De waarde van "big data" om therapietrouw op populatie niveau te bestuderen

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2

Wat aan bod komt

- Hoe kunnen we therapietrouw meten met 'big data'?
- Wie lopen er risico: selectie op basis van apotheekdata?
- Relatie therapietrouw - uitkomsten

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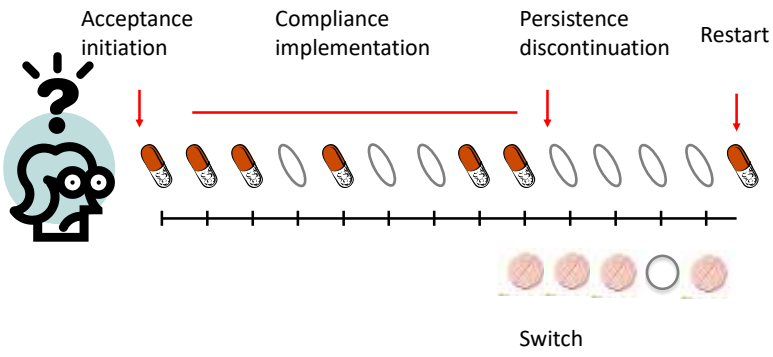
3

Adherence phases



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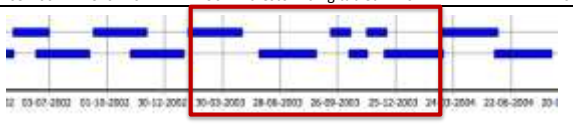
Database with prescriptions: longitudinal data

Date	ATC	Quantity	Drug	Use	Strength
07-05-2002	C10AA01	56	zocor 20mg tablet	1D1T	20
12-06-2002	C10AA01	84	zocor 20mg tablet	1D1T	20
09-09-2002	C10AA01	84	zocor 20mg tablet	1D1T	20
06-11-2002	C10AA01	84	zocor 20mg tablet	1D1T	20
05-02-2003	C10AA01	84	zocor 20mg tablet	1D1T	20
26-05-2003	C10AA01	90	simvastatine merck 20mg tab	1D1T	20
15-09-2003	C10AA07	30	crestor 10mg tablet filmomh	1D1T	10
13-10-2003	C10AA07	30	crestor 10mg tablet filmomh	1D1T	10
10-11-2003	C10AA07	30	crestor 10mg tablet filmomh	1D1T	10
08-12-2003	C10AA07	90	crestor 10mg tablet filmomh	1D1T	10
04-03-2004	C10AA07	90	crestor 10mg tablet filmomh	1D1T	10



Medication Possession Ratio (MPR):
Σ supply of drug in period = 354/393 = 0.9

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Same MPR, different pattern

Drug	MPR	1	2	3	4	5	6	7	8	9	10
A	0.5										
B	0.5										
C	0.5										

- Evaluation period in relation to expected duration of prescriptions
- Data exploration and cleaning: expected duration/dosing of drugs, deal with overlapping prescriptions

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Multiple drug regimen

Drug	1	2	3	4	5	6	7	8	9	10
A										
B										
C										

- Patient using 3 different antihypertensives
- Is the patient adherent?
  - Drug A: nonpersistence or switch to C
  - Drug B: noncompliance of drugs collected elsewhere
  - Drug C: see A & B, noncompliance or nonpersistence
- Define start, stop, switch, restart at class/drug level
- Adherence to at least 1, to all, average?

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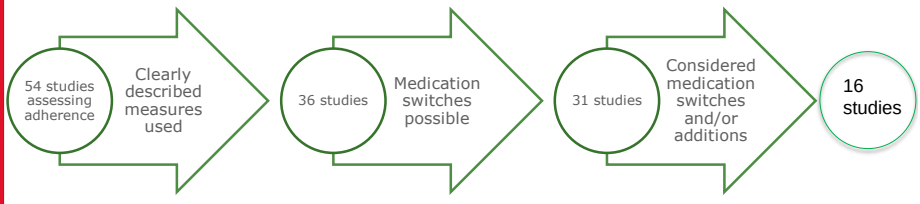
Systematic review multiple medication regimes for diabetes/cardiovascular drugs



- Not clear (18)
- Adherence to at least 1 drug (12)
- Adherence to both/all medication (16)
- Average adherence (19)

Alfian SD et al, J Clin Epidemiol 2019; ;108:44-53

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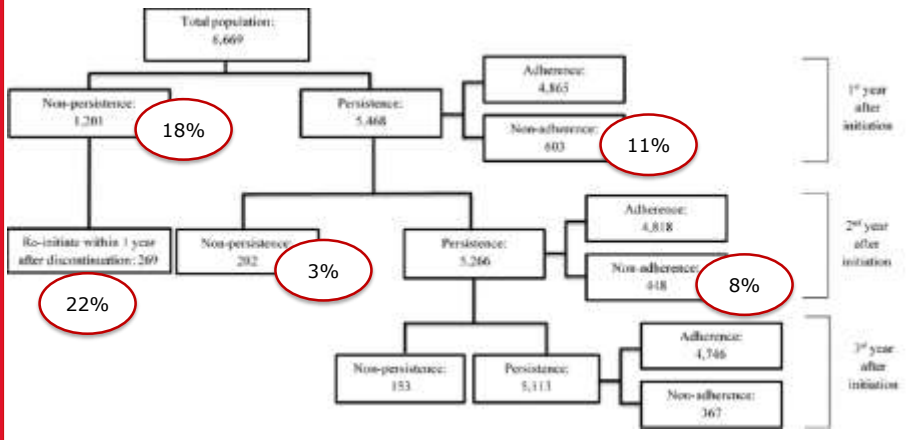
Diabetes patients initiating on antihypertensives



Alfian SD et al, PLoS One 2019, accepted

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Selection of patients using pharmacy data?

	Non-adherence	Non-persistence	Re-initiation
Gender		+ (female)	
Age		+ (age > 80 yr)	
Type of prevention	+ (secondary prevention)		
Type of initial class	+ (diuretics compared to agents acting on renin-angiotensin system)	+ (diuretics, BB, CCB compared to agents acting on renin-angiotensin system)	
Duration of persistence			+ (longer duration of persistence)

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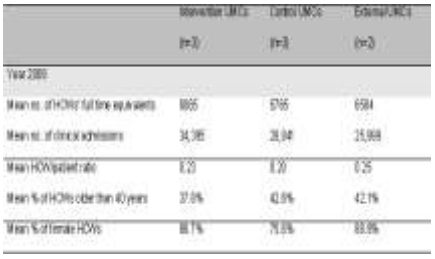
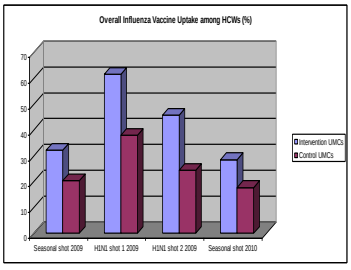
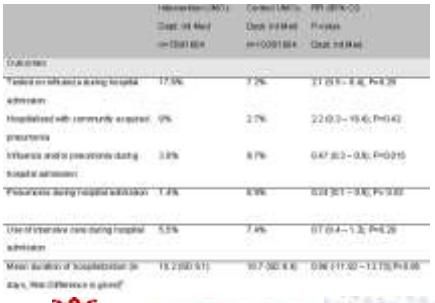
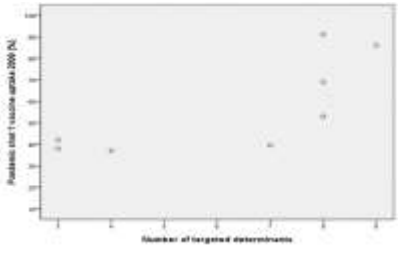
Grote Big Data trials: Pragmatische geclusterde gerandomiseerde gecontroleerde trial









Riphagen J, et al. Eurosurveillance, 2013

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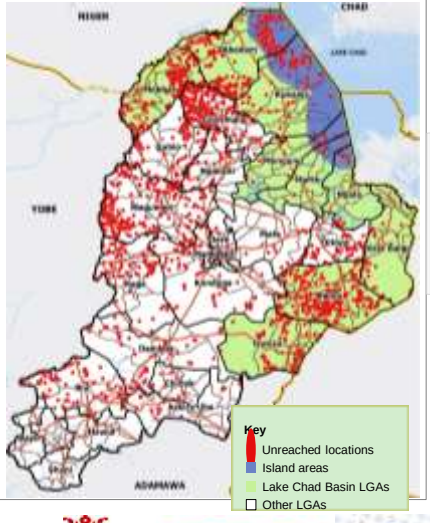
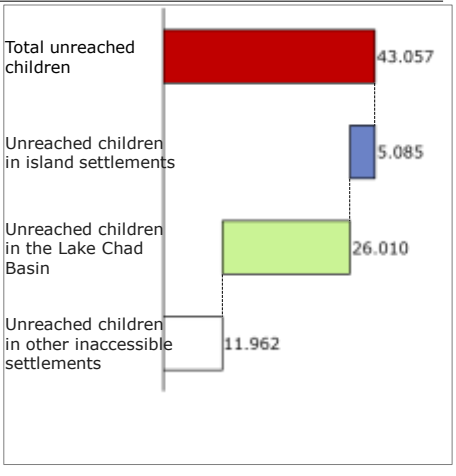
UNREACHED POPULATION ANALYSIS – SPECIAL POPULATIONS: Borno state, Nigeria

72% (31,095) of the 43,057 unreached children are in the Lake Chad islands and other settlements in the Lake Chad Basin

Map showing all unreached locations highlighting special populations, as @ August 2019



Breakdown of unreached U-5 children among all special populations as @ August 2019 *(Number of children)*



Source: Tally sheet summary, adjusted satellite imagery data v 7.7

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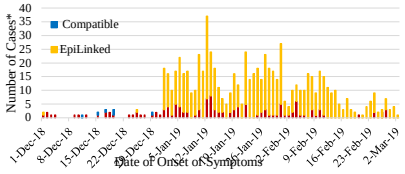
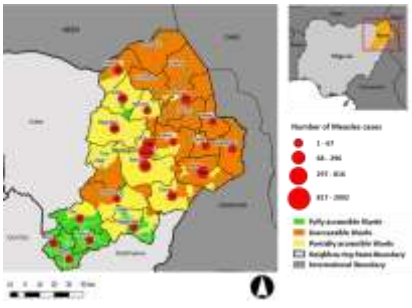
Epidemic curves of measles cases in security compromised areas, Borno state, Nigeria

43,057 children < 5 years are trapped in security compromised areas of the state





Anne Baptiste, thesis work 2019

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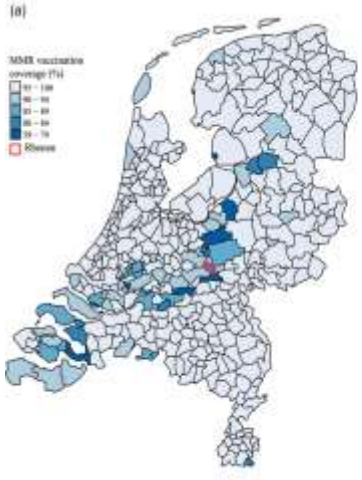
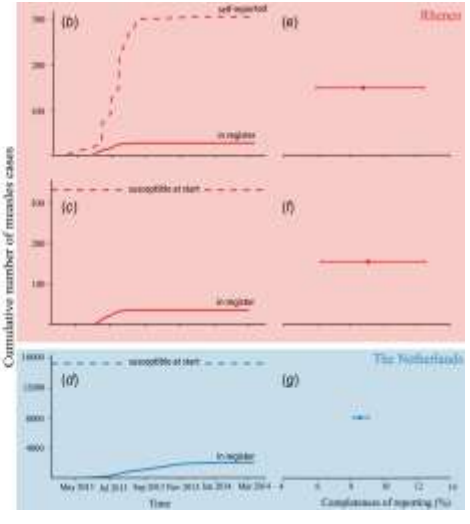
Measles epidemic 2013-2014





Woudenberg T, et al. Infect Epidemiol 2019

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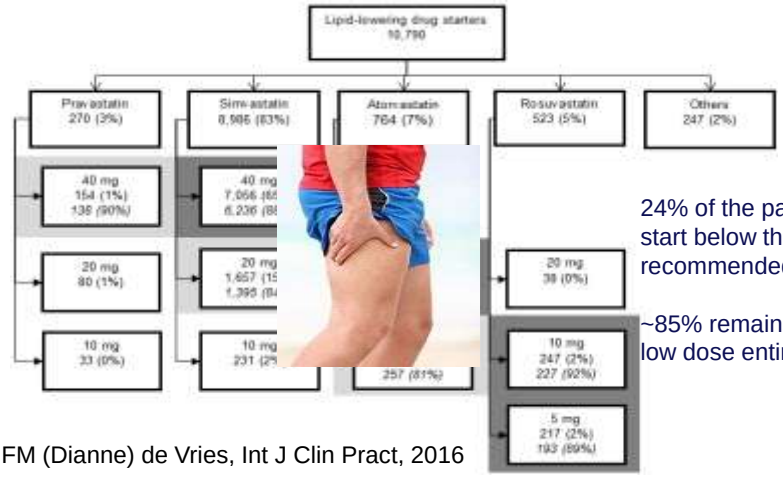
Statin use among Dutch diabetes type II patients (GIANTT data)



24% of the patients start below the recommended dose

~85% remains on low dose entire year

FM (Dianne) de Vries, Int J Clin Pract, 2016

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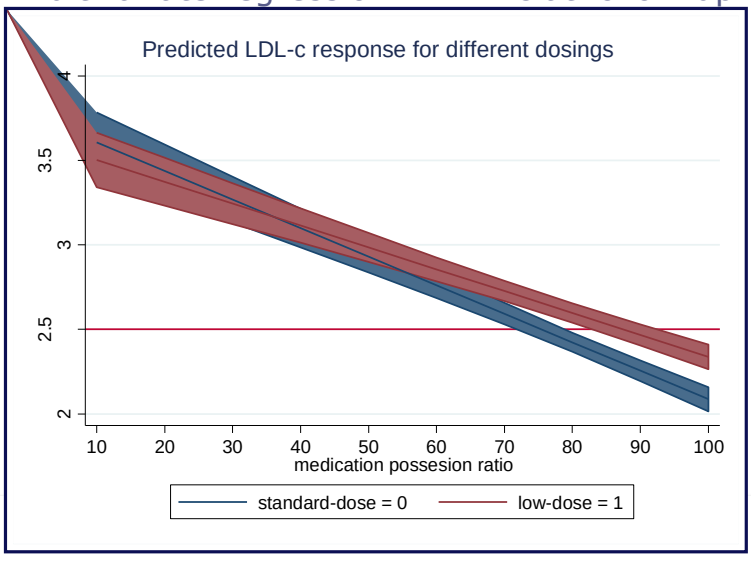
Effect low vs. standard-dose

Multivariate regression -- LDL-c at follow-up



Sex disparities in statin prescriptions/effects

Approx. 80,000 participants

Rudolf de Boer & Eelko Hak

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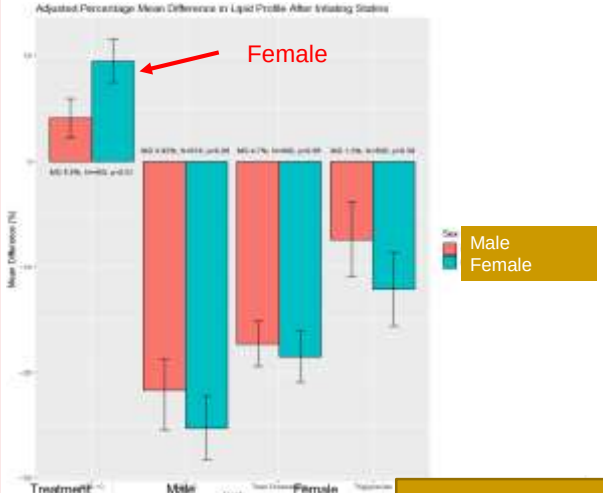

Treatment group	Male N	Male %	Female N	Female %
All	340	53.5	340	57.4
Primary	140	52.6	162	58.5
Secondary	42	56.8	33	52.4

Lisa Emmens, Sylvi Irawati, Eelko Hak, Rudolf de Boer

Data confidential, unpublished

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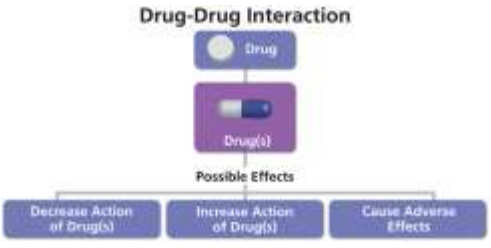
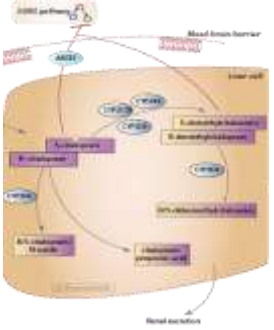
Drug-Drug-Interaction (DDI)

- **External factor ->**

  the presence of CYP modulators (CYP2C19/3A4/2D6 inhibitors/inducers).





https://aidsinfo.nih.gov

Muh. Akbar Bahar[1], Pauline Lanting[2], Jens H.J. Bos[1], Rolf H. Sijmons[2], Eelko Hak[1], Bob Wilffert[1]

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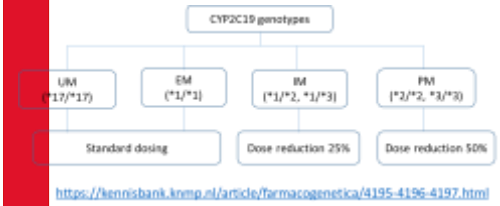
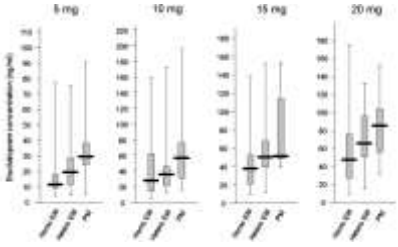
Drug-Gene-Interaction (DGI)

- **Internal factors →**

  genetic polymorphisms → SNP.



https://kennisbank.knmp.nl/article/farmacogenetica/4195-4196-4197.html



↑ (Es)citalopram = PM > IM > EM/NM > UM

Homo EM= EM/NM
Hetero EM = IM

Tsuchimine, Shoko, et al. ,2018

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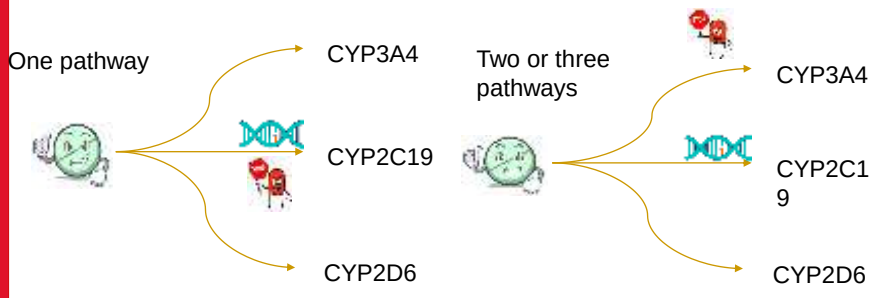
Drug-Drug-Gene-Interaction (DDGI)

- **Combination of the existing deviating alleles of CYP2C19/3A4/2D6 and the presence of a CYP2C19/3A4/2D6 modulator.**



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Outcomes (switching + dose reduction)

Variables (*n* Yes, %)	Switch or Dose red (*n*= 31)	aOR (95%CI)	P value
CYP2C19 & CYP3A4 phenotypes			
CYP2C19 phenotypes*			
CYP2C19 NM	12 (38.7)	Ref.	
CYP2C19 IM	18 (58.1)	3.16 (1.41-7.09)	0.01
CYP2C19 PM	1 (3.2)	0.545 (0.07-4.52)	0.57
CYP2C19 UM	0 (0)	*NA*	
CYP3A4 phenotypes**			
CYP3A4 NM	23 (74.2)		
CYP3A4 IM	8(25.8)	1.37 (0.55-3.39)	0.50
CYP3A4 PM	0 (0)	*NA*	
Phenotypes combination***			
CYP2C19 NM + CYP3A4 NM	9 (29)	Ref.	
CYP2C19 IM/PM + CYP3A4 NM	14 (45.2)	2.35 (0.96-5.76)	0.06
CYP2C19 IM/PM + CYP3A4 IM/PM	5 (16.1)	3.46 (1.02-11.75)	0.05
CYP2C19 NM + CYP3A4 IM/PM	3 (9.7)	1.11 (0.28-4.43)	0.88
CYP2C19 UM + CYP3A4 NM/IM	0 (0)	*NA*	

Variables (*n* Yes, %)	Switch or Dose red (*n*= 31)	aOR (95%CI)	P value
CYP modulator#			
No inhibitor/inducer of CYP2C19/3A4/2D6	27 (87.1)	Ref.	
CYP2C19 inhibitor alone	4 (12.9)	2.36 (0.67-8.32)	0.18
CYP3A4 inhibitor alone	0 (0)	*NA*	
CYP2D6 inhibitor alone	0 (0)	*NA*	
Combined exposures^			
No exposures			
CYP2C19 NM + CYP3A4 NM + No CYP Modulator	7 (22.6)	Ref.	
DDI			
CYP2C19 NM + CYP3A4 NM + Yes CYP Modulator	2 (6.5)	2.82 (0.49-15.97)	0.24
DGI			
CYP2C19 IM/PM + CYP3A4 NM + No CYP Modulator	13 (41.9)	2.75 (1.04-7.29)	0.04
CYP2C19 IM/PM + CYP3A4 IM/PM + No CYP Modulator	5 (16.1)	4.38 (1.22-15.69)	0.02
CYP2C19 NM + CYP3A4 IM/PM + No CYP Modulator	2 (6.5)	1.02 (0.19-5.24)	0.98
CYP2C19 UM + CYP3A4 NM/IM + No CYP Modulator	0 (0)	NA	
DDGI	2 (6.5)	2.33 (0.42-12.78)	0.33

Adjusted for: *CYP3A4 phenotypes, CYP modulator & N of co-prescriptions; **CYP2C19 phenotypes, CYP modulator & N of co-prescriptions; ***CYP modulator & N of co-prescriptions; #CYP2C19 & CYP3A4 phenotypes & N of co-prescriptions; ^N of co-prescriptions.

Akbar Bahar, promotie February 4, 2020 om 11 uur precies

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SAMENGEVAT: een uitgebreid kleurenpalet

Therapietrouw meten en patiënten selecteren met 'big data' vraagt:
- heldere definities van starten, stoppen, switch, herstart
- kennis van te verwachten voorschrijf/aflever patronen/ruis in data
- aandacht voor gebruik meerdere middelen bij 1 indicatie
- onderscheid tussen onregelmatig gebruik en stoppen

Invloed therapietrouw op uitkomsten is afhankelijk van:
- geneesmiddel
- setting
- gedrag van de patiënt
- aanwezigheid comedicatie
- genetische profiel

"Je gaat het pas zien als je het door hebt."
Johan Cruijff

Contact: e.hak@rug.nl en p.denig@umcg.nl

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