable mutations in, for example, tutor specimens) are considered. Immune-histochemical tests, such as the one for HER2/neu, are also considered a PGx test." (Swen, Huizinga et al. 2007). In this way, we aim to focus on the most recent developments and issues in PM.

2 Methodology

2.1 Website and database searches

The first step was to create an overview of current applications in the Netherlands. For this, we used the data in Annex 4 of our previous report (RIVM-report 360211001/2013 '*Personalized medicinal products: an evaluation of the regulatory framework*') and updated it (Weda 2014). This update was performed by checking the website of the U.S. Food and Drug Administration's Table of Pharmacogenomic Biomarkers in Drug Labelling[2]. This table contained about 120 active substances. Some substances were approved in the U.S., but not in the European Union; these substances were excluded. The table was supplemented with information on products evaluated by the Dutch Pharmacogenetics Working Group (KNMP Werkgroep Farmacogenetica) and information available on the websites of the National Cancer Institute at the U.S. National Institute of Health (www.cancer.gov) and the Pharmacogenomics Knowledge Base hosted by Stanford University, U.S. (www.pharmgkb.org). For each active substance, the latest version of the Summary of Product Characteristics (SmPC) present at the websites of the European Medicines Agency (EMA) or the Dutch Medicines Evaluation Board (CBG-MEB) was checked. The following information was collected:
- active substance;
- pharmacotherapeutic area;
- disease;
- biomarker;
- clinical effect related to the biomarker;
- type of action prescribed in SmPC;
- year of authorization;
- 1st or 2nd line health care.

2.2 Literature search

The second step was to identify current developments and future perspectives. For this purpose, we searched scientific literature in Medline. The search was limited to the 2008-2015 period and to review articles. Search terms were 'personalized medicine' combined with 'developments' or 'future'. The final search string was developed by the RIVM information specialist. For the various disease areas, the latest review was included. In order to produce an overview of challenges from research and development for the use of PM in clinical practice, a search was made in Medline, with search terms 'personalized medicine' combined with 'challenges' or 'recommendations'. This search was complemented with a Google search for (Dutch) reports published in 2011-2015.

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[2] http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

2.3 Interviews

The third step was meant to complement the literature search on current developments and future perspectives, as well as on challenges, by interviewing nine experts that covered the different (bio)medical fields in which personalized medicine is of current interest. For an overview of the experts, see Annex A. The topic list is depicted in Annex B. Each interview was audio-recorded and summarized in an interview report based on these recordings. The outcome of the interviews was combined with the outcome of the literature study (i.e. all information was summarized per topic).

As mentioned before, we split PM into three categories, two of which will be described in this report: a) optimizing drug response on the basis of gene-drug interactions, and b) gene-based drug targeting. Each of these two areas has a different complexity, different clinical potential, different hurdles and different future perspectives. We discussed these for each area, although this sometimes led to overlap. Subsequently, we generated an overall view of challenges that were specific to the Netherlands and described directions that can be used as input for policymaking.

3 Optimizing drug response: gene-drug interactions

3.1 The potential of optimizing drug response

The concept that variation in drug response is related to genetic variation is widely recognized. Insight into the genetic make-up of a patient could lead to treatment optimization and the prevention of adverse events, such as toxicity and hypersensitivity reactions. Together with other well-known factors, such as kidney function, liver function and the interaction between medicinal products, it is suggested that this causes variation in the response to treatment between patients in the magnitude of 25-60% (Swen and Houwink 2015). Moreover, there is increasing notion that there are differences between the response of medicines in women and men, triggering the Dutch Ministry of Public Health, Welfare and Sport to financially support research in this area (ZonMw 2016).

The prevalence of typical pharmacokinetic and pharmacodynamic genes in the Caucasian population has been estimated: about 95% of the Caucasian (including the Dutch) population has at least one pharmacogenetic variant for which advice on drug use is available (Bank, Swen et al. 2014).

PGx will be of great clinical relevance to patients with a negative prognosis when rapid follow-up is needed to prevent a worsening of the prognosis. For treatments that may show severe side effects, possibly with permanent consequences, PGx will also be of great significance. Apart from these obvious examples, PGx can have a profound effect in cases involving drugs for which the response is difficult to predict, or when evaluation of a drug's effect is only possible months or even years after administration (Houwink, Rigter et al. 2015).

The presence of genetic variants can be tested pre-emptively (i.e. before the need to use a medicinal product arises), on an obligatory basis (i.e. when a medicinal product should only be used in a specified subset of patients, tested by a companion diagnostic) or reactive basis (after a side effect appears or efficacy of a medicinal product is not as expected). Although the premise of PGx is there, PGx is still mainly used responsively, when the efficacy of treatment is lacking or when (severe) side effects emerge. However, hospitals are increasingly conducting experiments to screen for PGx variations beforehand. It is expected that the use of PGx testing will increase in hospitals and will spread to primary care. How its adoption will spread, and whether it will truly lead to clinical value and cost-effectiveness will need to be investigated (Swen and Houwink 2015).

3.2 Current clinical applications

In Figure 3, an overview is given of the number of medicinal products with pharmacogenomics information in the SmPC aimed at optimizing drug response. The efficacy and/or safety of the majority of these products (24 out of 42) is affected by polymorphisms in CYP enzymes,

while 4 products bear usage warnings due to hypersensitivity reactions related to HLA-B mutations. For more information, see Annex C.
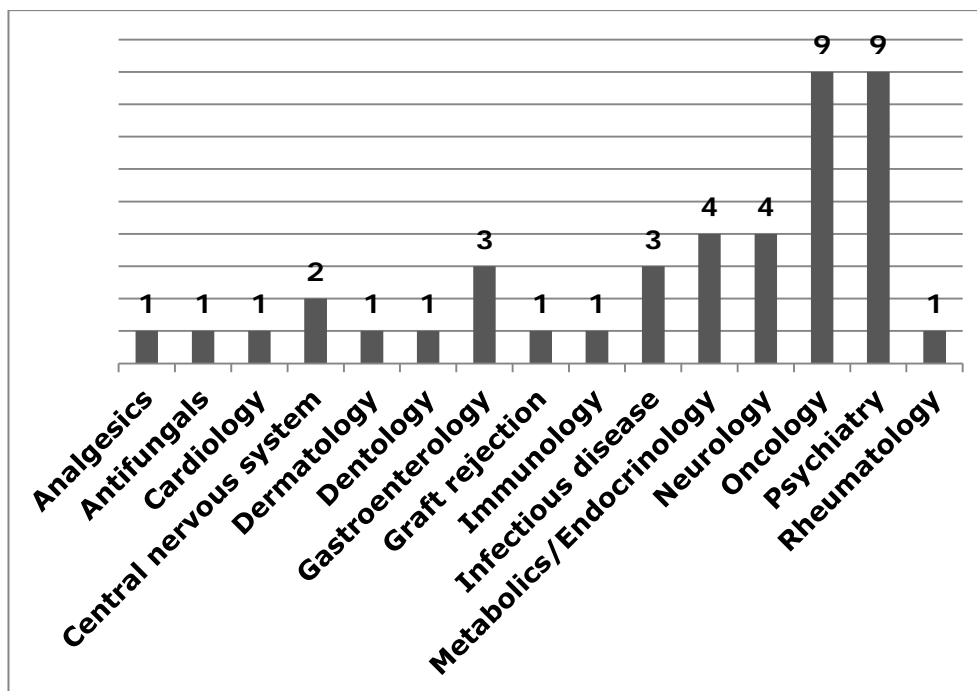
Figure 3. Number of registered medicinal products, per pharmacotherapeutic area, aimed at optimizing drug response by taking into account gene-drug interactions.

A step towards evidence-based pharmacogenetics has been taken by the Dutch Pharmacogenetics Working Group (KNMP Werkgroep Farmacogenetica). They have developed pharmacogenetics guidance for 80 medicinal products that is integrated into the G-standaard (a Dutch drug database used by pharmacists, doctors, wholesalers, health insurance companies) (Swen, Wilting et al. 2008) (Swen, Nijenhuis et al. 2011). This database contains decision-making support information and is incorporated into electronic prescribing systems and pharmacy information systems in (ref PharmGKB). The pharmacogenetics guidance consists of therapeutic (dose) recommendations for prescribers, assuming patients are genotyped pre-emptively. Both pharmacokinetic and pharmacodynamic gene-drug interactions have been included in the database. The drugs are associated with the following genes: CYP2D6, CYP2C19, CYP2C9, SLCO1B1, CYP1A2, CYP2B6, CYP3A4, UGT1A1, TPMT, HLA-B*1502, HLA-B*5701, CYP3A5, VKOR1, DPYD, and factor V Leiden. An up-to-date list can be found on www.farmacogenetica.nl. The guidelines are based on systematic literature studies and the collective opinions of experts in the Pharmacogenetics Working Group (Houwink, Rigter et al. 2015, Swen and Houwink 2015). A similar approach has been followed by the Clinical Pharmacogenomics Implementation Consortium (CPIC) of the NIH's Pharmcogenomics Research Network, freely available at https://www.pharmgkb.org/cpic/pairs.

Twenty-seven medicinal products for which pharmacogenetics guidance is available in the G-standaard database are regularly prescribed by general

practitioners, for example Simvastatin, Citalopram, Acenocoumarol and Omeprazole. But the application of these guidelines has been limited up to now. One of the reasons for this is the limited number of patients that have been genotyped (pre-emptively or not) (Houwink, Rigter et al. 2015). Pre-emptive genotyping of a panel of genes is commercially set up by the Dutch university hospital Erasmus MC. The price of a panel of 3-5 genes is a few hundred Euros. The person's genotype can be coupled to his/her electronic medical record on request (http://www.erasmusmc.nl/pgx/nieuws/n2015/dna.paspoort).

Nonetheless, the possibilities for pre-emptive pharmacogenetics genotyping are not well-known to the public, nor to Dutch health-care professionals as yet (Houwink, Rigter et al. 2015). One of the issues to be resolved before genotyping can become a standard is the discussion about the allocation of the costs and reimbursement of sequencing.

About 15% of the medicines approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) between 1995 and 2014 contain pharmacogenomics information on their label (Ehmann, Caneva et al. 2015). Still, only a subset of the corresponding genes is deemed actionable (based on current knowledge), a total of 7% (Relling and Evans 2015). So, for the slowly growing set of medications for which genomics is actionable, prescribing could be optimized if genetic testing was more widely and appropriately deployed in the clinic. In the meantime, the number of such actionable gene–drug pairs continues to grow, albeit at a slow pace (Relling and Evans 2015) (Swen, Nijenhuis et al. 2011). Currently, prospective testing is obligatory for only a small number of PGx tests, e.g. screening for HLA variants before treatment with antiretroviral Abacavir. For this gene-drug combination a randomized clinical trial has shown the effectiveness of prospective screening. One of the interviewees pointed out that this trial was funded by industry. The incentive seemed to be the avoidance of the drug being discredited.

3.3 Developments and future perspectives

Pharmacogenetic profiles add up to form possibilities for the better use of medicines. This has led to various initiatives to determine the genetic profiles of individuals, such as the 100,000 Genomes Project in the United Kingdom and the determination of 1 million individual genetic profiles on the initiative of the US National Institutes of Health (NIH) Pharmacogenomics Research Network (http://www.nih.gov/precisionmedicine/, http://www.genomicsengland.co.uk/). Although these efforts will lead to genome discoveries and their translation into diagnostics, it will take additional time and effort to translate these discoveries into an optimization of the selection and dosing of medicines for individual patients (Collins and Varmus 2015, Relling and Evans 2015). Besides creating new knowledge, implementation of existing knowledge into health care practice is another area of development. This has been acknowledged at a European level and has led to a huge pharmacogenomics project granted from the EU-programme Horizon 2020. This project is being conducted in seven European countries with the Dutch university hospital LUMC as coordinator, starting in January 2016 (http://upgx.eu). About 8,000 patients will be pre-emptively tested for pharmacogenes for which the evidence of gene-drug

interaction is considered strong enough to justify adjustment of the medicine prescription (e.g. lower or higher dosing, other medicinal product). Their genetic profile will be embedded into their EMR. The purpose is to introduce this information to routine health care practice and to evaluate effectiveness in terms of clinical utility and cost-effectiveness.

Besides these broad initiatives, research is focusing on several specific areas. These areas concern (1) diseases with a high prevalence or high burden of disease, (2) diseases for which the safety or efficacy of the medicines is known to be affected by genetics, or (3) specific patient groups.

3.3.1   *Asthma and COPD*
Inhaled β2-adrenegics (e.g., Salbutamol, Formoterol) and corticosteroids (e.g., Beclomethasone, Budesonide) are the cornerstone of asthma treatment (Meyers, Bleecker et al. 2014). One of the characteristics of asthma is resistance or reduced responsiveness to treatment. Genomic analysis may affect decision-making about asthma treatment and it offers several opportunities for future development. Until now, pharmacogenetic studies have mainly concerned the β2-adrenegic receptor gene. Additional research is needed, however, in order to evaluate the clinical utility of genomic testing, e.g. by means of genotype stratified trials. Moreover, different studies have shown that genetic variation influences patients' response to corticosteroid treatment. The development of a genetic scoring system for corticosteroid drugs could guide the selection of the type and dose of corticosteroid treatment. With respect to both leukotriene (e.g. Montelukast) and biological drugs, extensive additional research is needed to determine whether and to what extent the metabolism is affected by genetics and genomics (Meyers, Bleecker et al. 2014).

In COPD, research mainly focuses on diagnosis and prevention (Agusti 2014). Since the possible added value of PM for treatment decisions is recognized in this disease area, some very early studies are currently being conducted. These studies have shown that the effect of long-acting bronchodilators (Tiotropium versus Salmeterol) for preventing exacerbations is influenced by polymorphisms of the β2-adrenegic receptor gene.

In view of the large patient group (>500,000 asthma patients and >300,000 COPD patients) and the relatively high costs of pharmacotherapy to treat these patients, expanding the personalization of asthma and COPD treatment through genomic testing provides an attractive opportunity.[1] Yet evidence of clinical utility and cost-effectiveness still needs to be collected (Agusti 2014, Meyers, Bleecker et al. 2014).

3.3.2   *Diabetes*
Diabetes also concerns a large patient group. While diabetes is divided into two clinical categories (type I and type II), there are at least 27 single gene mutation subtypes of diabetes that have been identified (Malandrino and Smith 2011, Raciti, Nigro et al. 2014). The genetic make-up determines the clinical categorization, but could also be the

basis for specific treatment decisions. This has been shown for several genes that cause of the syndrome designated as *maturity-onset diabetes of the young* (MODY)[2]. MODY patients with specific mutations often have high sensitivity to sulfonylureas (e.g. Gliclazide). Treatment of these patients could be improved by changing the insulin regime into a sulfonylureas therapy. Other MODY patients have a mutation that may result in only limited improvements in clinical outcomes during treatment with hypoglycaemic agents or insulin. Additionally, polymorphic CYP450 genes influence the response to most antidiabetic drugs. Although testing in the Netherlands is still performed to a limited extent, the United Kingdom has established a specific diagnostic programme for MODY patients (Weinreich, Bosma et al. 2015).

3.3.3 Inflammatory disease

The treatment of *Rheumatoid Arthritis (RA)* is often initiated with a combination of corticosteroids and Methotrexate or other disease-modifying anti-rheumatic drugs (Karsdal, Bay-Jensen et al. 2014). When drug response is absent or inadequate biological agents are recommended. The first attempts within the research conducted show that some RA patients respond significantly better to rituximab therapy than do others. The first initiatives in biomarker fingerprinting do seem to be fruitful. A specific biomarker (C1M) has been shown to describe 55% of the biologic variation associated with structural benefits from treatment with tocilizumab (Karsdal, Bay-Jensen et al. 2014). Currently, PM is not used in RA therapy, but it is viewed as being highly desirable, especially for treatment with the relative expensive biological drugs.

To date there are no effective and approved disease-modifying drugs for the treatment of *osteoarthritis (OA)* (Tonge, Pearson et al. 2014). Aside from surgery to replace the diseased joint, all applied drugs (NSAIDS or corticosteroid injections) are associated with high levels of severe side effects (mainly renal and cardiovascular effects). Currently available genomic information has not enabled researchers or physicians to categorize OA patients into subgroups for treatment. However, since RA and OA are both very heterogeneous diseases with varying root causes across subgroups of patients, identification of subgroups of patients based on this heterogeneity will probably contribute significantly to improved outcomes of therapy. Additional research into possible options for PM in these disease areas is therefore desirable (Karsdal, Bay-Jensen et al. 2014, Tonge, Pearson et al. 2014).

3.3.4 Infectious disease

During the last decades, *Hepatitis C* has, as standard procedure, been treated with a combination of pegylated-interferon-α (PEG-INF) and Ribavirin (Gatselis, Zachou et al. 2014). The outcome of this treatment is suboptimal in genotype 1 Hepatitis C patients and is associated with severe adverse side effects. Over 40 genes have already been identified to modulate, but research has mainly focused on two SNPs: interleukin 28B (IL28B) and inosine triphosphatase (ITP*A*). IL28B genotype can, together with a specific biomarker, identify patients who are most likely to undergo spontaneous clearance and those in need of early antiviral therapy. The ITP*A* gene-related research mainly focused on a reduction of anaemia as an adverse side effect of RBV treatment. Yet the effect of ITP*A* SNPs on therapeutic outcomes is still unclear and deserves further

attention in research (Gatselis, Zachou et al. 2014). Nonetheless, major advancements have been made in therapy: in 2014 and 2015 several new medicinal products entered the market. The combination of Ledipasvir and Sofosbuvir was a major breakthrough for the treatment of genotype 1 virus infected patients (Zhang, Nguyen et al. 2016). IL28B non CC genotype has been associated with lower response rates to interferon-based therapies.

3.3.5   *Chronic pain*
The use of opioid analgesics for the management of chronic pain has increased significantly over the past decade. There are, however, some safety issues with respect to high-dose opioid prescribing. In addition, long-term use of opioids may be ineffective and not well-tolerated by about one-third of the chronic pain patients. Negative side effects include constipation, nausea, sedation, respiratory depression and death. Individuals with specific variants of the CYP2D6 gene are unable to convert codeine to morphine, resulting in insufficient pain reductions, while individuals with multiple copies of the CYP2D6 gene metabolize codeine extremely fast, which could result in morphine intoxication. For safety reasons, the European Medicines Agency judged that Codeine should not be used in people of any age who are known to be ultra-rapid metabolizers. Several preliminary studies investigated the use of genome-wide association study data to match dose-prescription to genetic variation. Moreover, SNPs of the mu-opioid receptor gene and the catechol-o-methyltransferase gene may alter the metabolism of opioid and may increase opioid abuse risk. Substantial additional research is needed, however, to specify these associations in detail (Bruehl, Apkarian et al. 2013).

3.3.6   *Pregnancy*
About 65% of women take prescription drugs, other than supplements and iron, during their pregnancy (Haas 2014). This makes them a very relevant target population for PM. CYP2D6 is an enzyme that is highly polymorphic and is induced through the course of pregnancy. This influences the metabolism in regard to different types of medicines for different pregnancy related complaints. First of all, based on their SNP, women might poorly, extensively or ultra-rapidly metabolize codeine into morphine, which influences its effect as a pain reliever. In addition, mothers' SNP, leading to the ultra-rapid metabolism of opioid, and an infants' UGTB7*2 genotype can lead to the toxicity of morphine during breastfeeding. The SNPs of the CYP2D6 also play a part in hypertension medication. Since CYP2D6 increases during pregnancy, women who had previously been treated for hypertension by β-blockers (for instance Metoprolol and Propranolol) may begin to develop hypertension again. CYP2D6 may also influence medication decisions for anti-depression and nausea. It decreases concentrations of SSRIs (antidepressant drugs) in the third trimester of pregnancy, while depression complaints typically increase during this stage. Regarding nausea and vomiting, extensive or ultra-rapid metabolizing CYP2D6 enzymes result in ineffective treatment with Ondansetron, while polymorphic serotonin receptors (5HT3, 5HT3*B*) result in the increased binding and efficacy of nausea medication. Finally, extensive research has already been conducted on medication for the prevention of preterm labour. Nifedipine is a medicine often used to stop contractions and delay birth, but studies show that

polymorphisms in CYP3A5 and the use of CYP3A inhibitors impact the concentration in maternal blood. In addition, polymorphic CYPaC9 and CYP2C19 enzymes might influence the effectiveness of prostaglandin inhibitors, but research on this topic is warranted. Finally, antenatal corticosteroids (e.g. Betamethasone) are used in cases of preterm labour. Initial studies on this topic showed that the treatment outcome is influenced by both maternal and foetal genotypes (Haas 2014).

4   Gene-based drug targeting

4.1   The potential of gene-based drug targeting

This chapter focuses on medicinal products that have been developed to target a certain gene or gene pathway that is affected by disease. One can distinguish between gene-based drugs targeting of somatic variations, as seen in oncology, and germline variations, as is pursued in genetically-based diseases, e.g. Cystic Fibrosis, or disease risks, e.g. VKORC.

Targeted drugs are best understood in the light of stratified medicine, which is "the targeting of treatments (both pharmacological and non-pharmacological interventions) according to the biological or risk characteristics shared by sub-groups of patients" (Stratton, Campbell et al. 2009).

4.2   Current clinical applications

So far, most advances have been made in the field of oncology, in which molecular and genetic tumour profiling is increasingly used to predict therapy response and/or prognosis. The greater part of the registered medicinal products is thus indicated for oncological diseases (see Figure 4). For more detailed information, see Annex C.
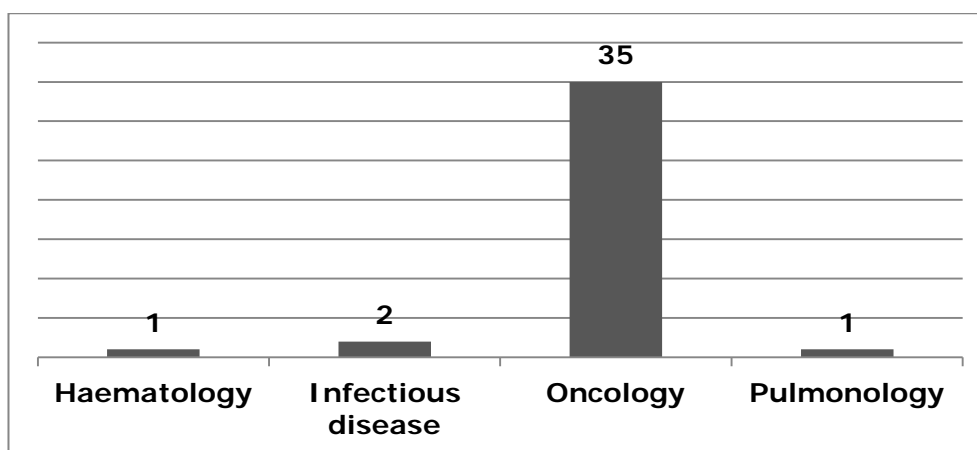
Figure 4. Number of registered medicinal products, per pharmacotherapeutic area, aimed at gene-based drug targeting.

An important factor in the success of tumour profiling is the development of targeted therapies in which drugs block the tumour by binding to tumour-specific molecules. But, according to criticasters, there is little evidence that overall cancer survival has been improved by these medicinal products (Joyner and Paneth 2015). This is thought to be because they block only one part of the pathway, leading to a shift in tumour growth via another part of the pathway. A such, most cancers are quite complex with regard to genomics. Combining two or more (targeted) medicinal products is acknowledged as a way forward to improve overall survival in cancer. In cases involving a consistent genetic defect that allows for the development of a drug specifically

targeting this defect, the chance of successful treatment will also be higher.

4.3 Developments and Future perspectives

On an international level, various initiatives focus on the collection of sequence data in cancer in order to understand the molecular basis of cancer and to elucidate possible targets for therapy. Examples of this are The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC), both providing public access to data. TCGA is a joint effort of the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), both centres of the US National Institutes of Health (http://cancergenome.nih.gov/abouttcga). ICGC is a voluntary scientific organization coordinated by Canada and funded by participating nations that promotes the collaboration of cancer and genomic researchers all over the world (https://icgc.org/). These initiatives reveal the complexity of human cancer and, in particular, the role and interplay of genomic, transcriptomic and epigenomic aberrations in tumour genesis (McDermott 2015).

Another data sharing project is the American Association for Cancer Research project GENIE, an acronym for Genomics, Evidence, Neoplasia, Information, Exchange (http://www.aacr.org/Research/Research/Pages/aacr-project-genie.aspx#.VuKRQ9IUWUk). Several large US and European university medical centres pool all data on patients' tumour genomes and their clinical outcomes from tens of thousands of cancer patients. The centres do not work with a standard gene panel, but continue to use their own instead (Kaiser 2015). The Dutch Center for Personalized Cancer Treatment is also involved.

At a national level, the 100,000 Genomes Project in the United Kingdom intends to combine genomic sequence data with the EMRs of 70,000 NHS patients ((http://www.nih.gov/precisionmedicine/). The causes, diagnosis and treatment of disease will be investigated. The project focuses on cancer and rare diseases. In the Netherlands, three cancer centres and various hospitals are collaborating in the Center for Personalized Cancer Treatment (CPCT; http://www.cpct.nl/nl/home/); all patients with metastasized disease are asked to participate. Mutations in 2,000 cancer-related genes of biopsies are being assessed by next generation sequencing in order to identify predictive and prognostic biomarkers (Vijverberg 2013).

As mentioned earlier, a (tumour) DNA sequence can provide useful information, but it is only one part of the puzzle. More information about the phenotype of a cancer – and any disease in general - can be obtained through transcriptomics, epigenetics, proteomics, metabolomics, etc. Complementary to these technologies, advances in "organoid technology" hold great promise for the improved phenotyping of disease.

To summarize, the scientific community is focusing on more information to enable the improved phenotyping of disease. Through a multi-systems approach, information from different modalities is being

integrated to provide a detailed picture of the disease state, which in turn may lead to a better fit in treatment, i.e. personalized medicine. But tying different data sets of this magnitude together analytically remains a serious challenge (Ritchie, Holzinger et al. 2015).

Besides the above-mentioned broad initiatives, research is focusing on several specific areas.

4.3.1 Oncology

To date, there is a compelling body of evidence that, for an increasing number of drugs used in the clinic, the likelihood of a patient's cancer responding to treatment is strongly influenced by alterations in the cancer genome (McDermott 2015). Over time, several molecular tools have been developed to serve a personalized therapeutic approach in cancer. Historically, immunohisto-chemistry was used to stratify patients with breast cancer according to the presence of certain biomarkers and it is currently used to determine the expression of ER and HER2 (Hammond, Hayes et al. 2010, Wolff, Hammond et al. 2013). Fluorescence in situ hybridization (FISH) analysis was then developed as a method to quantify copy number. Genetic profiling is now showing the potential to further tailor therapy. In cancer, four potential uses of genomics in PM are currently being pursued (Arnedos, Vicier et al. 2015).

1) The first one is mechanism-based drug targeting through the identification of oncogenic drivers. A genomic driver can be defined as the molecular alteration responsible for cancer progression, the 'Achilles heels'. Thus targeting this gene is expected to have a therapeutic effect, namely by blocking the activity of a mutated or over-expressed oncogene (Garnett, Edelman et al. 2012) or by blocking a pathway the tumour has become overly reliant on (Greystoke and Chaturvedi 2015). An example of this is Imatinib, which is used in chronic myeloid leukaemia.

2) Molecular alterations can also be used as biomarkers to identify the patients most likely to benefit from a particular treatment, or vice versa, to select the right drug for the particular genetic make-up of a patient's tumour. Recent examples of this are PARP inhibitors, which have been shown to be effective, specifically in patients with BRCA1/2 mutations (Arnedos, Vicier et al. 2015).

Companion diagnostics testing for a single gene or a gene panel can aid in selecting the right patient for the right therapy and are increasingly used in the selection of the right patients for clinical trials. Examples of this are assays using either RT-PCR (Oncotype DX®) or DNA array (Mammaprint®)(Arnedos, Vicier et al. 2015). Yet other techniques are evolving as well, such as comparative genomic hybridization (CGH) arrays, single nucleotide polymorphism (SNP) analyses and high-throughput whole exome sequencing (WES)(Arnedos, Vicier et al. 2015).

In the end, genotype-directed therapy may be associated with a better survival rate (Kris, Johnson et al. 2014). Still controversy remains on the added value of selecting patients according to their molecular profile ('basket' trial structure). It seems that tissue context might be vitally

important as well. Molecular profiling for trials may have the most utility in either rare tumour types or rare molecular abnormalities, where it is not feasible to perform evaluations in cohorts of patients with tumours arising from a single tissue of origin (Gagan and Van Allen 2015, Redig and Janne 2015).

3) The third possible application of genomics is the identification of genomic alterations responsible for secondary resistance. Secondary mutations are acquired in these targets during the development of drug resistance. For example, the initial response to EGFR tyrosine kinase inhibitors in lung cancer declines in the majority of patients within one to two years (McDermott 2015). In about 60% of the cases, a new EGFR mutation is found which hinders the binding of EGFR inhibitors to their target. This has resulted in the development of a new generation of irreversible inhibitors of EGFR in order to overcome this resistance mutation (McDermott 2015).

4) Another area of application is the use of the immune system. Genomics can potentially be used to evaluate various different aspects of the immune system for the purpose of PM. Examples of medicinal products that target the immune system are the immune checkpoint inhibitors ipilimumab, nivolumab and pembrolizumab.

To summarize, developments in both diagnostic and therapeutic approaches in oncology are being pursued. Tailored guidelines for the roll-out of diagnostic approaches that stratify patients and guide therapeutic decisions are beginning to be introduced (Greystoke and Chaturvedi 2015). Mechanism-based drug targeting drives treatment individualization in order to improve health outcomes in each individual.

4.3.2 Rare diseases

Multiple Sclerosis (MS) treatment can consist of acute relapse management or long-term treatment (Wiese, Suppiah et al. 2014). Typically, relapse is treated with anti-inflammatory agents (e.g. corticosteroids), while long-term treatment generally includes long-standing first-line agents such as IFN-β, glatiramer acetate (GA) and Mitoxantrone, but new treatment options have quickly emerged over time (e.g. Lizumab, Figolimob, Teriflunomide and Dimethyl fumarate). Multiple studies were conducted on INF-β and GA, but most were underpowered. For now, it can only be concluded that patients with high persistent titres and neutralizing antibodies do not respond to IFN-β treatment. Natalizumab was the first drug proven effective for targeted therapy of highly active, relapse-remitting MS patients. While several drugs have been developed, each of which target different genes, future research is needed to identify patient groups that will benefit most from either treatment option (Wiese, Suppiah et al. 2014).

Cystic Fibrosis (CF) is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene and is categorized by molecular defects into six classes for which different treatments are recommended (Amaral 2014). Three classes are considered 'severe' (classes I–III), with little or no CFTR activity, and two are considered 'mild' (classes IV and V), in which protein function is reduced. Class I, II and III mutations have the greatest number of patients. The main targets are

to improve CFTR function (the so-called potentiators used in class III and IV genetic mutations) to increase the surface expression of CFTR (the so-called correctors in class II mutations) and to promote the transcription of CFTR in class I mutations (the so-called production correctors) (Brodlie, Haq et al. 2015). Ivacaftor is approved for the treatment of cystic fibrosis in persons having one of ten specific mutations in the CFTR protein, related to class III. Research in the other classes is still ongoing.

4.3.3   *Organoid technology*
Organoids are in vitro structures resembling whole organs that are generated in 3-D culture systems in which pluripotent stem cells or isolated organ progenitors differentiate to form a tissue that exhibits multiple cell types that self-organize into an organ-like structure in vivo (Lancaster and Knoblich 2014, Sachs and Clevers 2014). Mini-guts, for example, reproduce the epithelial architecture of the small intestine and colon (Sachs and Clevers 2014).

The basis for growing human intestinal organoids was laid by the discovery of the culture conditions of mouse intestinal organoids. Intestinal stem cells possess the capacity to form epithelial structures in vitro that closely resemble the self-renewing cryptvillus architecture of the gut. Subsequently, protocols have been developed to grow human epithelial mini-guts from biopsies. The protocol was applied first for the study of cystic fibrosis (CF), for which now a biobank is being set up to screen all CF patients in the Netherlands (Sato and Clevers 2013, Sachs and Clevers 2014)(The HUB, foundation for Organoid Technology).

Because the success rate of establishing the cultures from individual patient samples is nearly 100%, this enables the prospective generation of large "living biobanks," side-by-side with healthy tissue from the same individual (Sato and Clevers 2013). Organoids have the potential to model developmental disease, degenerative conditions and cancer. Genetic disorders can be modelled by making use of patient-derived, induced pluripotent stem cells or by introducing disease mutations (Lancaster and Knoblich 2014). Up to the present, organoids have been generated from intestinal, pancreas, heart, kidney, brain and liver organoids (see Figure 5) (Lancaster and Knoblich 2014).
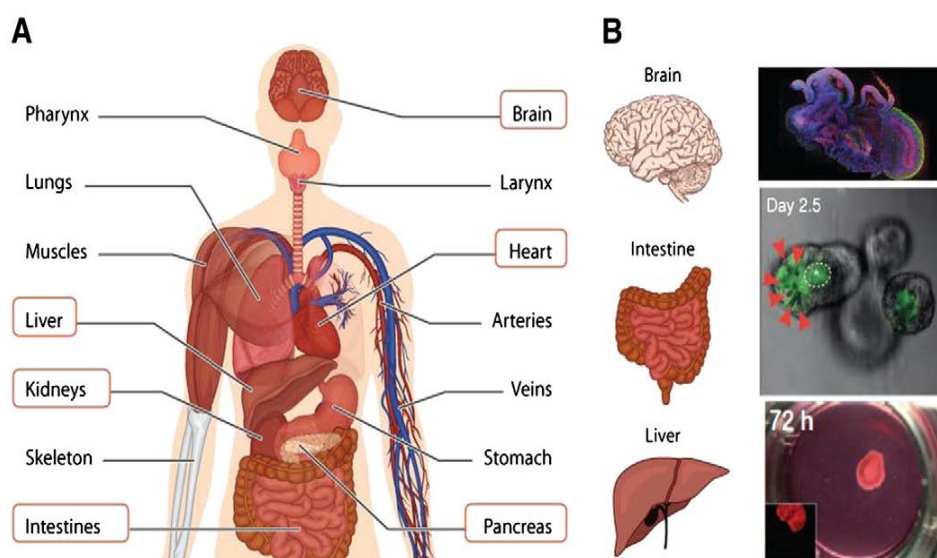
Figure 5. Current organoid models. (A) An ever-increasing number of organs have in vitro organoid equivalents; (B) Cerebral, intestinal and hepatic organoids are prominent examples of organoid cultures that have potential applications in drug discovery (Lancaster and Knoblich 2014).

Applications of organoid technology are diverse, ranging from diagnosis to drug development and personalized treatment (Sato and Clevers 2013). For example, in oncological therapy, organoids of the tumour can be tested for the combination of drugs that eradicates the tumour the most with as few as possible drug-resistant clones.

Furthermore, tissues derived in vitro could be generated from patient cells to provide alternative organ replacement strategies. Unlike current organ transplant treatments, such autologous tissues would not suffer from issues of immune-competency and rejection (Lancaster and Knoblich 2014, Ranga, Gjorevski et al. 2014).

Finally, organoids present the opportunity to bridge the current experimental gap between deep-sequencing efforts in cancer and patient outcome. Currently used preclinical tumour models (cell lines, mouse models) are very limited in their accuracy. As a consequence, many drug candidates that perform well in preclinical models fail to deliver in clinical trials, resulting in suboptimal patient treatment and wasted resources (Sachs and Clevers 2014). Liver organoids, in particular, represent a system with high expectations, particularly for drug testing, because of the unique metabolic profile of the human liver (Lancaster and Knoblich 2014, Ranga, Gjorevski et al. 2014). Taken all together, organoids have great potential, yet more research is needed to see whether organoids can truly live up to expectations.

5 Overview of challenges

Nowadays, health care systems place greater emphasis on evidence-based clinical practice, particularly as they are operating within an increasingly budget-scarce environment. PM could improve clinical outcomes for patients and thereby help to achieve more effective use of health care resources. Hence, demonstrable evidence of clinical-effectiveness and cost-effectiveness is urgently needed to support the use of personalized medicine in health care. Yet various barriers are encountered when translating PM to the clinic/the public, such as those reviewed by Joyner and Paneth (Joyner and Paneth 2015). Here we focus on the most relevant barriers and specific barriers encountered in the Netherlands.

5.1 Implementation in clinical practice, after evaluation

For the challenges related to implementation in clinical practice, we take into account the elements included in the ACCE model (see Figure 6). This model has been developed with the support of the U.S. Office of Public Health Genomics (OPHG) of the Centers for Disease Control and Prevention (CDC) and is meant to systematically collect, evaluate, interpret and report data about DNA (and related) testing for disorders with a genetic component, allowing policymakers to take informed decisions on the introduction of DNA testing in public health.
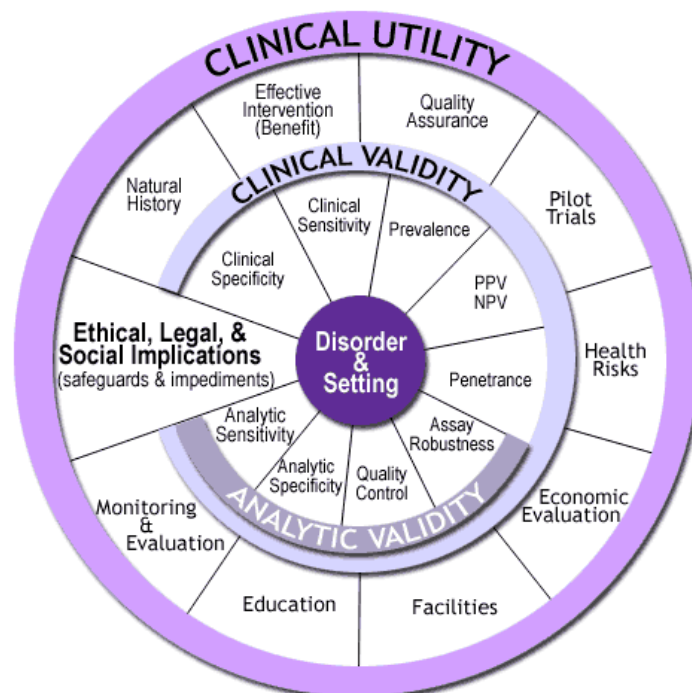

Figure 6. The ACCE model

5.1.1 Analytical validity
Before being used in a clinical setting, genetic tests must meet certain criteria concerning their analytical validity, clinical validity and clinical utility (Burke 2014). Analytical validity is the determination of whether a

test can accurately detect the presence or absence of a pharmacogenetic variant, thus assessing the assay performance (https://ghr.nlm.nih.gov/handbook/testing/validtest).

The choice of assay method
Current assay options involve monogene, multigene (next-generation sequencing, NGS), whole exome sequencing (WES), or whole genome sequencing (WGS) (Gagan and Van Allen 2015). Whole genome sequencing results in more information than monogene sequencing. Yet, depending on the setting, the confidence of detecting a variant of low allele fraction may be less than it would be had a gene panel been used.

Apart from that, the kit used to perform sequencing is a factor to be taken into account, as is the choice of clinical sample, type of data analysis and method to interpret genetic data (Gagan and Van Allen 2015). Because of this, genetic data gathered from different laboratories vary in reliability (i.e. diagnostic quality) if no clear standardization agreement is made (Burke 2014, Gezondheidsraad 2015). This issue was also mentioned by one of the interviewees, who explained that cross validation of sequencing results is by no means common practice in university hospitals. There is as yet no common standard by which one can compare the quality of genomic data between different laboratories. It is therefore of the utmost importance to define internationally accepted definitions of data quality, creating appropriate validation strategies and standards and protocols for proficiency testing for genomics-based tests. The FDA and the European Medicines Agency have convened specific groups to begin to address these issues (Evans, Burke et al. 2015). It should be noted, as pointed out by one of the interviewees, that market domination of one testing platform from one supplier would be undesirable: assay related errors will only become evident when more platforms are used in practice. Eradicating these errors will ultimately improve the accuracy of diagnostics.

Quality of data analysis
Another challenge to implanting sequencing technology into clinical practice, and specifically into clinical trials, is the need for novel bio-statistical approaches to analyse clinical outcome data when combined with the large number of data points from any NGS/WES/WGS sequencing application. Such multidimensional data, where genes can interact with each other or clinical variables, will by necessity require new approaches for their analysis and thought must be given to this when considering the size and design of any clinical study.

Additionally, some thought should be given to how we imagine complex genomics data can be interpreted by the clinician and the patient such that clinical management is improved rather than hindered. It is likely that, in the future, a single patient's genome sequenced in the clinic will be referenced against a database containing thousands of patients with that same disease/phenotype. Matching this single patient against such a dataset would truly enable personalized treatment, but it would need to be visualised in a way that provides clarity for the treating physician and for the patient (McDermott 2015).

Actionability of knowledge
Finally, a whole exome or whole genome analysis dramatically expands the information provided by generating detailed information about hundreds or thousands of genes, including genes unrelated to the diagnostic question.
While WGS/WES may be cost-efficient, the approaches may produce many findings that are difficult to interpret or are of uncertain clinical significance, at present anyway. By using WES/WGS, the border between diagnostics and screening is blurred, which means some thought must be given to the ethical implications of this trend (Burke 2014). In addition, this blurring may also require changes in the way health care is financed/ reimbursed.

5.1.2   *Clinical validity*
Clinical validity and clinical utility form the cornerstone of evidence-based medicine. Both terms pose various challenges in the different fields of PM. The term clinical validity was proposed by the NIH-DOE Task Force on Genetic Testing to describe the accuracy with which a genetic test identifies a particular clinical condition (Holtzman and Watson 1999); in other words, the determination of the statistical association between a genetic variant and the outcome of drug therapy (https://ghr.nlm.nih.gov/handbook/testing/validtest). It is described in terms of sensitivity, specificity, positive predictive value and negative predictive value, preferably performed with a prospective randomized controlled trial (Burke 2014).

Role of genomic information
With pharmacogenomics, several problems arise. Firstly, genetic variants can (and often do) differ according to ancestry, such as in the case of the response to warfarin in relation to variants in the VKORC1 gene. Secondly, drug effects can be influenced not by one single gene, but by multiple variants in the same gene — some of which are rare — and by variants in multiple genes within the same patient (Relling and Evans 2015). Thirdly, complex pathways are involved in the action and metabolism of most drugs and non-genetic influences also contribute to drug response (Maitland, DiRienzo et al. 2006). PGx testing for single polymorphisms may therefore account for only part of the variability in drug response. The diagnostic test criteria sensitivity, specificity and predictive value are applicable to tests for which response is determined as a dichotomous variable. Drug response cannot however always be considered an all-or-none phenomenon. In these situations, the relative contribution of the genotype to the variability in response, i.e. a risk estimation, provides additional information in the clinical decision-making process (Swen, Huizinga et al. 2007). The clinical importance of the estimated risk depends on the severity of the consequence and is therefore always a personal consideration. As one of the interviewees pointed out, the chance of becoming deaf is of greater significance to a blind person than to someone who is not visually impaired.

With gene-based targeting, similar problems are seen. In general, it can be said that genomic information can be useful, but it is not enough to target a therapy. A comparison of the RNA sequencing with the genomes/exomes revealed that only 36% of validated somatic single nucleotide variations were observed in a transcriptome sequence

(Arnedos, Vicier et al. 2015). Moreover, successes in differentiating driver events from passenger events have been moderate, causing response rates to be rather low compared with the number of trials being undertaken. Thus, it is paramount to identify and target the actionable genomic driver events and to differentiate them from passenger events. To address this issue, large-scale sequencing projects and the associated catalogues of somatic mutations are being increased. Computational biology is used for the identification of highly mutated genes.

In addition, temporal and spatial intra-tumour heterogeneity forms a serious problem to genotyping, specifically in cases of oncology. When choosing chemotherapy directed according to a tumour site of origin, a biopsy of any site (either primary or metastasis) can be performed to confirm the diagnosis. But molecular profiling may show dramatic differences in the genotype between the primary site and metastases, and even within different areas of the primary tumour (Greystoke and Chaturvedi 2015). Whether these abnormalities will respond equally to targeted therapy is unclear, but it is unlikely. For this reason, biopsies are increasingly also taken from metastases. Equally it is clear that the tumour evolves over time, particularly under the selection pressure of therapy. Selection of drug resistant clones that are probably present at diagnosis occurs rapidly and may even be associated with a change in histology (Greystoke and Chaturvedi 2015). From a clinical standpoint, early detection of resistance is crucial to optimizing therapy, but the way to handle secondary resistance is still unclear; cell eradication seems the only way (Arnedos, Vicier et al. 2015). A promising development is the application of organoid technology combined with ultra-deep sequencing in multiple regions of a tumour to determine which drug or combination of drugs would have the highest chance of preventing and/or counteracting resistance.

Lastly, with respect to therapeutics, more fundamental criticism has been given by Joyner et al in JAMA. He is rather sceptical about the transformative power of targeting dysregulated "-omic" pathways: "*…the benefit of (..) drugs on overall cancer survival has been limited, perhaps because of the adaptive nature of cancer. There is little evidence that targeted therapy will interrupt the cycle of expectation and disappointment that has typified many of the new approaches to cancer therapy*" (Joyner and Paneth 2015). Indeed, targeted therapies have not resulted in major decreases in the number of cancer deaths. In that sense, all kinds of measures, including the traditional public health measures of screening, early detection, and lifestyle changes such as smoking reduction, seem to be necessary to reduce mortality in cancer.

Clinical trials
Apart from that, measuring clinical validity depends on the types of performance parameters that are chosen. For example, one can measure the penetrance of genetic variation on drug effects through retrospective studies. But one can also measure the effect a certain genetic variation has on an intermediate phenotype, such as drug-metabolizing enzyme activity. Additionally, data can be gathered from in vivo pharmacokinetic or other functional studies, in vitro functional studies, and preclinical and clinical studies that link pharmacological effects or drug concentrations to genetic variation. Further sources of

data include case reports, family studies and randomized controlled trials that compare the outcomes of genetics-based prescribing with the outcomes of prescriptions that are not based on genetic-test results (Relling and Evans 2015).

Currently, randomized controlled trials (RCTs) form the cornerstone of evidence-based medicine and are seen as the gold standard to prove clinical effectiveness. Due to the small populations described, multiple factors that drive a certain drug effect and the lack of knowledge about this, the results from genetic testing for stratified medicine have been disappointing.

Especially in the field of oncology, major attention is being paid to the problem of trials for patient stratification. In cancer, most of the current candidate drivers are detectable in less than 10% of the patients. This approach generates two major issues: firstly, when a patient is tested for a single gene alteration, the likelihood of it being positive and, therefore, treated with a drug matched to a genomic alteration is very low. One solution to address this issue is to use high-throughput genomic approaches to detect all present genomic alterations and enable the patient to be assigned to a specific therapeutic trial. The second issue is the need to screen a large number of patients in order to perform a clinical trial, accrue data and gain enough statistical power. Several solutions are being experimented with, such as the use of 'basket' and 'umbrella' trials. See the reviews of Hollingsworth and Arnedos et al for more information on cancer trials (Arnedos, Vicier et al. 2015, Hollingsworth 2015).

Specifically for the pharmacogenetics of drug metabolism genes, such as the CYP genes, RCTs are not feasible because many drugs are metabolized by certain CYP enzymes. In these cases, the gene is not a target of the drug itself, but rather a generic mediator. Many of the interviewees argue for a direct implementation of the found polymorphisms in clinical practice, so that dose adaptations can be made for the medications that are metabolized by the specific gene.

Again, on a higher level, one can argue that evidence-based medicine and the use of randomized controlled trials at all contradicts the principle of personalized medicine. The goal of personalized medicine is therapy targeted to the unique genome of an individual (or tumour), so what relevance does a clinical trial have for individuals who do not share that genome? As one of the interviewees said "stratified medicine (red.: subgroups) seems to be the only feasible option in evidence-based medicine". Some scientists are calling for n=1 trials, others are arguing for alternatives to RCTs, such as retrospective cohort studies. They accept that prospective evidence-based medicine is simply not feasible for personalized medicine (Janssens and Deverka 2014, Joyner and Paneth 2015).

Indeed, one of the interviewees called for the design of more 'adaptive trials', e.g. setting up an off-label programme in which existing drugs are tested with patients whose genetic profile is suspected to have impact on the pharmacotherapeutic effect, based on knowledge available in literature or other trial data. With 8 to 10 patients, one

could evaluate the results and decide whether proceeding (in the form of a classical RCT) was viable.

The concerns are amplified by the ongoing debate in the oncology community about appropriate outcomes for cancer trials and the predictive utility of surrogate end points. With increasing emphasis being placed on the quality of life at the end of life, limited gains in overall mortality and disease-free survival may become less important (Joyner and Paneth 2015). Moreover, improved outcomes in survival cannot be attributed to the application of genomics on its own, but are also or largely due to adherence to best practices.

5.1.3   *Clinical utility*
In addition to clinical validity, one must assess a test's clinical utility – that is, the determination of whether the use of the test leads to improved health outcomes or an assessment of the risks that occur as a result of testing, i.e. the actionability. It addresses a test's health care value (Burke, Burton et al. 2010).

Yet the criteria to reach clinical utility vary depending on the medical, ethical, legal, social and economic context of their application (Gillis and Innocenti 2014). Various institutes have developed a definition, such as the WHO: "Clinical utility indicates whether a test results in information that can be used to develop a clinical intervention" (http://www.who.int/genomics/policy/quality_safety/en/index1.html#Determining the Validity of a Genetic Test). But this definition refers to genetic testing in the sense of disease genetics, while pharmacogenetic testing is different in the sense that a PGx test always informs treatment decisions. This renders the WHO definition of clinical utility unsuitable for PGx testing. Consensus on a framework to establish an adequate level of evidence has not yet been reached by the scientific community. Currently, no consensus has been reached about what kind of outcomes determine clinical utility (Relling and Evans 2015). Full consensus on the definition of acceptable clinical utility is, however, not feasible, since the utility will depend on the context (which may differ per case) (Dotson, Bowen et al. 2015). In all cases, the advantages and disadvantages have to be weighed.

The demonstration of clinical utility is critical for the widespread adoption of pharmacogenetics medicine, the more so as reimbursement policies focus increasingly on cost-effectiveness and added value. Defining robust metrics for measuring utility is an important and timely objective, as regulatory decisions, health care funding, investments and patient access to reimbursed testing are all conditional on judgements about clinical utility (Gillis and Innocenti 2014). In all cases, transparency about the considerations given to clinical utility is desirable.

Among the factors that are considered when deciding on the actionability of pharmacogenomic variation, one could include: cost-effectiveness tests, the therapeutic index of a drug (the ratio of the toxic dose to the therapeutic dose), the severity of the drug's toxicity, the severity of the underlying disease, the consequences of prescribing behaviour and the availability of an alternative therapy (Dunnenberger, Crews et al. 2015, Relling and Evans 2015). But patient satisfaction and the influence on adherence may also be important to take on board. Genomics tells only a part of the story; the diseases for which this part

is more relevant in terms of the pharmacotherapeutic effect of a medicinal product than other factors is still largely unknown, especially those diseases that do not have a clear genetic cause (contrary to hereditary diseases and oncology). For optimal clinical utility, therefore, starting with those diseases/conditions that carry a high medical need could be an alternative starting point for implementation of PM, as proposed by interviewees.

5.2 Adoption in clinical practice

Guidelines

A major barrier that prevents the widespread use of pharmacogenomics to guide the prescription of drugs is the lack of incentives for clinicians to conduct those tests (Relling and Evans 2015). This is especially the case in first-line health care. For this reason, the Royal Dutch Pharmacists Association (KNMP) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have started to create standardized guidelines on how to use genomic data to inform prescribing. These guidelines are evidence-based, peer-reviewed and publicly available (Swen, Wilting et al. 2008, Swen, Nijenhuis et al. 2011, Relling and Evans 2015). They call for pre-emptive pharmacogenetics as an essential parameter concurrent to documentation of family history or kidney function assessment (Ratain and Johnson 2014). But it is not clear who should initiate pharmacogenetics testing and at what moment.

However, different guideline-generating groups sometimes disagree on the required level of evidence for the many contradictory or inconclusive results that randomized prospective controlled trials and meta-analyses of them have produced (see Section 5.2). Well-known examples on which there has been disagreement include the drugs warfarin and clopidogrel (Relling and Evans 2015). This heterogeneity in genetic-variation databases (and subsequently in health-care record systems) hinders the use of pharmacogenetic test results longitudinally, as well as across each of the health care systems.

Another problem with the current guidelines is that they constantly change as new evidence arises. As deep sequencing becomes more widespread, further variants will be discovered in pharmacogenes. The challenge will be to design an easily updatable system in the health-care record systems (Relling and Evans 2015).

This lack of standardization around guidelines that incorporate PM is a great cause of concern among physicians. This might be overcome if clear policies were adopted (van Rooij, Wilson et al. 2012). Policymakers may play a key role, therefore, in selecting and implementing guidelines for PM, as well as in establishing reimbursement criteria. If these policy issues are not addressed, PM will probably find itself in a situation of diminishing returns, as research and biobanks alone will not result in large market uptake (van Rooij, Wilson et al. 2012). For that, policymakers need to be convinced that the clinical endpoints and outcomes of PM outweigh its costs. This calls for a rigid framework to compare effectiveness (van Rooij, Wilson et al. 2012).

Education
The use of genomics in clinical practice, either through screening or genetic targeting, will only increase over the coming years. But the (post-graduate) curriculum of medical students is not keeping pace. Health care providers, including physicians, pharmacists and nurses, need to be trained to interpret (pharmaco)genomic data (and other – omics data). They also need to learn how to make clinical decisions based on –omics data and to discuss genetic risks with patients.

Future health professionals will need to be well-versed in the scientific underpinnings of personalized care (Garcia, Kuska et al. 2012). As genetic testing becomes more common, it is unclear how well-prepared health care providers will be to interpret them. Medical schools will need to incorporate more genetics and genomics in their professional curricula and clinicians will need to keep up with rapidly changing technologies, including but not limited to '-omics', to keep abreast of the modern clinical care patients expect (Garcia, Kuska et al. 2012). Indeed, many of the interviewees underscored the importance of more genetics and technology education.

Also important is the algorithm for obtaining the decision or a recommendation. If clinicians are able to perform calculations by hand and the rules are easy to interpret, acceptance of the biomarker(s) is more likely than if some kind of ''black box'' is required. Therefore, classifications and probabilities estimated by a logistic regression model are more likely to be accepted by clinicians than results obtained by machine learning methods, such as artificial neural networks or support vector machines, although these generally may look quite impressive (Ziegler, Koch et al. 2012). While personalized medicine offers many opportunities to improve treatment, it may also make clinical decision-making more complex instead of simpler and maybe unable to fulfil the promise of informing the patients with certainties (Laksman and Detsky 2011). We should be aware that, just as with current clinical algorithms and diagnostic tools, patients should be informed about their increased or decreased probability of responding to therapy (Laksman and Detsky 2011).

Finally and importantly, not only do clinicians need to be educated, but also the patient – and the public in general – needs to be well informed in order to understand the possibilities and limitations of genetic testing. This will prevent them from forming misplaced anxieties or expectations (Vijverberg 2013).

Other factors
When new health care practices are adopted, the time from their introduction to their uptake into the guidelines for standard care differs greatly. The HER2/neu test was introduced relatively fast, while it took more than 20 years for X-rays to become a standard tool in medical practice. A powerful factor in the introduction of the HER2/neu overexpression test was the requirement of this test by the regulatory agencies upon the market introduction of Trastuzumab. As a consequence, HER2/neu testing was actively advocated by the pharmaceutical company that manufactured the drug and by patient advocacy organizations. With regard to PGx testing, this requirement

suggests that obligatory testing prior to drug prescribing might give a strong stimulus to the clinical uptake of PGx.

In a more general sense, the adoption of genetics in health care calls for more close collaboration and communication between geneticists and non-geneticists, and must take into account the perceived need of stakeholders (patients, payers, doctors, etc.) to introduce these new services (Rigter, Henneman et al. 2014).

5.3 Costs and reimbursement

Another barrier to the implementation of sequencing/genomics technology is the cost of genotyping and its reimbursement. When performed as a stand-alone diagnostic with a need for rapid turnaround, the cost-effectiveness of single-gene genotyping is difficult to obtain. Genotyping multiple genes in a single assay is more cost-effective and uses the DNA in the sample more efficiently. Finally, the most efficient analysis is to sequence a complete genome. The cost of sequencing a whole genome has dropped dramatically in the last 10 years (Figure 7). Currently, the costs are around $1,000 and that price is expected to fall even more when more commercial sequencing facilities are built (Ratain and Johnson 2014).
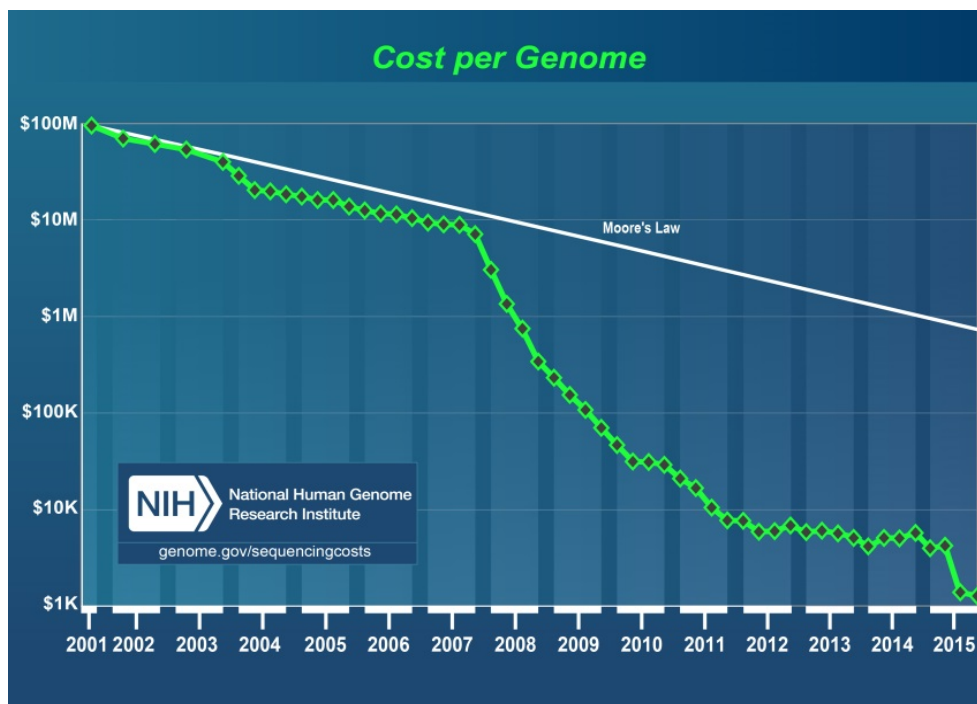
Figure 7. Decrease in costs per genome sequencing over time. Available at: www.genome.gov/sequencingcosts. Accessed the 4th of March 2016 (Courtesy: National Human Genome Research Institute)

In the near future, pre-emptive genotyping of the whole genome may therefore become an option, although opinions on the desirability of this differ. Once a whole or partial genome genotype is obtained, the results can be useful for the patient's entire life. Ideally, the genotype would be embedded in the patient's EMR, with prescribing aided by a decision-

support system. It is likely that this information will render clinical value, if not today then at some other time in the patient's life. However, this change of practice from a reactive approach (in which a fresh genetic test is ordered every time it is required) to a pre-emptive approach (in which a single sample is assessed for many likely-to-be actionable genes at the same time) is difficult to assess in terms of cost-effectiveness.

Assuming the costs will drop, cost-effectiveness studies could focus on how to interpret and deploy genetic variants to improve medication prescription. The aspect of timing also needs to be debated. Is it better to sequence early in life in advance (the results will be available for clinical use throughout their lifetime) or only when genotyping is requested? Yet informed consent in (pre-emptive) genotyping remains a challenge, fuelled by the patient's and his/her family's "right to know" and their "right not to know", which will potentially conflict with the clinician's duty of care (Rigter, Henneman et al. 2013).

Altogether, the reimbursement of pre-emptive genetic testing is not covered by health insurers to date, partly due to the transformative path of the pre-emptive approach, i.e. screening. Pharmacogenetic analysis is only reimbursed after initial medication in cases in which the medication turned out to cause severe side effects or was ineffective. Health insurers seem to be hesitant to reimburse screenings (Horgan, Jansen et al. 2014, Horgan, Paradiso et al. 2015). One of the barriers that impedes the clinical integration of genomics is the scepticism of providers and payers about the added value of genomics to improve patient care (Garcia, Kuska et al. 2012). This reluctance is driven in part by the somewhat sparse evidence of clinical usefulness. Certainly, public and private insurers will require robust evidence of the clinical-effectiveness and cost-effectiveness of prognostic tests and personalized treatment approaches before they endorse these approaches in health care. The lack of clear clinical utility criteria also contributes to this situation.

In cases involving 'therapeutics with companion diagnostics', another challenge arises with respect to the pricing and reimbursement authority, because it forms a combination of a medical device (the test) with a drug. This leads to new reimbursement assessment procedures. The way companion diagnostics are currently reimbursed differs greatly between (European) countries (Vijverberg 2013).

Still, it is difficult to compare the cost-effectiveness of genomic profiling efforts with classical medication therapies, since the procurement procedures differ. Diagnostics are funded as a part of a 'diagnosis-treatment combination' ('DBC/DOT')' (i.e. falling under the yearly budget that is hospital-specific), while medicines are financed separately. This hampers cost-benefit assessments according to interviewees.

On a higher level, the debate continues on the supposed cost-reduction benefits of PM in general. It is suggested that medical care costs will be reduced if personalized medicine addresses prevention rather than therapy (Dzau, Ginsburg et al. 2015). This was also stated by one of the interviewees. The very nature of personalized medicine, which is targeted, specific and personalized, must inevitably produce interventions

that are much more expensive than historically successful preventive interventions that have been applied broadly to populations. Joyner et al criticizes the fact that gene variant information increases physician visits, laboratory tests and patient anxiety, while genomic risk markers do not seem to improve patient compliance with risk-avoiding behaviours (Joyner and Paneth 2015). On the other hand, as one of the interviewees depicted, with the current debate on expensive medication, PM in the sense of genetic profiling could facilitate a better selection of patients (i.e. fewer patients) to enrol in extremely expensive drug therapies. Apart from this, conditional approval could help with the selection of the most effective medicine. And as one of the interviewees said, "Nowadays, only new medicines are being evaluated; why would we not do this for medicines that are already being marketed? In this way, we could aim for substitution instead of addition."

5.4   Data infrastructure

Various issues concerning data infrastructure arise. First of all, after genotyping, individual genomes are being stored at the centre where the sequencing took place. In the Netherlands, this is often a university hospital. However, as commercial facilities pop-up and the need for data sharing rises, policymakers should make a more conscious decision about how and where to store genomic data, as well as decide about the ownership of the data and the rights and duties that come with ownership. Consensus has yet to be reached regarding best practices in the governance of patient data.

Another aspect is the growing number of genomic banks. Catalogues of disease-related genes are being developed globally. Sharing these data and learning from them enable better insight into the disease and provide an expansion of therapeutic options. Especially in oncology, great efforts are being made to characterize the genomic landscape of tumours in order to identify oncogenic drivers and couple genetic alterations to treatment outcome. In the Netherlands, the Center for Personalized Cancer Treatment (CPCT) is the first large oncological gene profiling database that systematically analyses tumour genomes by Whole Genome Sequencing through the charity-funded Hartwig Medical Foundation (HMF).

Other profound challenges present are the harmonization of data and databases, patient privacy, cybersecurity and data sharing. Interviewees point to the government as the enabler of standardization and the interoperability of systems. From the clinician/research point of view, a cultural change is needed with respect to the willingness of researchers and clinicians to share their hard-earned data, although their sharing could violate their success of publication. A project in which this is seemingly overcome is GENIE, a transatlantic oncology data-sharing project. After sequencing a patient's tumour, GENIE members have three months to submit the data to Sage Bio networks, a non-profit organization in Seattle, Washington. For the next 6 months, only the contributing institution can see that patient's record within SAGE's database. For the subsequent 6 months, it will be open to the full consortium. Finally, the patient's data becomes available to the broader research community (Kaiser 2015).

Another question is how to update genomics data that is used for clinical decision-making to reflect the latest scientific discoveries. The consequences of certain variations in genes or gene panels today might turn out to be an overestimation or underestimation tomorrow. It is therefore crucial to revise information that is used in the clinic frequently. Agreements need to be reached on re-evaluating the significance of genes/gene panels and how frequently this is done (Gezondheidsraad 2015).

As mentioned in the previous chapter, data storage and computational capacity might cost much more than the sequencing activity itself. Indeed, sequencing technologies are producing data faster than most underlying IT infrastructures can support and store (Mardis 2011). Moreover, it is argued that the analysis of the files may require 5 to 10 times more storage than the storage of the raw data itself (Noor, Holmberg et al. 2015).

Lastly, additional issues specific to the Netherlands are the way in which research and clinical practice are separately funded and the way biobanks (patient databases in general) are viewed in terms of privacy, security requirement, regulatory requirements, etc. In the case of genomic databases where patient data is being collected from which to learn, such as the database of the CPCT/HMF, clinical and research practice are intertwined. Yet under the current regulatory system and governmental funding structures, this is very difficult to set up. As one of the interviewees said, "If we do not invest in a system that enables biomedical research to learn from patient profiles today, we won't be able to help patients in the near future."

5.5   Marketing authorization system

The marketing authorization of medicinal products is facing the challenges presented by products produced for smaller patient groups and, hence, changes in the level of benefit-risk evidence. Since RCTs may not be feasible owing to small groups of patients, alternative trial designs (e.g. n=1 trials) and other ways of providing clinical evidence (e.g. computer modelling, retrospective studies) are inevitable with a decrease in the level of evidence. This more limited amount of clinical data on the efficacy and safety of a drug may also affect reimbursement decisions and, hence, accessibility. For a general discussion on the sustainability of the marketing authorization system, reference is made to the RIVM report "Minds open: Sustainability of the European regulatory system for medicinal products".

A specific challenge is the alignment of medical device legislation, on the one hand, and medicinal products, on the other. For a discussion on this challenge, reference is made to the RIVM report "Personalized medicinal products: evaluation of the regulatory framework". The absence of alignment also affects reimbursement, with the dynamics of market access being different for medicines from what it is for companion diagnostics.

5.6 Research & development

Drug companies tend to develop medicinal products based on sales made to the general population or to specific disease populations for which no cure yet exists. In the case of stratified medicine, however, the market becomes more segmented and is thus smaller. When the volume of the drug prescription shifts from an initial broad indication to a narrower, yet highly effective indication, their return on investment is reduced. From a societal point of view, however, the stratification can lead to significant cost reductions and less deception of patients.

Moreover, companies have pursued the development of companion diagnostic tests only for new compounds and not for drugs already marketed. This has led to very limited research and development on a particular biomarker discovery for companion diagnostics (Ahmed, Saaem et al. 2014). Yet for new compounds, a companion diagnostic can reduce the costs of trials and ameliorate the success rate as it provides a better inclusion criterion for patients to enter the trial. Still, this renders companion diagnostic testing only viable in the trial setting.

As trials are increasingly being funded by industry, this poses a challenge for the implementation of stratified medicine in the clinic. As expressed by interviewees, research and trials on existing medicines, especially off-patent medicines, are not worthwhile to the industry. This gap should be covered by funding agencies (including health insurers and governmental agencies). They should recognize the need for clinical validity (including the desired level of evidence) and clinical utility studies, including cost-effectiveness studies, on:
> 1) current medicines for which pharmacogenomics could significantly reduce severe adverse events, improve treatment outcome and reduce health care costs (through substitution), and
> 2) companion diagnostics that can differentiate between subgroups that will and won't benefit from a certain therapeutic treatment.

Lastly, when quantifying the benefits or effectiveness of a certain medicine, HTA bodies focus mostly on health-related outcomes. Yet especially with regard to PM, only valuing the health gain seems insufficient. At a societal level, the information from a companion diagnostic will potentially enable a reduction in the waste of scarce resources by preventing the use of expensive medicine in patients who will not respond. At an individual level, both patients and clinicians may be reassured that the additional information from a test, even though it's probabilistic, will help to more accurately target a medicine. The clinician may feel more certain about treatment selection and patients may feel more certain that they are receiving the best possible treatment (Payne and Annemans 2013, Shabaruddin, Fleeman et al. 2015).

5.7 Ethical, legal and social issues

Ethical, legal and social issues are given broad attention within the area of genetics. Below, we only briefly touch on the elements under discussion.

Privacy is a frequently mentioned aspect of concern and is linked to the ownership of data, access to data and liability. Privacy is much more of a concern in genomics than it is in other –omics technologies and even

biobanks, because a genetic profile is a permanent, lifelong, unique signature of a person – a 'gene passport', as it were. It doesn't change in time, except for somatic mutations. Moreover, due to the large amount of information from PM that might be captured in biobanks, informed consent to use the patient data for research/innovation is increasingly challenging. For that reason, a layered and staged model of consent has been proposed: some information becomes immediately available to everyone; more detailed information becomes available to those who seek to keep the core information comprehensible and manageable. Moreover, informed-consent information is not provided all at once, so patients are provided with more time to absorb the information step by step (Joly, Saulnier et al. 2014).

Interfamilial privacy issues are a next topic of interest (Joly, Saulnier et al. 2014). The rights of patients' relatives to receive medical information that may impact them should be carefully weighed against individual patient privacy and autonomy. Also, there is a clear difference between storing genetic and genomic data for research and storing it for clinical purposes. Storing all genetic information of clinical use might result in more privacy issues. Making data available to different health care workers or researchers may increase the amount of information that becomes available to third parties, such as insurance companies or employers. This leads to the following concern that genetically at-risk individuals might be excluded from many goods, services and activities. Policymakers are therefore motivated to implement legislative solutions to overcome and prevent genetic discrimination. In addition, insurers at both the national and international levels should adopt policies that explicitly state that they will not seek access to the results of genetic tests (Joly, Saulnier et al. 2014).

The introduction of multigene or whole genome sequencing further blurs the distinction between data used for scientific research, for clinical trials, for medical practice (e.g. diagnostics) and for public health interventions (e.g. screening). Moreover, knowledge on genetic make-up does not necessarily mean that there is a suitable therapeutic (or preventive) option in cases of disease (risk). Finally, when new scientific insights are gained which have clinical implications (for example, knowledge of cancer risk), it can be questioned whether a person/patient should be re-contacted or not (Gezondheidsraad 2015).

6   Considerations and recommendations

6.1   Remarks on this report

The current clinical applications in Chapters 3 and 4 have been restricted to medicinal products with marketing authorization in the Netherlands (including products registered via EMA/EC), which include pharmacogenomics information in the SmPC. So medicinal products for which pharmacogenomics information is only available in literature or guidelines (but not in the SmPC) were excluded. This choice was made because literature data and guidelines do not reflect the outcome of a formal benefit-risk assessment by competent authorities.

The developments and future perspectives of PGx described in Chapters 3 and 4 are based on reviews published in scientific literature. It is conceivable that there is more on the horizon than seen in these reviews because recent developments may not yet have been subjected to review articles. However, by choosing reviews as the basis for these chapters, we feel we have captured the majority of areas in which substantial progress has already been made and in which perspectives on any future applications are, in most cases, clearer than expected for very recent research findings in other areas. Moreover, research in the field of PGx is abundant, with more than 9,000 hits in Pubmed when searching for 'personalized medicine' or 'targeted therapy' within the period 2010-2015. Taking only reviews into account made the literature search surveyable without compromising the aim of this study (i.e. a helicopter view aiming to support policymakers in prioritizing actions in the field of PGx).

6.2   Helicopter view

Ever since the Human Genome Project in 2001, there have been high expectations for pharmacogenetics in health care. PGx has the potential to gain insight into the inter-individual variation and thereby contribute to 'customized' therapy. However, the contribution of genomics to observed differences in effects should not be overestimated; other biological processes also account for observed phenotypes (disease states), such as mRNA sequences (transcriptomics), DNA structure dynamics (epigenomics), protein turnover (proteomics), metabolites and gut flora (metabolomics). In addition, many other physiological, environmental and social factors may influence the outcome of pharmacotherapy. Examples of contributing factors are co-medication, co-morbidity, disease stage, age, kidney function, liver function, adherence to therapy, food and smoking. The relative contribution of each factor to a specific disease state will be of great importance to assessing what information is clinically relevant and which technique is needed to obtain that information.
Within PGx, two different directions are being pursued for each different potential and challenge. Research focuses either on optimizing the drug response or on the development of new drugs that specifically targeted a gene.

In optimizing drug response based on gene-drug interactions, for various medicinal products research has led to usage warnings, monitoring requirements or contra-indications in the SmPC due to potentially severe side effects. But for the majority of products with PGx information in the SmPC, no action is mentioned or considered necessary when testing is performed. This lack of information has been partly overcome by professional health care guidance. Yet clinical validity and utility are still debated and form two essential factors that currently hamper reimbursement and adoption in clinical practice. Research in this area of optimizing drug response focuses on the implementation of PGx in first-line health care, on specific disease areas with large numbers of patients, such as COPD/asthma and diabetes, and on areas where early effective treatment will make a difference, such as inflammatory diseases.

In the last few years, substantial progress has been made in the development and market approval of new medicinal products aimed at gene-based targeting of a disease, especially in cancer treatment. Currently, substantial efforts are being devoted to the development of genetic banks to enable better stratification of subgroups (for example the CPCT in the Netherlands). But opinions differ as to whether this progress currently contributes, to a large extent, to overall cancer survival. A consistent genetic defect allows for the development of a drug specifically targeting this defect. However, most cancers / diseases are quite complex in terms of genomics. Research in the gene-based targeting of a disease focuses on oncology, rare diseases and organoid technology. Organoids present the opportunity to bridge the current experimental gap between sequencing efforts in cancer and patient outcome. They have great potential, yet more research is needed to see whether organoid technology truly lives up to expectations.

There are still many challenges ahead for the implementation of PM in health care. This starts with (the funding of) research and development. But it also includes amendments to the marketing authorization system and the system for reimbursement may be necessary due to changes in the amount and nature of clinical (evidence) data that becomes available. Specific attention should also be paid to clinical utility: the determination whether the use of a genetic test leads to improved health outcomes. It is not yet clear what kind of data is necessary to assess clinical utility. And finally, another element that is important to address is data infrastructure and the ethical, legal and social issues related to this.

6.3 Recommendations for Dutch policy

Research funding
1. Prioritize research-funding of PM based on potential clinical utility. Focus on (existing) medicinal products and the development of suitable diagnostic techniques enabling the efficient use of these medicines. Give priority to:
- Diseases for which the effectiveness of medicinal products is largely variable, leading to (unacceptable) variability in the burden of disease;

- Medicinal products with serious side effects that may be prevented by the application of PM;
- Medicinal products for which the time needed to evaluate the clinical effects is relatively long, while the nature of the disease is progressive;
- Medicinal product groups with high budget impact (either due to price or volume).
  Establish priority areas (diseases/medicines/diagnostics) in dialogue with patients' organizations, health care professionals and other experts. Call stakeholders with a financial interest to account for their (social) role as co-financers.

Rationale behind this recommendation: Technical progress in PM tends to focus on what can be measured, without necessarily taking into account what would be useful to measure. The clinical relevance of testing is not always clear and also cost-effectiveness data are largely missing. In addition, there are currently no incentives to invest money in clinical trials with medicinal products that are out of patent, while for some products important clinical problems may be (partly) addressed by PM research. Finally, there are high medical need areas in which PM research could result in (new) pharmacotherapeutic options.

2. Start a route to intertwine research and clinical practice more extensively, including the financing of both. This should be done in such a way that data from clinical practice can be used for research more easily and research knowledge van be used more quickly in clinical practice. Before starting this route, it is imperative to map out the opportunities and challenges in this intertwinement.

Rationale behind this recommendation: The increasing number and affordability of new measuring techniques in PM will lead to the expansion of genomics (and other -omics) data obtained in medical practice. Because of the technological advancements and the need for patient samples in research from which to learn, research disciplines and clinical practice are becoming intertwined. Moreover, implementing and using PM in clinical practice requires knowledge and input from many disciplines, such as biology, pathology, pharmacology, mathematics, genetics, physics, bioinformatics and medical science. Interdisciplinary co-operation between researchers and the various disciplines within medical practice will foster knowledge building that can better guide individualized patient care.

Data infrastructure
3. Put a suitable framework in place for patient data generated and stored within the scope of Personalizsed Medicine. Think of the preparation of guidelines for storage, ownership and possibilities to couple databases. Labour for counterbalancing and/or preventing the fragmentation of initiatives for data storage. Establish what will be necessary for the good governance of data for research, implementation in health care and reimbursement decisions.

Rationale behind this recommendation: Currently, data on genotyping are often generated by university centres. The future expectation is that other (commercial) parties or institutions will increasingly provide these

facilities. This raises questions regarding data ownership, privacy and data exchange, as well as quality, standardization and the costs of (decentralized) testing. This is applicable to both raw and analysed data. Besides these challenges, opportunities arise to increase our knowledge of disease mechanisms, therapeutic options and the effects of therapeutic interventions owing to the generation of huge amounts of electronically available data. However, the full potential of this data can only be exploited when it is shared and connected with other (clinical) data. Currently, there is a patchwork of various national and international initiatives in this area. It is however unclear how the data can be used optimally for research, health care and reimbursement decisions.

Regulatory system
4. Assess the implications of changes in the amount and nature of clinical evidence data for the regulatory systems of marketing authorization, reimbursement and health care economics. Also check whether there are any hurdles to be overcome in the application of Personalized Medicine.

Rationale behind this recommendation: PM implies the prescription of a medicinal product to a subset of patients or even tailored to one single patient. The current standards for marketing authorization and cost-effective analysis, usually a randomized controlled trial, are not always possible, often due to the small number of patients. Therefore, other trial designs and other levels of evidence in order to prove clinical efficacy and safety may be necessary. Examples of this are n-of-1 clinical trials, adaptive designs, models for prediction of response, the use of longitudinal data and the use of real life data. Research on these alternative ways of designing and analysing trials is currently performed as part of various research programmes. In addition, it is expected that in the near future pre-emptive genomic testing will increase, which enriches the availability of data at an early stage and during patients' lives. The question arises as to what consequences these changes in available patient information and clinical data would have for the current regulatory systems; for example, regarding the method used to assess risk-benefit and cost-effectiveness, and setting conditions for (continued) approval or reimbursement.

5. Activate the European Medicines Agency and Heads of Medicines Agencies to extend the existing Summary of Product Characteristics (SmPCs) of medicinal products with guidance on how to handle them in cases of specific genetic variants if handling perspectives are known and supported by adequate scientific evidence. Check how SmPCs can be kept up to date as the state-of-the-art science changes quickly in PGx research.

Rationale behind this recommendation: For a number of medicinal products, including many medicines that have been assessed by the Dutch Pharmacogenetics Working Group, the SmPC mentions the possible genetics variants that may influence the efficacy and/or safety of the product. However, in many of these SmPCs, information on how to handle them in cases of specific variants is missing. From a legal viewpoint, SmPCs should reflect current scientific knowledge relevant to the safe and effective use of a product. This is especially important

because the SmPCs are directly or indirectly used as an information source for formularies, prescription guidelines and databases used by health care professionals. Availability of up-to-date information will foster the implementation of PM in clinical practice. So, if knowledge of possible action in cases of genetic variants is available, this should preferably be included in the SmPC.

Implementation in clinical practice
6. Call on The National Health Care Institute (Zorginstituut Nederland) to take direction, in cooperation with the Dutch Medicines Evaluation Board, other (governmental) stakeholders and experts, to provide guidance on the kind of data needed to assess clinical utility and cost-effectiveness of PGx. Take into account any European / international developments in this area.

Rationale behind this recommendation: Although, for a significant number of active substances, scientific information on associations between genomics and drug behaviour in the body is available, implementation of the use of genomics in clinical practice is lagging behind, especially in first-line health care and disease areas other than oncology and rare disease. The barriers for implementation are well-known and are mostly related to aspects relevant for determination of clinical utility. One of these aspects is cost-effectiveness, which (partly) falls under governmental concern. For cost-effectiveness analysis, several specific characteristics of PM deviate from conventional one-size-fits-all pharmacotherapy, e.g. prevalence of genetic polymorphisms and their relative contribution to variability in drug response, availability of genomics information due to pre-emptive testing, and (im)possibilities regarding level of evidence. In order to support the implementation of useful and cost-effective genotyping with subsequent pharmaceutic intervention, it would be helpful to establish what kind of data is needed to assess clinical utility. This can be done for various scenarios taking into account disease characteristics, mechanistic knowledge on gene-drug interaction, size of the effect of the pharmaceutic intervention, availability of genomic information in advance, etc.

7. The recommendation is to raise awareness and understanding amongst the general public regarding the possibilities and limitations of genetic testing and to empower patients to make informed decisions. Rationale behind this recommendation: Genetic testing will inevitably reach an increasing patient population in due course. Awareness activities should focus on informing people about possible applications and the kind of testing options that may be offered to them, including the issues related to genetic testing (e.g. privacy, data ownership, incidental findings, risk concepts). Empowerment is necessary for shared decision-making in cases in which genetic testing will be offered as an opportunity in pharmaceutical care or other health care options, including prevention. Informing the general public may avoid uninformed testing on one's own initiative.

8. Stimulate the preparation of guidelines for the collection of genetic data and information and other data that may be needed for Personalized Medicine. These guidelines should at least standardize:
  * clinical sampling;

- analytical testing;
- data analysis;
- data interpretation;
- data storage;
- data exchange;
- visualization of data for health care professionals and patients.

Rationale behind this recommendation: Implementation of PM in clinical practice is partly hampered by the lack of standardization in genomics data generation and handling. Also, data should be visualized in a way that provides clarity for the treating physician and for the patient. Stakeholders such as health care professionals, health insurance companies and testing facilities should join forces to boost standardization.

9. Stimulate the uptake of Personalized Medicines in guidelines for health care professionals in order to advance application in clinical practice. Take into consideration clinical utility in the preparation of these guidelines.

Rationale behind this recommendation: Guidelines will play a crucial role in the uptake of PM in clinical practice. The inclusion of PM in guidelines should be supported, together with efficient ways to quickly update guidelines when new information becomes available. These guidelines should be prepared by health care professionals in consultation with patients, when possible.

Education
10. Health care providers, including physicians, pharmacists and nurses, need to be trained more intensively to generate (pharmaco)genomic data and other –omics data, to interpret these data and to learn how to make clinical decisions based on these data. Education is also needed for them to be able to discuss the pros and cons of genetic testing with patients.

Rationale behind this recommendation: Currently, implementation of PM seems to be partly hampered by the limited knowledge of the health care professionals.

11. Stimulate education of bio-informatics' experts/statisticians in order to be able to interpret large datasets related to personalized medicine.

Rationale behind this recommendation: In the near future, a lot of individual data will be generated and electronically stored. The potential knowledge that may be gained from these data is huge, but needs the expertise of 'big data' analysts.

7 Conclusion

Many of the hurdles in translating PM research to clinical practice that have been mentioned in this report are interconnected. A great deal seems to be caused by the very nature of PM and its findings. Results do not seem to fit in well with the current (regulatory) assessment designs. This is especially the case with the assessment of clinical validity (trial designs), clinical utility (which criteria, incl. cost-effectiveness) and reimbursement (how to deal with pre-emptive testing). In addition, a whole new dimension is being added to the system, namely that of privacy-sensitive patient data (i.e. genomic profile) that raises many questions about how data-sharing is becoming a requirement for good clinical and research practice, together with its infrastructure set-up (how to, who, ownership, etc.). Policymakers should address these issues and provide citizens with safe and effective solutions, or at least facilitate/stimulate their development.

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Annex A List of interviewees

Prof. dr. Hans Clevers, Hubrecht Institute (NL); Princess Maxima Center (NL)
Prof. dr. Edwin Cuppen, UMC Utrecht (NL)
Prof. dr. Alain van Gool, Radboudumc (NL)
Prof. dr. Henk-Jan Guchelaar, LUMC (NL)
Prof. dr. Cecile Janssens, Emory University (USA); VUmc (NL)
Dr. Anke-Hilse Maitland-van der Zee, UU (NL)
Prof. dr. Maarten Postma, RUG (NL)
Prof. dr. Peter van der Spek, Erasmus MC (NL)
Prof. dr. Bob Wilffert, RUG (NL); UMCG (NL)

Annex B Interview topics

Application of current knowledge

1. What kinds of applications are currently broadly used in your area of expertise?

2. Is all relevant available knowledge currently used in clinical practice or is specific knowledge not applied? If not, why not?

Future applications

3. What kinds of applications are currently developed and are expected to be used in the upcoming 5 to 10 years? What chances does this give? Are there any inhibitory factors?

Chances and hindrances

4. What chances do you see in the future development and application of PM (such as implementation in health care, pricing and reimbursement, data infrastructure, ethical and privacy aspects, education, research funding, any other aspects)?

5. What hindrances do you see in the future development and application of PM (such as implementation in health care, pricing and reimbursement, data infrastructure, ethical and privacy aspects, education, research funding, any other aspects)?

Annex C Currently approved medicinal products with pharmacogenomics information in the SmPC

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Abacavir	Infectious disease	HIV infections	HLA-B*5170	Carriers of HLAB*5701 have a significantly higher risk of Abacavir hypersensitivity reaction.	Usage warning	ODR	2nd line	1999
Afatinib	Oncology	Lung cancer	EGFR	Afatinib is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).	Indication	GBDT	2nd line	2013
Allopurinol	Metabolics/ Endocrinology	Hyperuricemia	HLA-B*5801	Carriers of HLAB*5801 have a significantly higher risk of Allopurinol hypersensitivity reaction and Stevens-Johnson syndrome/Toxic epidermal necrolysis.	Usage warning	ODR	1st line	1968
Amitriptyline	Psychiatry	Depression	CYP2C19 and CYP2D6	Amitriptyline is mainly metabolized by CYP2C19. Therefore, poor activity of CYP2C19 will result in higher plasma levels and more adverse events.	Dose adjustment	ODR	1st line	1972

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Anastrozole	Oncology	Mammacarcinoma	ER receptor	Treatment of hormone receptor positive breast cancer.	Indication	GBDT	2nd line	1995
Arsenic trioxide	Oncology	APL leukemia with translocation of t(15;17) and/or presence of PML/RARα fusion protein	PML/RARα	Arsenic trioxide is indicated in patients with the PML/RARα fusion protein and/or translocation of t(15;17).	Indication	GBDT	2nd line	2005
Atomoxetine	Psychiatry	ADHD	CYP2D6	CYP2D6 poor metabolizers have a significantly higher risk of developing adverse events.	Dose adjustment	ODR	1st line	2008
Atorvastatin	Metabolics/ Endocrinology	Hypercholesterolemia	SLCO1B1	Patients with genetic polymorphism SCLO1B1 521TC - 521CC have an higher risk on developing myopathy because of decreased transport to the liver.	Contra-indication/dose adjustment	ODR	1st line	1997
Azathioprine	Rheumatology	Rheumatoid artritis	TPMT	Patients with poor TPMT status have a higher risk of developing excessive drug toxicity (myelosuppression and opportunistic infections).	No action	ODR	2nd line	1963

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Boceprevir	Antivirals	Hepatitis	IL28B	The genetic variation IL28B rs12979860 is a strong predictor of drug response.	No action	GBDT	2nd line	2011
Bosutinib	Oncology	Chronic myelogenous leukaemia	BCR-ABL gene (Philadelphia Chromosome)	Bosulif is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia.	Indication	GBDT	2nd line	2013
Brentuximab	Oncology	Hodgkin lymphoma	CD30	Brentuximab is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma.	Indication	GBDT	2nd line	2012
Cabozantinib	Oncology		RET, RAS	RET mutation negative patients with no evidence of RAS mutation showed a decreased progression free survival benefit on cabozantinib (HR of 0.87) and a lower response rate of 18% compared to other mutational subgroups.	No action	GBDT	2nd line	2014
Capecitabine	Oncology	Cancer	DPD	DPD deficiency can lead to extreme toxicity.	Contraindication	ODR	2nd line	2001

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Carba-mazepine	Neurology	Epilepsy	HLA-B*1502	Presence of the HLAB*1502 allele is a strong predictor for the Stevens-Johnson syndrome.	Usage warning	ODR	2nd line	1965
Celecoxib	Analgesics	Pain	CYP2C9	Slow CYP2C9 metabolizers need caution with Celecoxib because the risk of dosage-dependant adverse events is increased.	Dose adjustment	ODR	2nd line	1998
Ceritinib	Oncology	Lung cancer	ALK	ALK-positive NSCLC status should be established prior to initiation of Zykadia therapy.	Indication	GBDT	2nd line	2015
Cetuximab	Oncology	Colorectal cancer	EGFR and KRAS	Cetuximab is indicated in EGFR expressing and KRAS wild-type metastatic colorectal cancer	Indication	GBDT	2nd line	2004
Citalopram	Psychiatry	Depression	CYP2C19 and CYP2D6	Citalopram is mainly metabolized by CYP2C19. Therefore, poor activity of CYP2C19 will result in higher plasma levels and more adverse events.	Dose adjustment	ODR	1st line	1995
Clopidogrel	Cardiology	Prevention of atherothrom-botic and thromboem-bolic events	CYP2C19	CYP2C19 PM status is associated with diminished response to Clopidogrel.	No action	ODR	1st line	1998

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Codeine	Central nervous system	Pain	CYP2D6	Ultrarapid metabolizers may experience opioid toxicity. Pore metabolizers may experience no adequate effect.	Contra-indication	ODR	1st line	unknown
Crizotinib	Oncology	Lung cancer	ALK	Indicatie for ALK-positive advanced non-small cell lung cancer.	Indication	GBDT	2nd line	2012
Dabrafenib	Oncology	Melanoma	BRAF V600E	Dabrafenib is indicated in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	Indication	GBDT	2nd line	2013
Dapsone	Dermatology/ Dentology	Leprosy	G6PD	More side-effects (haemolysis) in seriously G6PDdeficient patients.	Contra-indication	ODR	2nd line	1952
Dasatinib	Oncology	Leukaemia	BCR-ABL gene (Philadelphia Chromosome)	Dasatinib is effective only in Philadelphia chromosome-positive patients.	Indication	GBDT	2nd line	2006
Dextromet-horphan	Neurology	Cough and Pseudobulbar Affect in patients with ALS or MS	CYP2D6	CYP2D6 PM and EM patients have different first-pass effect.	No action	ODR	1st line and 2nd line	1953

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Eliglustat	Metabolics/ Endocrinology	Gaucher disease	CYP2D6	The recommended dose is 84 mg twice daily in CYP2D6 intermediate and extensive metabolizers. The recommended dose is 84 mg once daily in CYP2D6 poor metabolizers.	Dose adjustment	ODR	2nd line	2015
Erlotinib	Oncology	Lung cancer	EGFR	Erlotinib is effective only on EGFR-positive tumours.	Indication	GBDT	2nd line	2005
Escitalopram	Psychiatry	Depression and anxiety	CYP2C19	CYP2C19 PM has a twofold higher plasma level of Escitalopram than EM.	Dose adjustment	ODR	1st line	2004
Esomeprazole	Gastro-enterology	Gastro-oesophageal reflux	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 action	ODR	1st line	2000
Everolimus	Oncology	Mamma carcinoma	HR+ and HER2-	Everolimus is indicated for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer.	Indication	GBDT	2nd line	2009
Exemestane	Oncology	Mamma carcinoma	ER receptor	Exemestane is indicated as adjuvant therapy in post-menopausal women with ER-positive breast cancer.	Indication	GBDT	2nd line	1999

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Fluorouracil	Oncology	Treatment of common malignancies particular of the colon and breast.	DPD	DPD deficiency results in 5-FU toxicity.	Contraindication	ODR	2nd line	1962
Fluvoxamine	Psychiatry	Depression and obsessive compulsive disorders	CYP2D6	Differences in CYP2D6 status are not clinically relevant.	No action	ODR	1st line	1985
Fulvestrant	Oncology	Mamma carcinoma	ER receptor	Fulvestrant is indicated for oestrogen receptor-positive cancer.	Indication	GBDT	2nd line	2004
Galantamine	Neurology	Dementia and Alzheimer's disease	CYP2D6	Differences in CYP2D6 status are not clinically relevant.	No action	ODR	1st line	1991
Gefitinib	Oncology	Lung cancer	EGFR and CYP2D6	Gefitinib has no clinically relevant activity in EGFR mutation-negative tumours. CYP2D6 PMs have a greater risk of developing adverse events.	Indication and close monitoring	GBDT, ODR	2nd line	2002
Ibrutinib	Oncology	Chronic lymphocytic leukaemia	17p and/or TP53	Ibrutinib is indicated in patients with chronic lymphocytic leukaemia in the presence of 17p deletion or TP53 mutation.	Indication	GBDT	2nd line	2014

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Idelalisib	Oncology	Chronic lymphocytic leukaemia	17p and/or TP53	Idelalisib is indicated in patients with chronic lymphocytic leukaemia in the presence of 17p deletion or TP53 mutation.	Indication	GBDT	2nd line	2014
Imatinib	Oncology	Leukaemia	C-kit, BCR-ABL gene (Philadelphia Chromosome), PDGFR and FIP1L1-PDGFRα	Imatinib is indicated in one or a combination of the displayed biomarkers.	Indication	GBDT	2nd line	2001
Irinotecan	Oncology	Colorectal cancer	UGT1A1	Homozygous UGT1A1*28 patients have a higher risk of developing hematological toxicity at regular and high irinotecan doses (>150mg/m2).	Close monitoring	ODR	2nd line	1998
Ivacaftor	Pulmonology	Cystic fibrosis	CFTR	Ivacaftor is indicated for patients with cystic fibrosis with one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.	Indication	GBDT	2nd line	2012

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Lansoprazole	Gastro-enterology	Duodenal and gastric ulcer, reflux oesophagitis, Zollinger-Ellison syndrome, gastroesophageal reflux disease	CYP2C19	Exposure to Lansoprazole is much higher in CYP2C19 PM than EM.	No action	ODR	1st line	1993
Lapatinib	Oncology	Mamma carcinoma	Her2/neu	Lapatinib is effective in tumours over expressing Her2.	Indication	GBDT	2nd line	2008
Lenalidomide	Haematology/ Oncology	Myelodysplastic syndromes	Chromosome 5q	Lenalidomide is especially effective in patients with a deletion on chromosome 5q.	No action	GBDT	2nd line	2007
Letrozole	Oncology	Mamma carcinoma	ER receptor, PR and HER2	Letrozole is indicated as adjuvant therapy in postmenopausal women with ER-positive breast cancer	Indication	GBDT	2nd line	1997
Maraviroc	Infectious disease	HIV infections	CCR5	Maraviroc is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable.	Indication	GBDT	2nd line	2007
Mercapto-purine	Oncology	Leukaemia	TPMT	TPMT-deficient patients are likely to develop severe toxicity.	Close monitoring	ODR	2nd line	1967
Moclobemide	Psychiatry	Depression	CYP2C19	CYP2C19 PMs could have a decreased metabolism	No action	ODR	1st line	1991

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Nilotinib	Oncology		BCR-ABL gene (Philadelphia Chromosome)	Nilotinib is indicated in newly diagnosed Philadelphia chromosome-positive patients.	Indication	GBDT	2nd line	2007
Nortriptyline	Psychiatry	Depression	CYP2D6	The metabolism of nortriptyline is subject to genetic polymorphism (CYP2D6).	No action	ODR	1st line	1964
Olaparib	Oncology	Ovarian cancer, fallopian tube cancer, primary peritoneal cancer	BRCA1 and BRCA2	Patients must have confirmation of a breast cancer susceptibility gene (BRCA) mutation (either germline or tumour).	Indication	GBDT	2nd line	2014
Omeprazole	Gastro-enterology	Gastro-oesophageal reflux	CYP2C19	CYP2C19 PMs have different pharmacokinetic values.	No action. These differences have no implications on the dosage (SPC section 5.2)	ODR	1st line	1988
Panitumumab	Oncology	Colorectal cancer	EGFR and KRAS	Indicated for patients with the wild type KRAS protein.	Indication	ODR	2nd line	2006

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Pertuzumab	Oncology	Mamma carcinoma	Her2/neu	Pertuzumab is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.	Indication	GBDT	2nd line	2013
Phenytoïn	Neurology	Epilepsy	HLA-B*1502 and CYP2C9	HLA-B*1502 is possibly correlated with Stevens-Johnson syndrome in Han Chinese and Thai patients.	Usage warning	ODR	2nd line	1938
Ponatinib	Oncology	Leukaemia	BCR-ABL gene (Philadelphia Chromosome)	Ponatinib is indicated in Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) that are resistant to dasatinib	Indication	GBDT	2nd line	2013
Regorafenib	Oncology	Colorectal cancer, gastrointestinal stromal tumours	KRAS	In view of the substantial toxicity related to treatment, physicians are recommended to carefully evaluate benefits and risks when prescribing regorafenib in patients with KRAS mutant tumours.	Usage warning	GBDT	2nd line	2013

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Rituximab	Oncology	Non-Hodgkin's lymphoma	CD20	Rituximab is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma.	Indication	GBDT	2nd line	1998
Sertraline	Psychiatry	Depression, anxiety, obsessive compulsive disorder, post-traumatic stress disorder	CYP2C19	CYP2C19 PMs have 50% higher plasma concentrations than EMs.	Close monitoring	ODR	1st line	1990
Simvastatin	Metabolics/ Endocrinology	Hypercholesterolemia	SLCO1B1	Patients carrying the SLCO1B1 gene allele, coding for a less active OATP1B1 protein, have an increased systemic exposure of simvastatin acid and increased risk of myopathy.	Not mentioned in SPC	ODR	1st line	1988
Sofosbuvir	Infectious disease	Hepatitis C	IL28B	IL28B non CC genotype has been associated with lower response rates to interferon-based therapies.	No action	ODR	2nd line	2014

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Tacrolimus	Graft rejection	Immunosuppression after organ transplantation	CYP3A5	It has been shown that black patients may require higher doses than whites or Asians because of polymorphism in the CYP3AP1 pseudogene producing a change in CYP3A5 activity.	Not mentioned in SPC	ODR	2nd line	2007
Tamoxifen	Oncology	Mamma carcinoma	ER receptor, CYP2D6	Tamoxifen is indicated in hormone-dependent tumours. CYP2D6 PM may have lower response to Tamoxifen because of lower levels of Endoxifen.	Indication and no action	GBDT, ODR	2nd line	1982
Tegafur	Oncology	Gastric cancer	DPD	Tegafur is contraindicated for DPD PM patients.	Contra-indication	ODR	2nd line	2011
Telaprevir	Infectious disease	Hepatitis C	IL28B	Patients with the IL28B (IFNL3) CC genotype compared to those with CT or TT when treated with the telaprevir, peginterferon alfa-2a and ribavirin drug combination.	Not mentioned in SPC	ODR	2nd line	2011
Thioguanine	Oncology/ Immunology	Leukaemia, Inflammatory bowel disease	TPMT	TPMT-deficient patients are likely to develop severe toxicity.	Close monitoring	ODR	2nd line	1975
Toremifene	Oncology	Mamma carcinoma	ER receptor	Fareston is not recommended for patients with estrogen receptor negative tumours.	Indication	GBDT	2nd line	1996

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Tramadol	Central nervous system	Pain	CYP2D6	Poor metabolizers have been shown to have much lower median values of area under the concentration–time curves for the active metabolite. Poor metabolizers more often fail to exhibit analgesia.	Contra-indication	ODR	1st line	1992
Trametinib	Oncology	Melanoma	BRAF V600E	Trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	Indication	GBDT	2nd line	2014
Trastuzumab	Oncology	Mamma carcinoma	Her2/neu	Herceptin should be used only in patients with Her2 overexpression or Her2 gene amplification.	Indication	GBDT	2nd line	2000
Trastuzumab emtansine	Oncology	Mamma carcinoma	Her2/neu	Trastuzumab emtansine should be used only in patients with HER2 positive tumour status.	Indication	GBDT	2nd line	2013
Vandetanib	Oncology	Thyroid cancer	RET	Patients without RET mutation may have a decreased benefit from vandetanib treatment and the benefit/risk balance for this group of patients may therefore differ from that of the group with RET mutations.	No action	GBDT	2nd line	2012

Active substance	Pharmaco-therapeutic area	Disease	Biomarker(s)	Clinical effect related to the biomarker	Type of action prescribed in SmPC	GBDT or ODR*	1st/2nd line health care	Year of approval
Vemurafenib	Oncology	Melanoma	BRAF V600E	Before taking vemurafenib, patients must have BRAF V600 mutation-positive tumour status.	Indication	GBDT	2nd line	2012
Venlafaxine	Psychiatry	Depression, anxiety	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 action	ODR	1st line	1993
Voriconazole	Antifungals	Candida infection	CYP2C19	CYP2C19 PMs have a 4-fold higher exposure (AUC) to Voriconazole than EMs. CYP2C19 IMs have a 2-fold higher exposure.	No action	ODR	2nd line	2004

*GBDT = Gene-Based Drug Targeting; ODR = Optimizing Drug Response