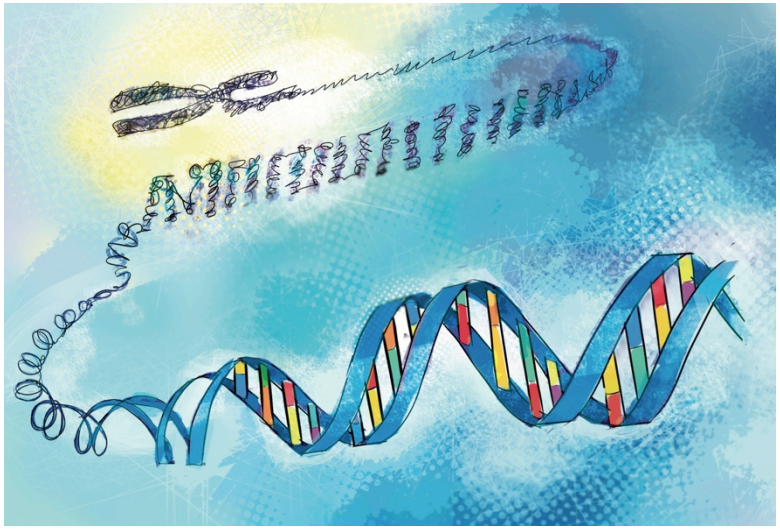
Personalisierte Medizin

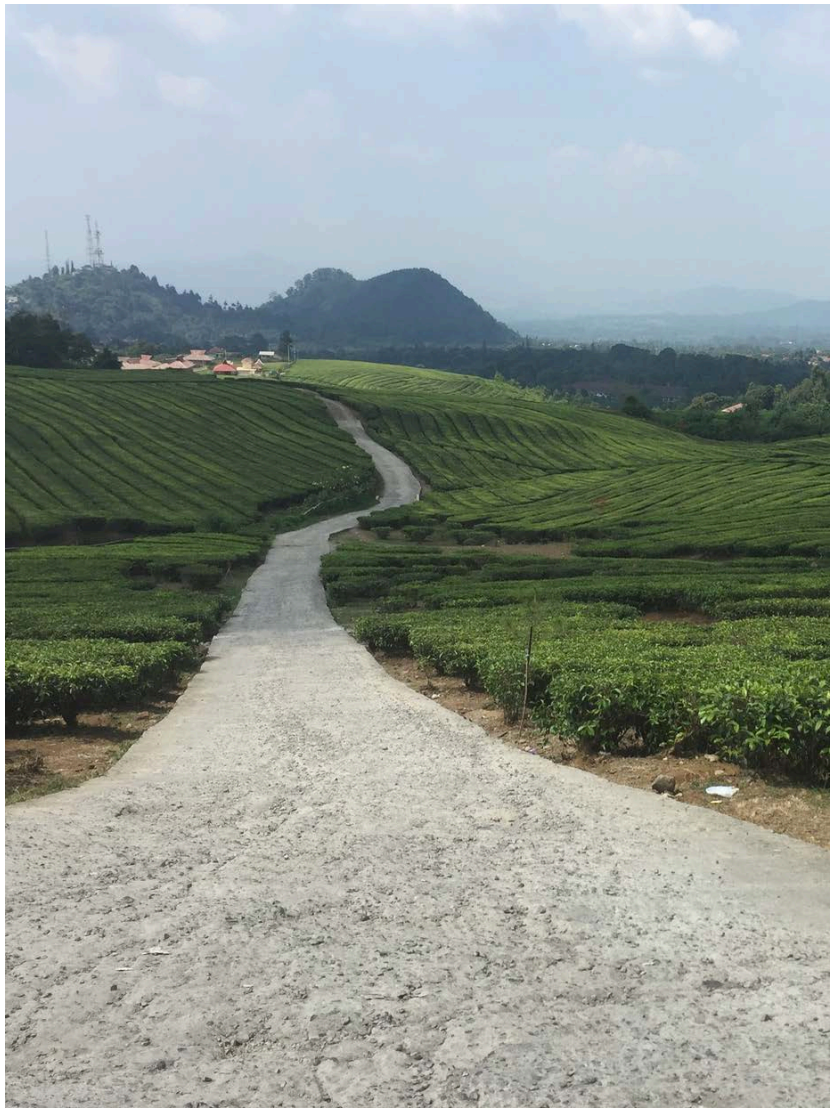


Thomas D. Szucs

Universität Basel & Klinik Hirslanden

Übersicht

- **Gezielte Therapie und Prävention**
- **Einfluss auf Compliance, Medikamentensicherheit, Versorgungsqualität**
- **Ökonomische Aspekte**
- **Ausblick in die Zukunft**



Personalisierte Medizin

Identifikation von Risikofaktoren

Identifikation genetischer Marker oder molekulare Basis von Krankheitsfaktoren

Prävention

Behandlung

Three definitions of personalized medicine

Definition 1

The use of combined knowledge (genetics, or otherwise) about a person to predict treatment response and thereby improve that person's health

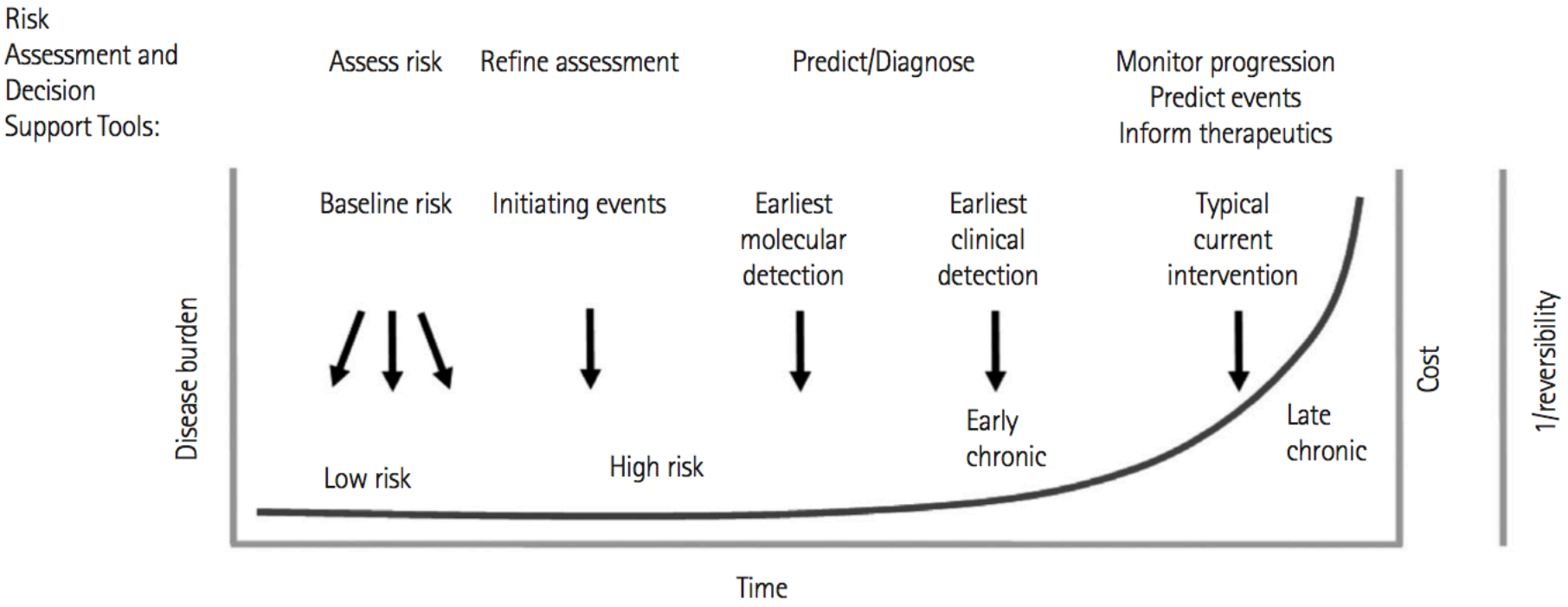
Definition 2

The use of combined knowledge (genetics, or otherwise) about a person to predict disease prognosis or treatment response and thereby improve that person's health

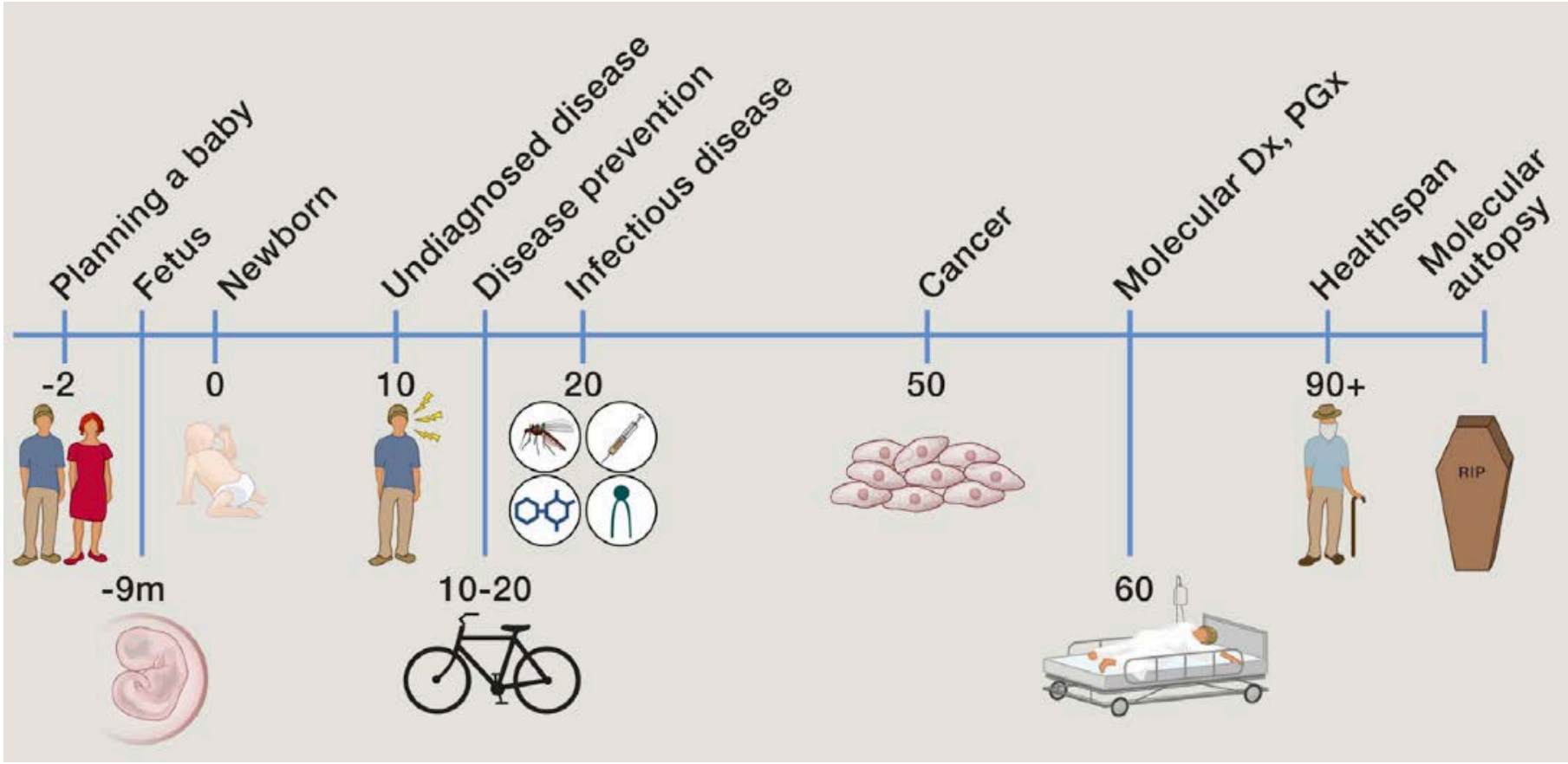
Definition 3

The use of combined knowledge (genetics, or otherwise) about a person to predict disease susceptibility, disease prognosis or treatment response and thereby improve that person's health

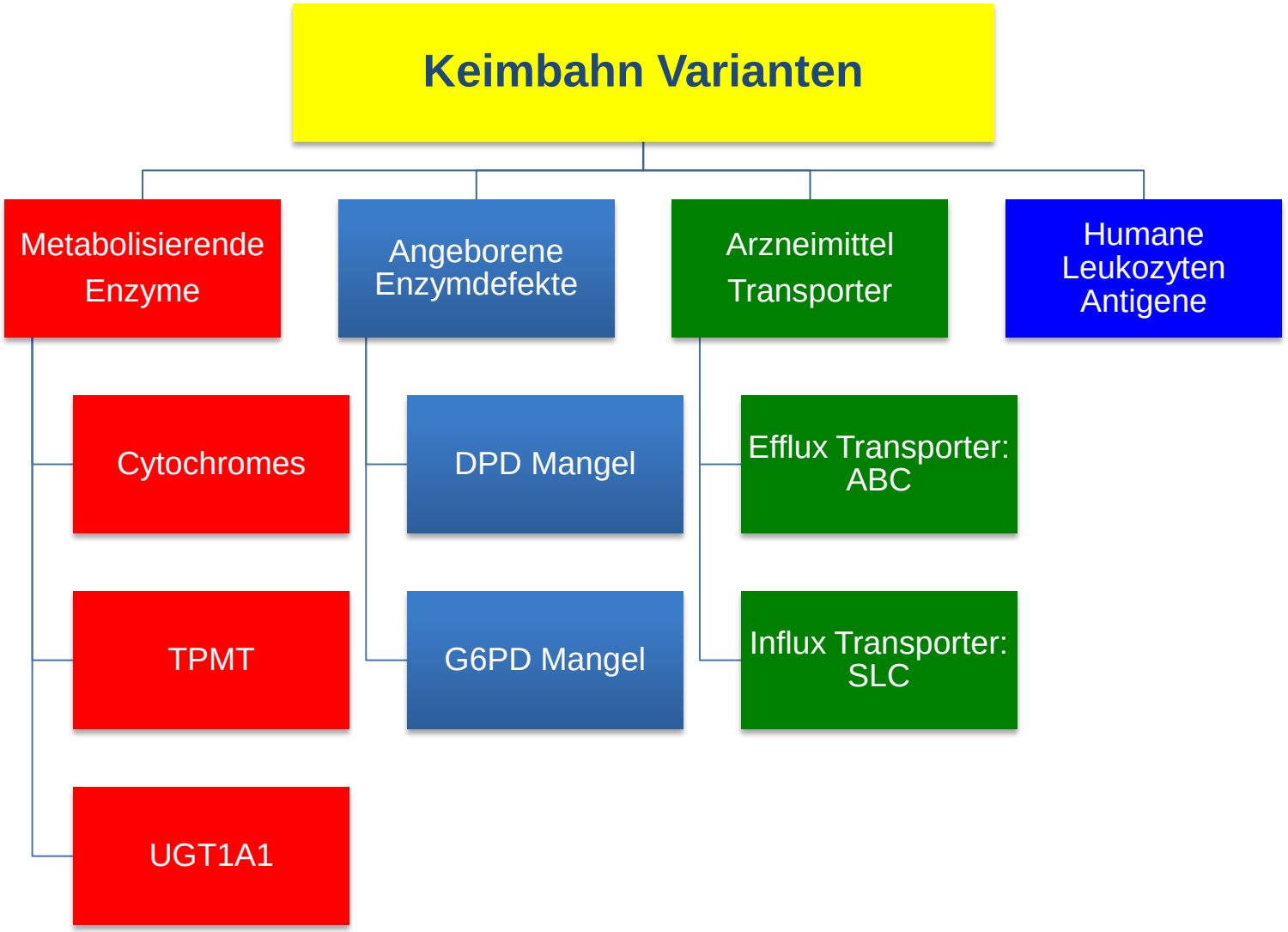
Kontinuum von Gesundheit/Krankheit



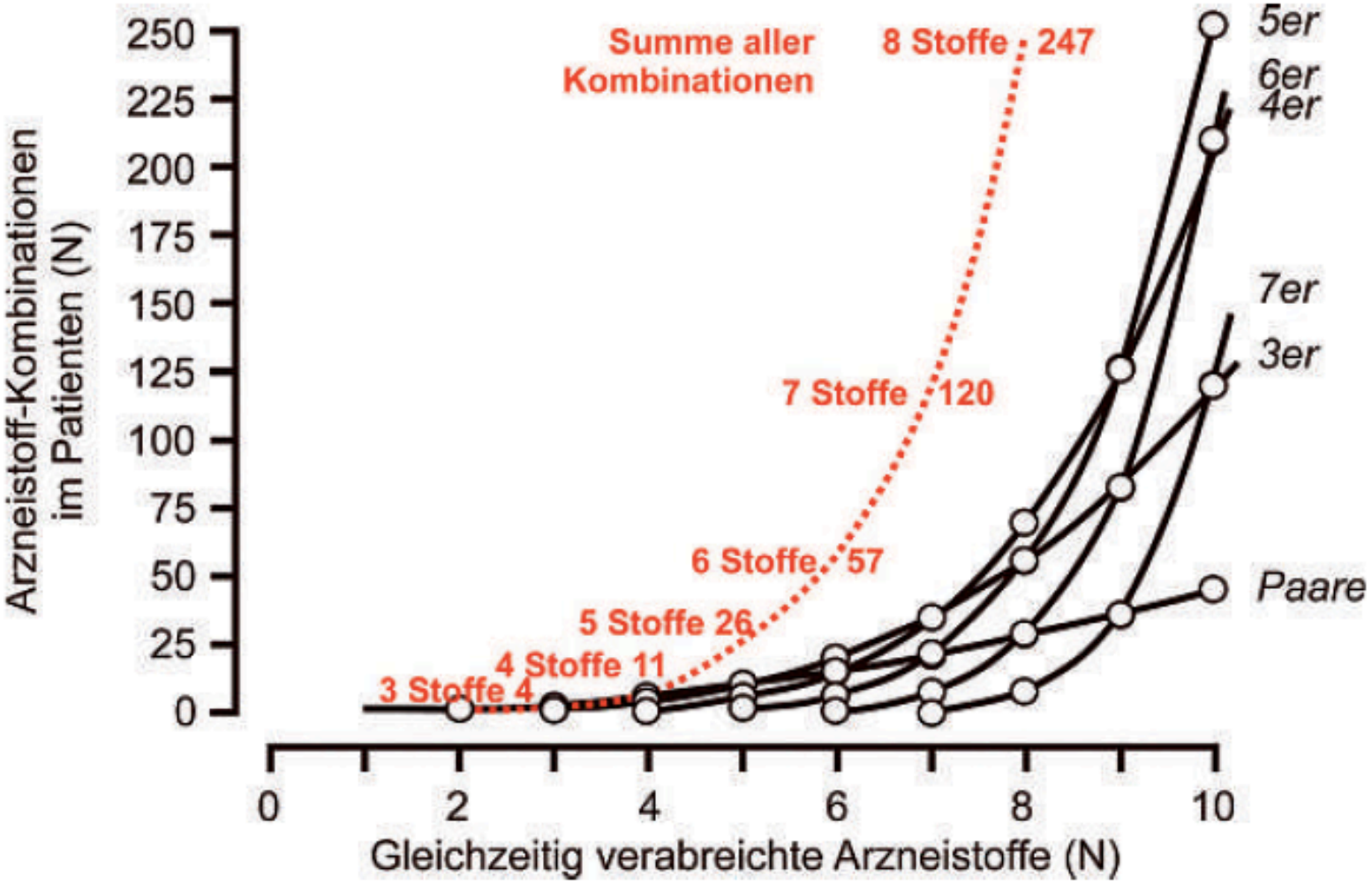
Personalisierte Medizin: Von der Empfängnis zur Bahre



Pharmakogenomik unerwünschter Arzneimittelwirkungen



Polypharmazie – Anzahl Kombinationspaare



Haefeli WE 2002

Ethnische Verteilung des CYP2D6 Phänotyps

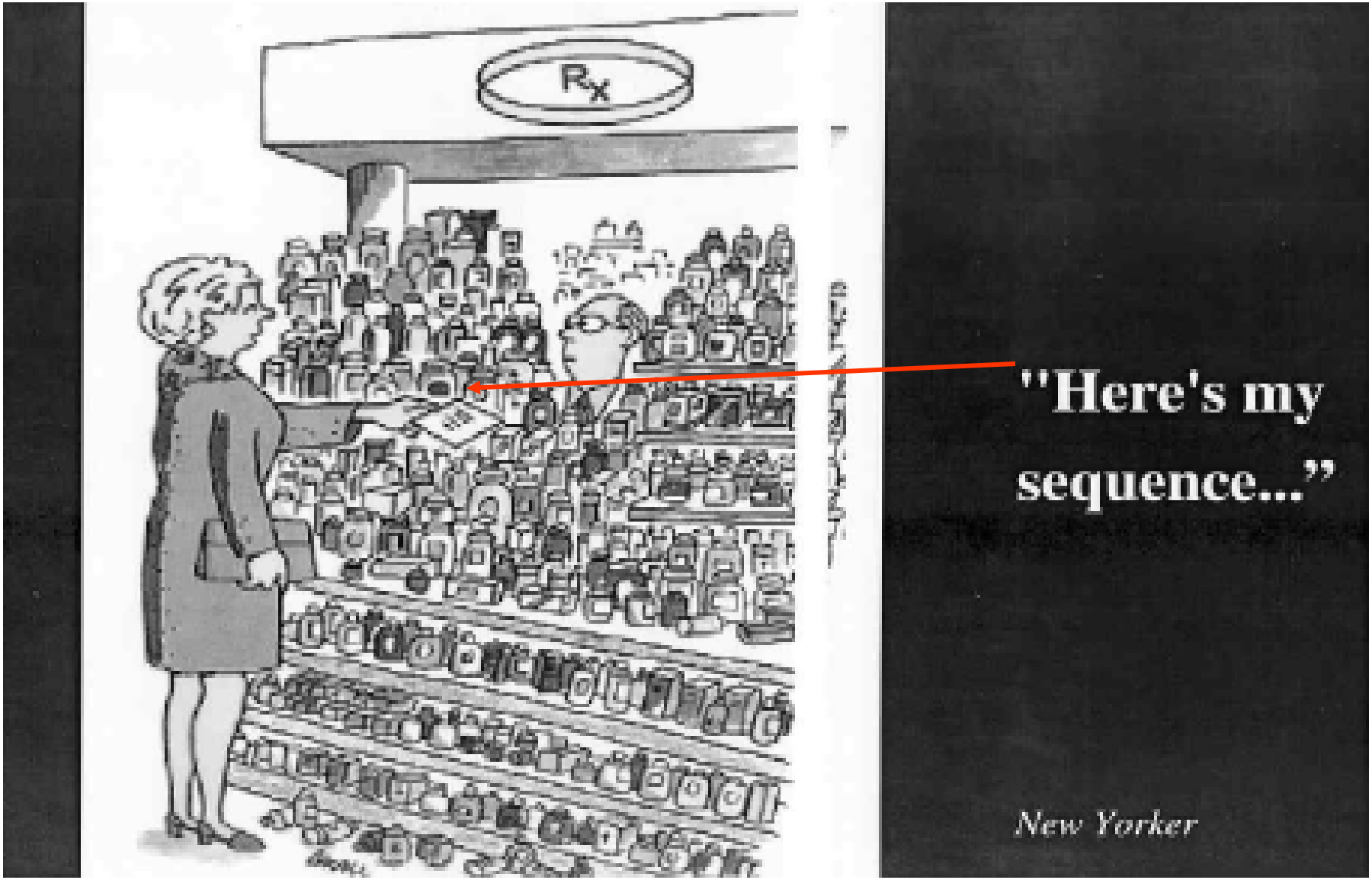
Bevölkerung	PM Phänotyp (%)	UM Phänotyp (%)
Nordeuropa	7.7- 8.9	1
Mittelmeerraum	2	8
Horn Afrikas	2	29
Süd Afrika	19	-
China	1	1
Saudi Arabien	1	21

The Oncologist 2006; 11: 126-135

Nutzen der Pharmakogenetik

Individuelle Probleme mit Arzneimitteln	Pharmakogenetische Lösungen und Ziele
Nebenwirkungen (leichte bis tödliche Reaktionen)	Individuelle Dosisanpassung Vermeidung/Verringerung von Nebenwirkungen
Wirkungslosigkeit, unzureichende Wirkung	Individuelle Dosisanpassung Optimierung der Wirksamkeit
Langdauernde Dosisfindung	Schnellere Dosisfindung
Wechsel der Medikation	Direkte Wahl des passenden Arzneistoffes in der richtigen Dosierung
Zunehmende Unsicherheit, Bedenken	Vermeidung und Verringerung von Folgeschäden
Angst vor Arzneimittelrisiken	Vermeidung von tödlichen Nebenwirkungen
Vermehrte Arztbesuche und mehr Zuzahlungen durch Umstellung der Medikation	Kosten-effektive Therapie

Die Zukunft?!



Fragen?

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- **Einfluss auf Compliance, Medikamentensicherheit, Versorgungsqualität**
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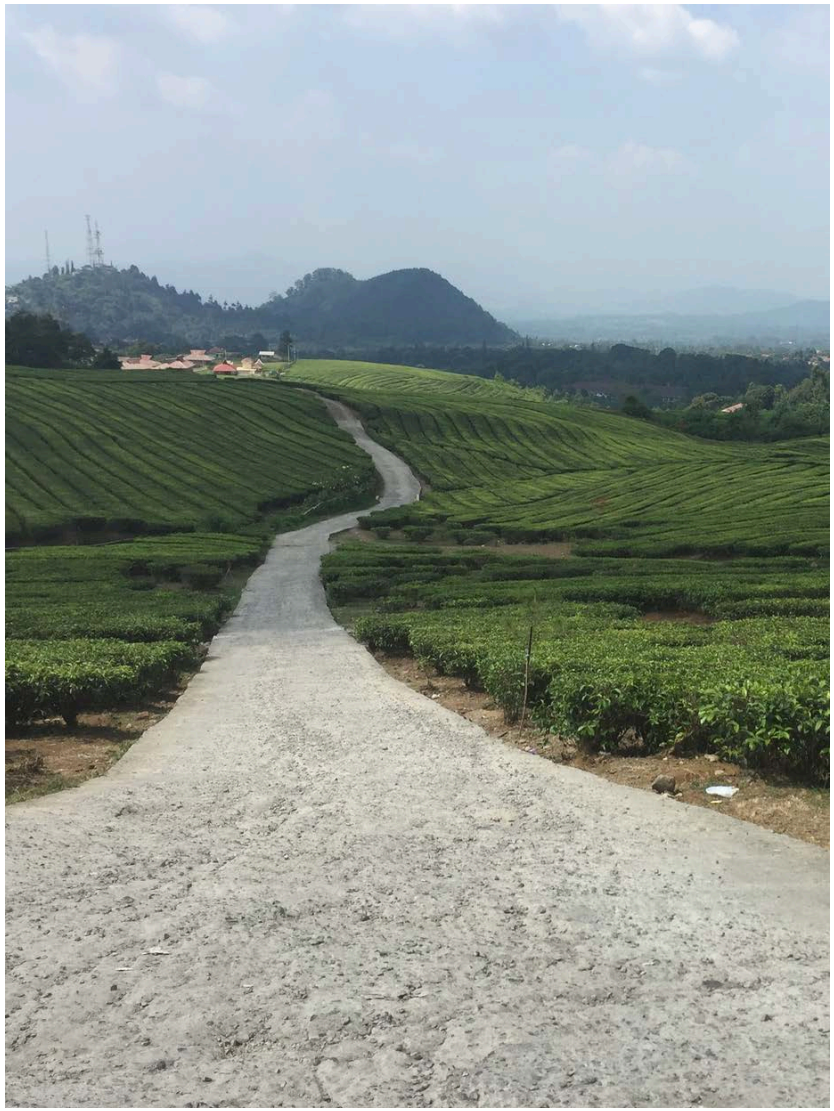
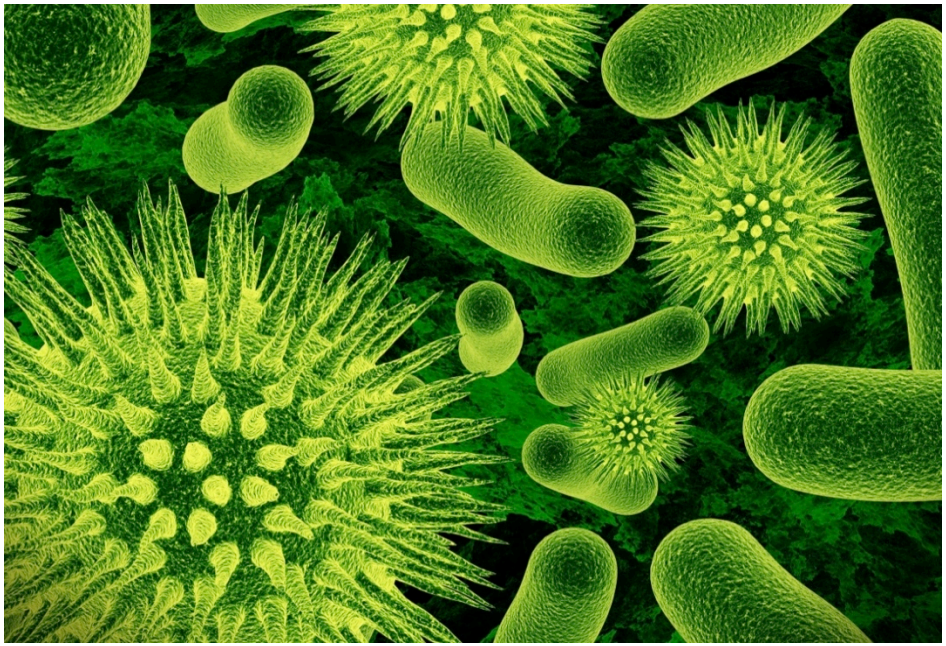
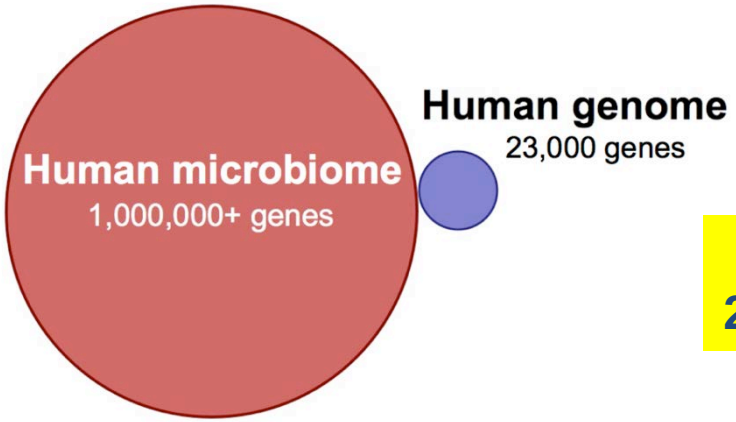




INFEKTIOLOGIE

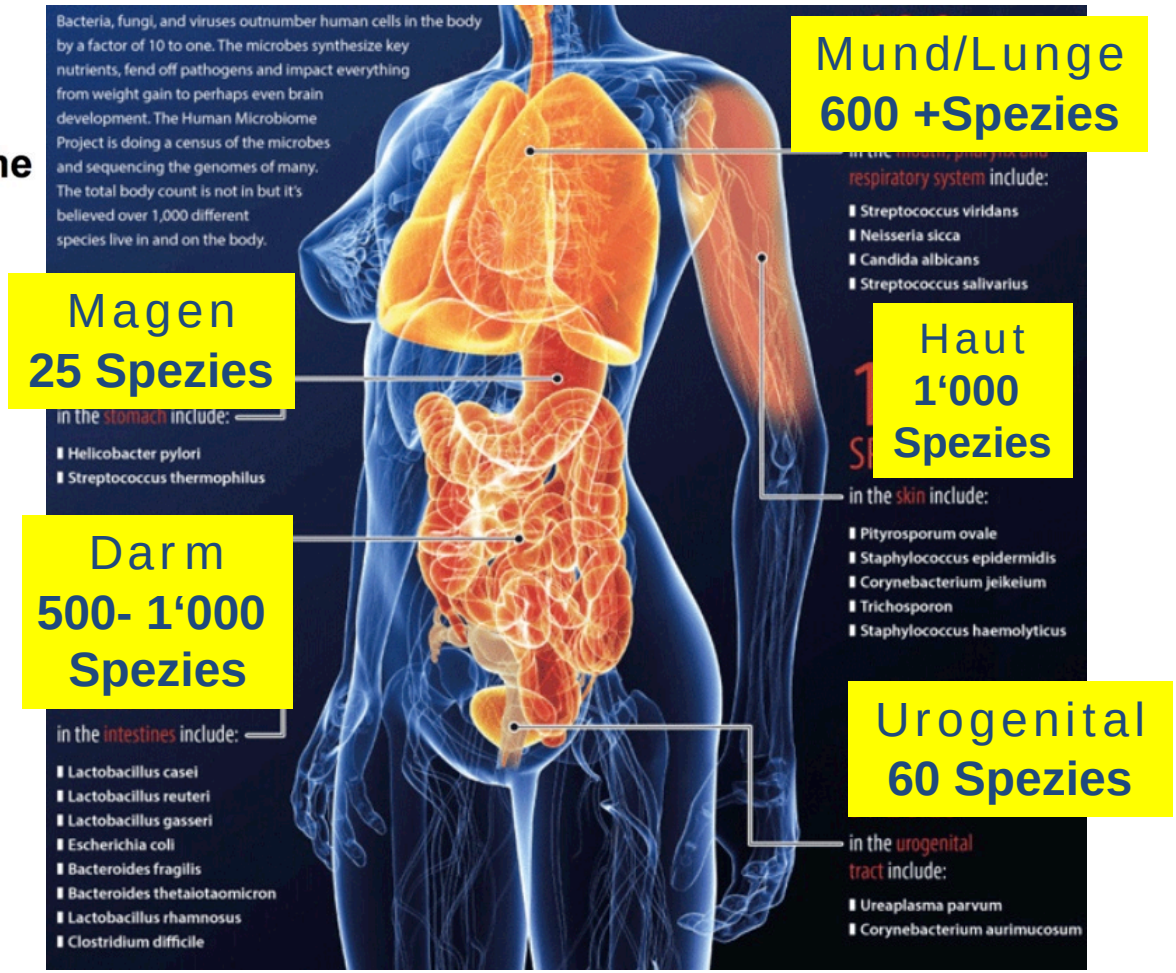

The Economist
The Catholic church's unholy mess
Paul Ryan: the man with the plan
Generation Xhausted
China, victim of the Olympics?
On the origin of specie
AUGUST 18TH–24TH 2012
Economist.com
Microbes maketh man
How 90% of the cells in your body are bacteria, the benefits of faecal transplants, and other things you would rather not know before breakfast

Mikrobiom: 10‘000 Spezies (2kg)

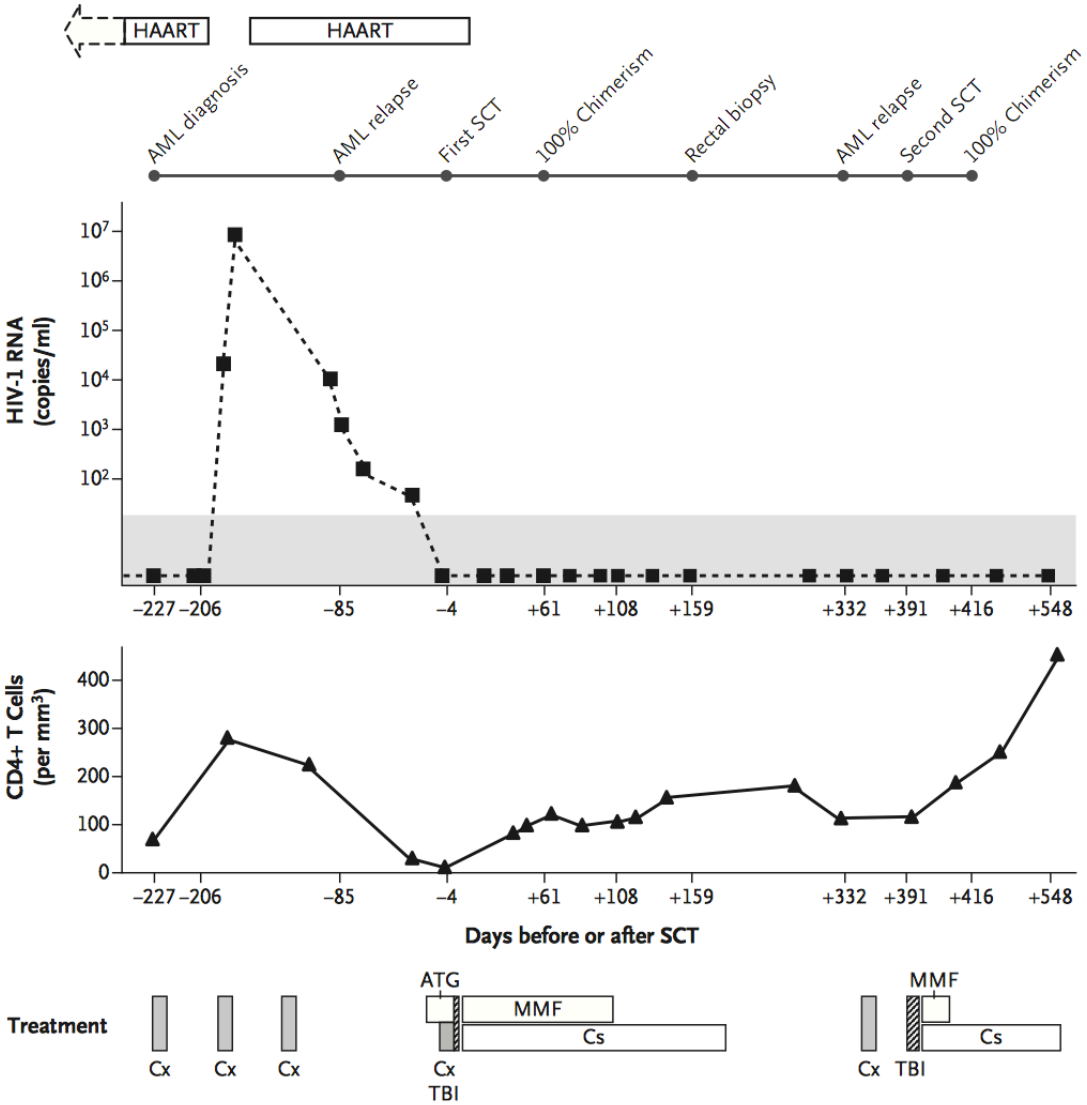


Körperzellen: $1 \cdot 10^{13}$

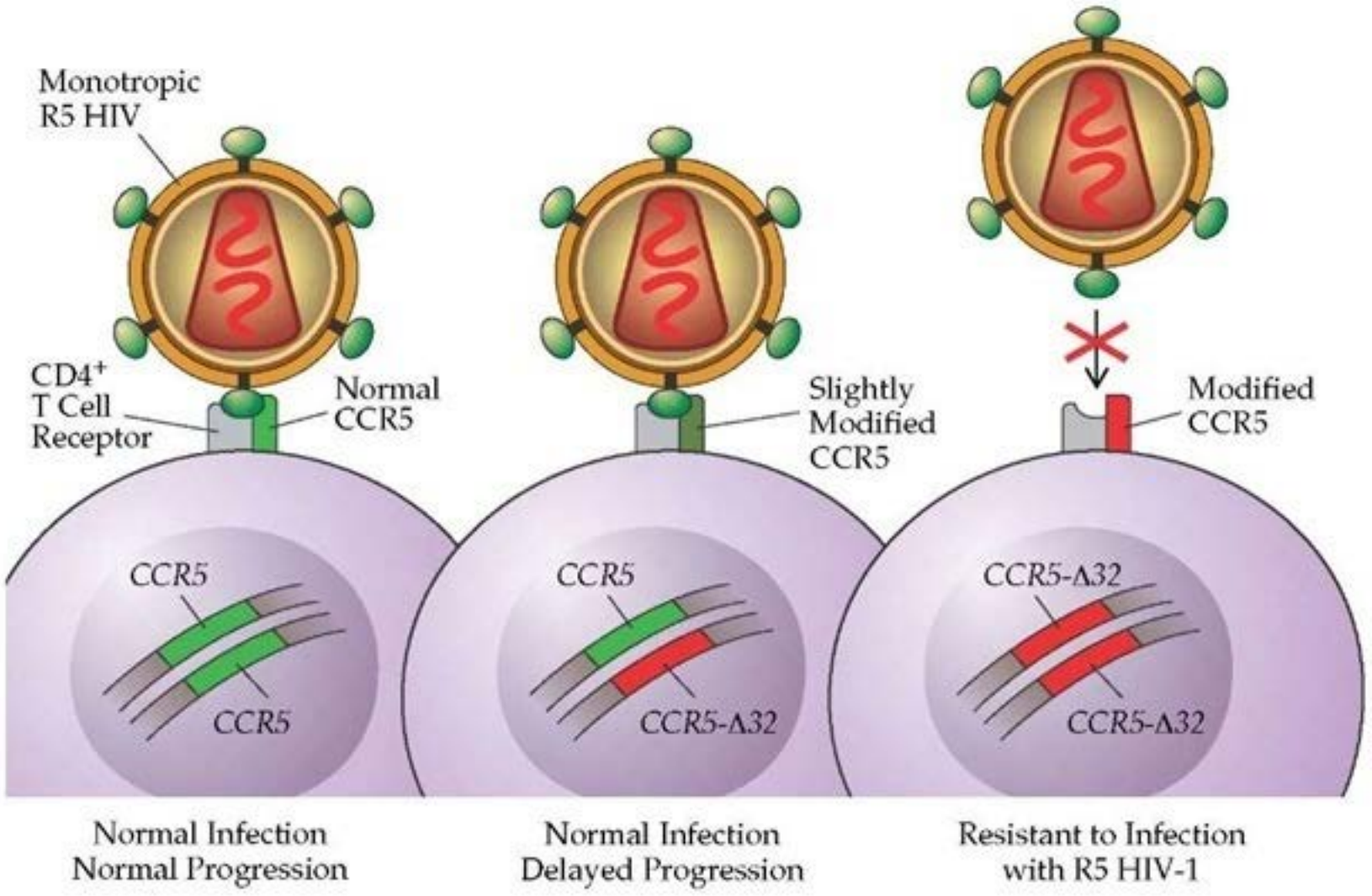
Mikroben: $9 \cdot 10^{13}$



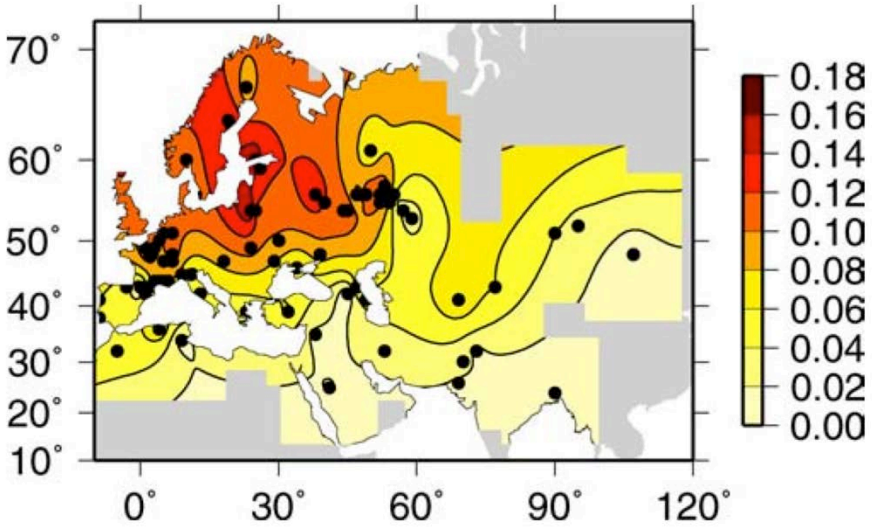
Der „Berliner Patient“ Timothy Brown

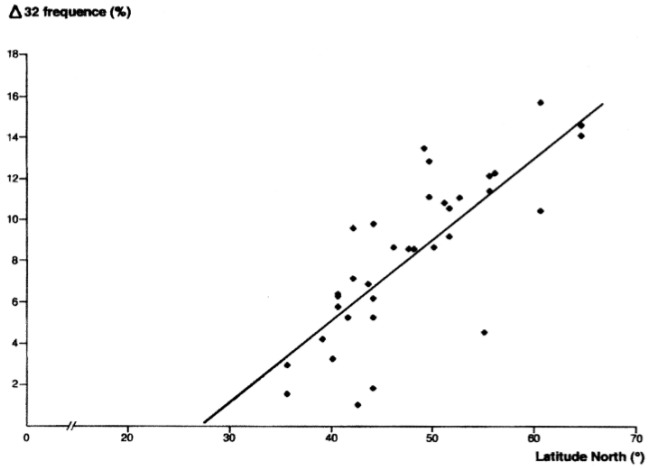


CCR5-Rezeptor Mutationen

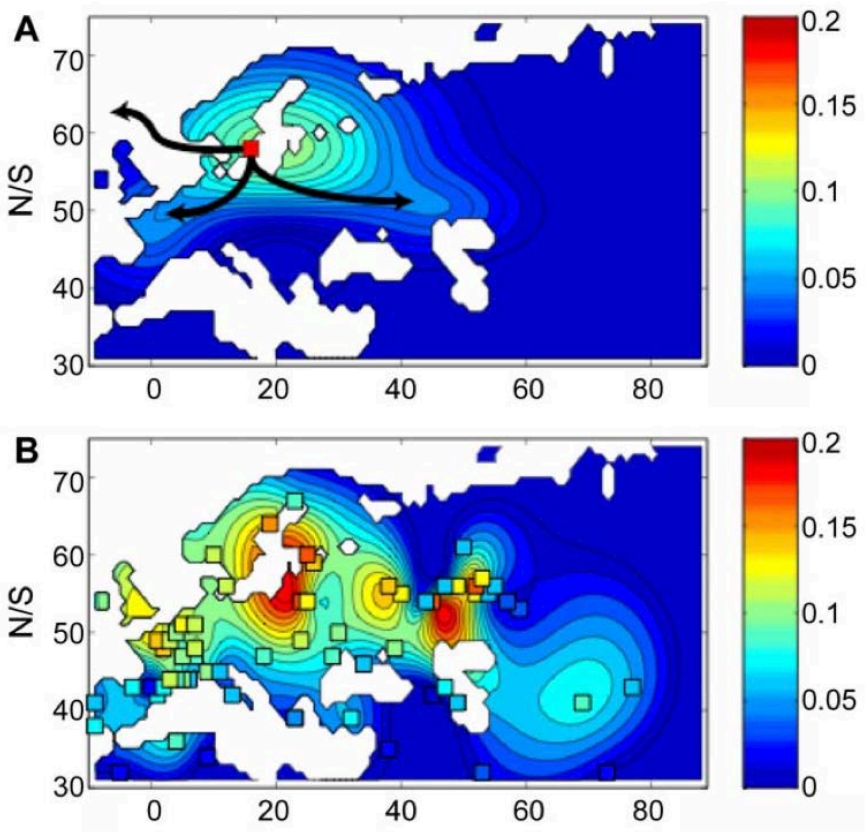


Geographische Verteilung der Δ32
Allel Frequenz





Viking hypothesis



Modern-day observed allele frequencies.

CCR5-D*32* is at average allele frequency of 10% across Europe, translating into a homozygote frequency of about 1%

Lucotte G 2001; Novembre J 2005, Galvani AP 2005

Genomik zur Analyse bakterieller Übertragungsmechanismen

- **Analyse direkte Übertragung zwischen Individuen**
  - **Sequenzierung von C. difficile zeigt: es gibt auch andere Übertragungswege (Eyre DW 2013)**
  - **Belege der direkten Person-Person Übertragung von M. Tuberculosis bei zystischer Fibrose mittels WGS und phylogenetischer Analyse (Bryant JM 2013)**
- **Analyse von Ausbrüchen (outbreaks)**
  - **WGS eines nosokomialen MRSA Ausbruches mit nachfolgenden Empfehlungen zur Spitalhygiene (Harris SR 2013)**
- **Analyse globaler Übertragungsmuster**
  - **Untersuchung Übertragungsprozesse zwischen Wirten und innerhalb von Wirten (Ypma RJF 2013)**
  - **Komplette Rekonstruktion der Evolution von M. Tuberculosis zeigt eine sehr viel frühere als gedachte Assoziation im humanen Wirt (Comas I 2013)**

Auftreten und globale Verbreitung von C. Difficile – genetische Analyse

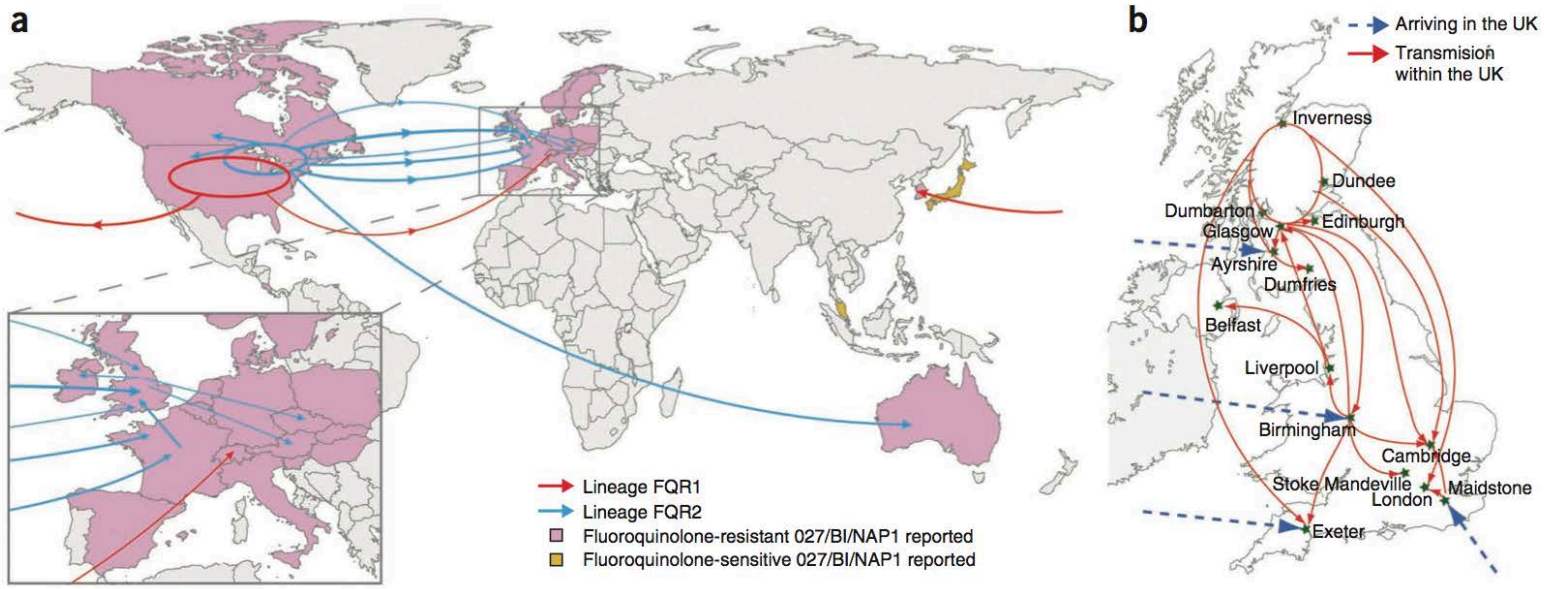


Table 1 Nonsynonymous homoplasic SNPs identified in the core genomes of *C. difficile* 027/BI/NAP1 isolates

Position	Region	SNP	Substitution	Antibiotic[a]
5420	DNA gyrase subunit B (*gyrB*)	c.1276G>A	p.Asp426Asn	Fluoroquinolone
6310	DNA gyrase subunit A (*gyrA*)	c.245C>T	p.Thr82Ile	Fluoroquinolone
95412	DNA-directed RNA polymerase β chain (*rpoB*)	c.1504C>A	p.His502Asn	Rifampicin
95422	DNA-directed RNA polymerase β chain (*rpoB*)	c.1514G>A	p.Arg505Lys	Rifampicin
103867	Translation elongation factor G (*fusA*)	c.1363C>A, c. 1363C>T	p.His455Asn, p.His455Tyr	Fusidic acid
104117	Translation elongation factor G (*fusA*)	c.1613C>T	p.Pro538Leu	Fusidic acid
1800920	Two-component response regulator	c.31G>A	p.Glu11Lys	
1802086	Two-component sensor histidine kinase	c.446C>T	p.Thr149Ile	
3170481	S-layer precursor protein (*slpA*)	c.467G>A, c.467G>T	p.Pro156Leu, p.Pro156Gln	
3170482	S-layer precursor protein (*slpA*)	c.466G>A, c.466G>T	p.Pro156Ser, p.Pro156Thr	
3938789	Putative membrane protein	c.996A>C	p.Tyr332*	

Positions refer to those in the R20291 genome. The alleles listed relate to the forward strand.
[a]Antibiotic to which the substitution confers resistance.

He M 2013

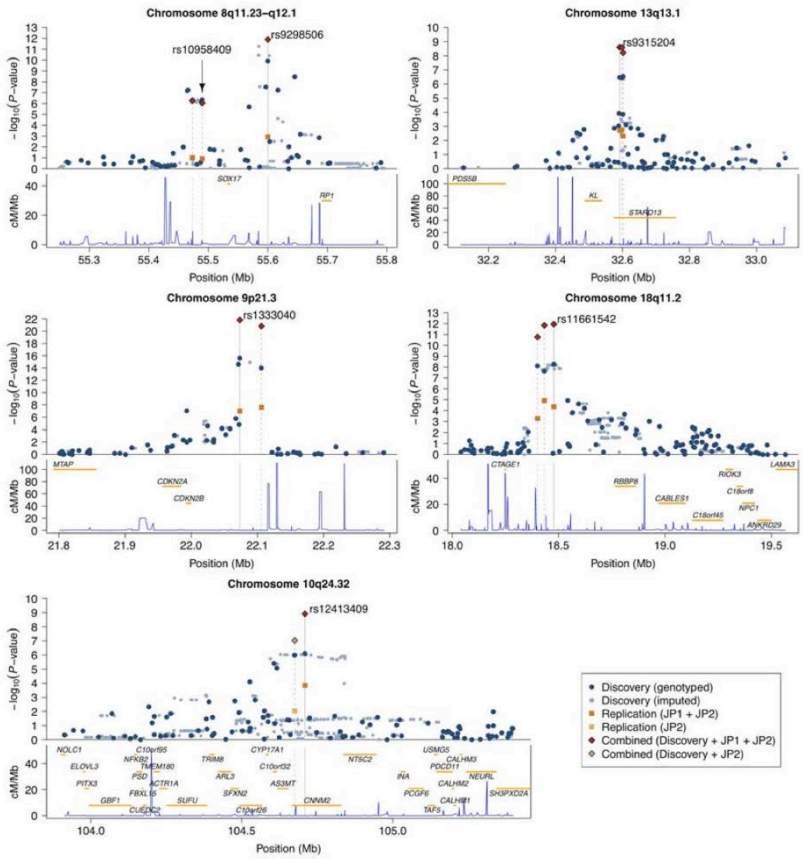
HGT in S. aureus

- **Akquisition von Virulenzgenen**
- **Phagen-bezogene Chromosomen Inseln**
- **Kodieren Superantigene (Enterotoxin B, Resistenz, etc.)**

Relman DA NEJM 2011

NEUROLOGIE/PSYCHIATRIE

GWAS Risiko Loci für intrakranielle Aneurysmen



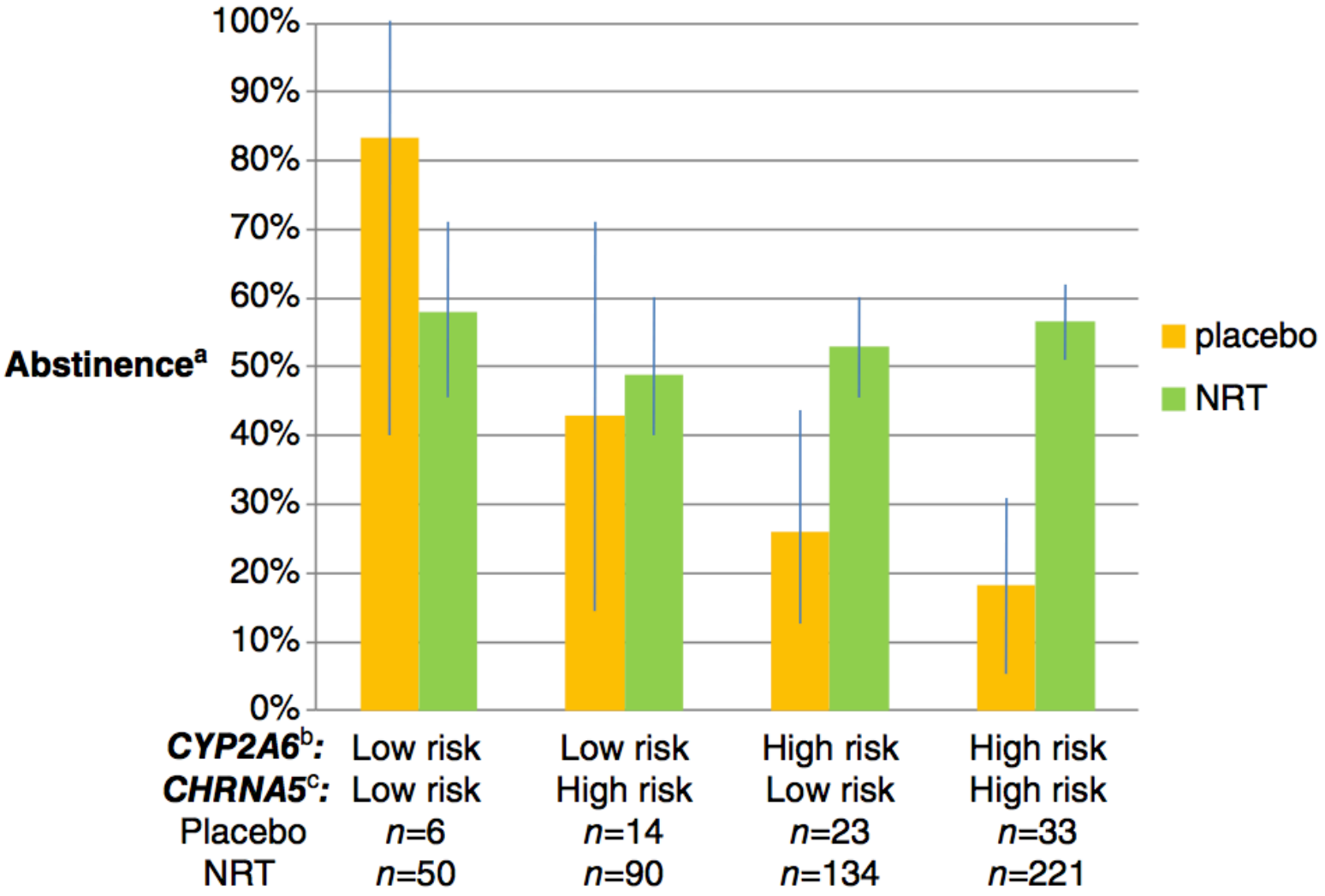
Locus	SNP	Position	Genes	Risk Allele	Cohort	*P*-value	$\log_{10}$(BF)	PPA	Per-allele OR (95% CI)	Control RAF	Case RAF
8q11.23	rs10958409	55,489,644	*SOX17*	A	Discovery	4.2×10^{-07}	4.64	0.8128	1.24 (1.14-1.35)	0.15, 0.19	0.18, 0.22
					Replication	0.12	-0.11		1.08 (0.98-1.20)	0.28	0.29
					Combined	9.0×10^{-07}	4.30	0.6685	1.17 (1.10-1.25)		
8q12.1	rs9298506	55,600,077	*SOX17*	A	Discovery	1.2×10^{-10}	7.94	0.9999	1.33 (1.22-1.45)	0.81, 0.76	0.85, 0.81
					Replication	0.0012	1.56		1.21 (1.08-1.36)	0.79	0.81
					Combined	1.3×10^{-12}	9.85	$1.0 - 1.4\times10^{-06}$	1.28 (1.20-1.38)		
9p21.3	rs1333040	22,073,404	*CDKN2A, CDKN2B*	T	Discovery	2.5×10^{-16}	13.41	$1.0 - 3.9\times10^{-10}$	1.32 (1.24-1.41)	0.56, 0.45	0.63, 0.53
					Replication	1.0×10^{-07}	5.18		1.31 (1.19-1.45)	0.66	0.72
					Combined	1.5×10^{-22}	19.48	$1.0 - 3.3\times10^{-16}$	1.32 (1.25-1.39)		
10q24.32	rs12413409	104,709,086	*CNNM2*	G	Discovery	7.9×10^{-07}	4.29	0.6621	1.38 (1.22-1.57)	0.91, 0.91	0.94, 0.93
					Replication	0.00014	2.34		1.23 (1.10-1.37)	0.74	0.77
					Combined	1.2×10^{-09}	7.00	0.9990	1.29 (1.19-1.40)		
13q13.1	rs9315204	32,591,837	*KL, STARD13*	T	Discovery	3.3×10^{-07}	4.73	0.8443	1.21 (1.13-1.31)	0.21, 0.33	0.24, 0.39
					Replication	0.0019	1.36		1.18 (1.06-1.31)	0.24	0.27
					Combined	2.5×10^{-09}	6.72	0.9981	1.20 (1.13-1.28)		
18q11.2	rs11661542	18,477,693	*RBBP8*	C	Discovery	5.6×10^{-09}	6.39	0.9959	1.21 (1.14-1.30)	0.49, 0.44	0.54, 0.47
					Replication	4.5×10^{-05}	2.79		1.22 (1.11-1.34)	0.61	0.65
					Combined	1.1×10^{-12}	9.92	$1.0 - 1.2\times10^{-06}$	1.22 (1.15-1.28)		

3 neue Risiko Loci:

- RBBP8 (18q11.2)
- STARD13-KL (13q13.1)
- Genreiche Region 10.q24.32

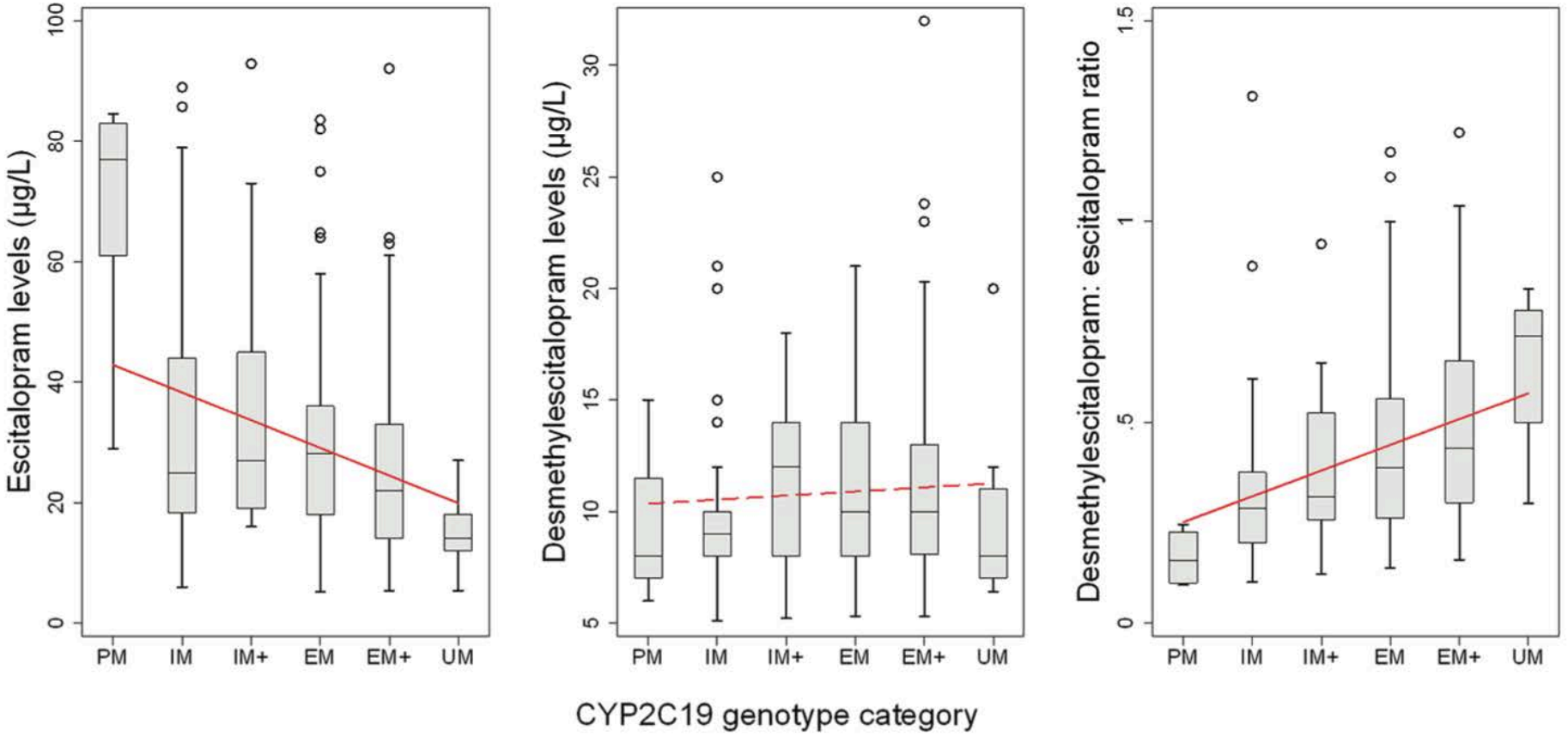
Yasuno K 2010

Genetische Determinanten bestimmen Ansprechen auf Nikotinersatztherapie



Chen LS 2013

Beziehung zwischen CYP2D6/CYP2C19 Genotyp und Antidepressiva Blutspiegel



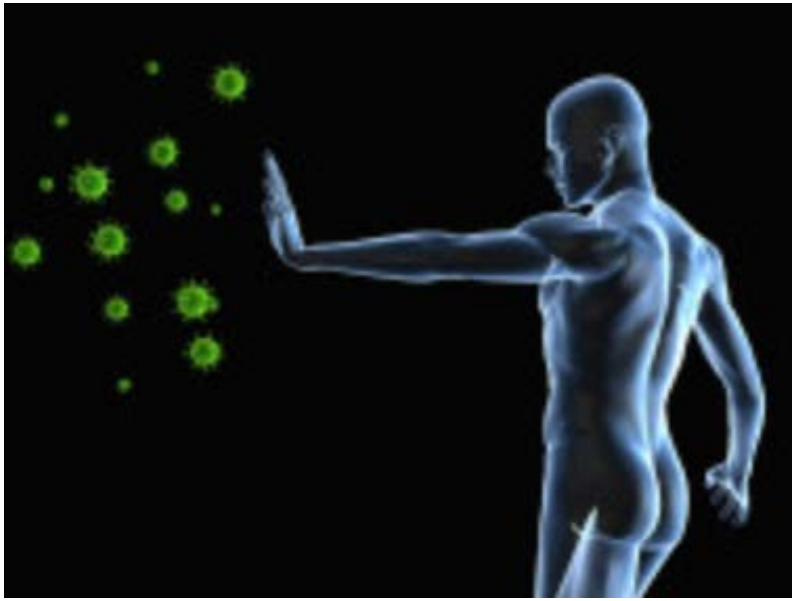
Hodgson K 2014

Antidepressiva: Ausmass der CYP Hemmung

Antidepressiva und CYP

Medikament	CYP1A1	CYP2C	CYP2D6	CYP3A4
Fluvoxamin	++++	++	0	+++
Fluoxetin	0	++	++++	++
(Metabolit)			(++++)	(+++)
Sertralin	0	++	+	++
(Metabolit)		(++)	(++)	(++)
Paroxetin	0	0	++++	0
Citalopram	0	0	0	0
Nefazadon	0	0	0	++++
Venlafaxin	0	0	0	0
(Metabolit)			(+)	
Bupropion	0	0	0	0
Mirtazapin	0	0	0	0

Note. 0 = unknown or insignificant; + = mild and usually insignificant; ++ = moderate and possibly significant; +++ = moderate and usually significant; ++++ = potent.
Source. In vivo and in vitro results: Crewe et al. 1992; Nemeroff et al. 1996; von Moltke et al. 1994, 1995.

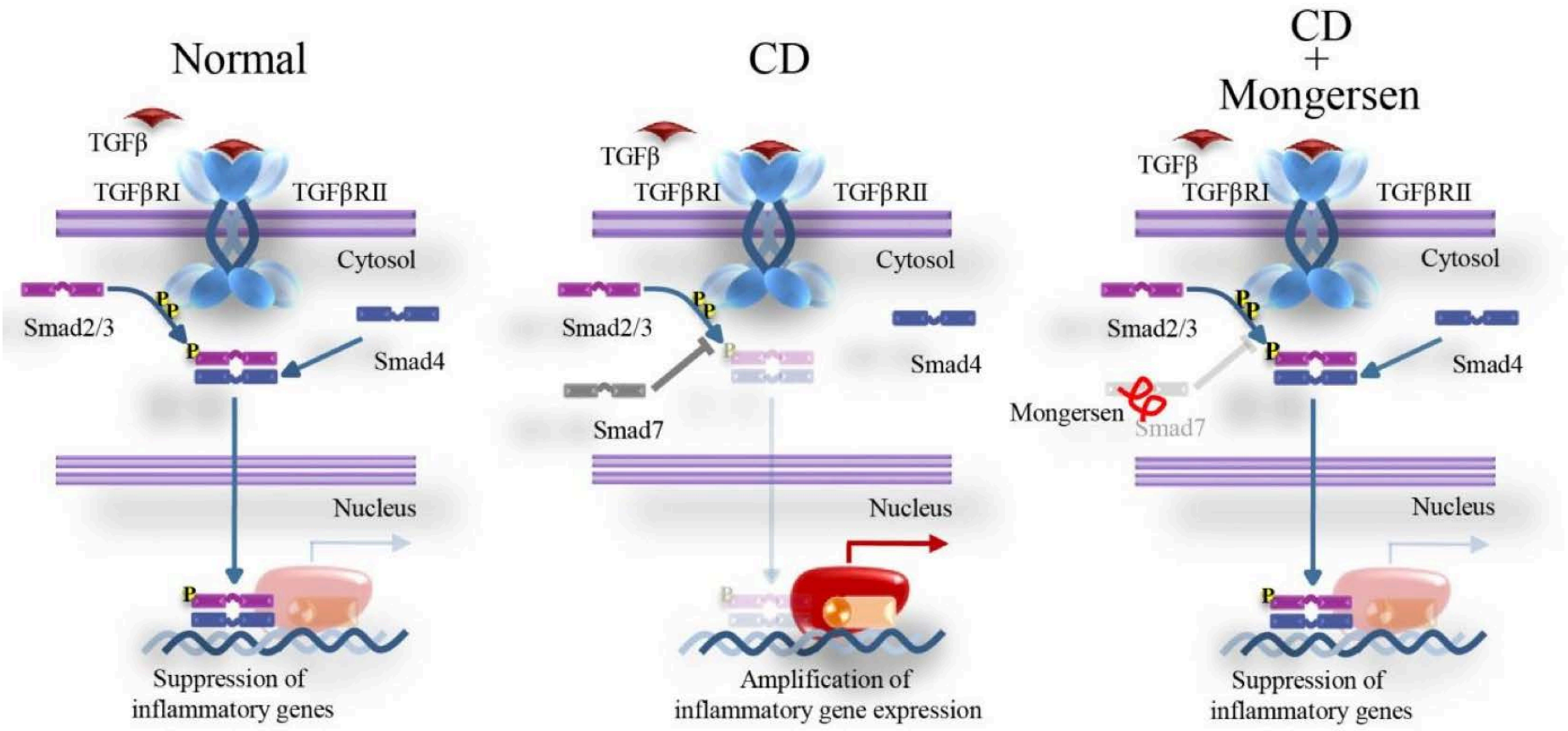


AUTOIMMUN KRANKHEITEN

HLA und Autoimmun-Krankheiten

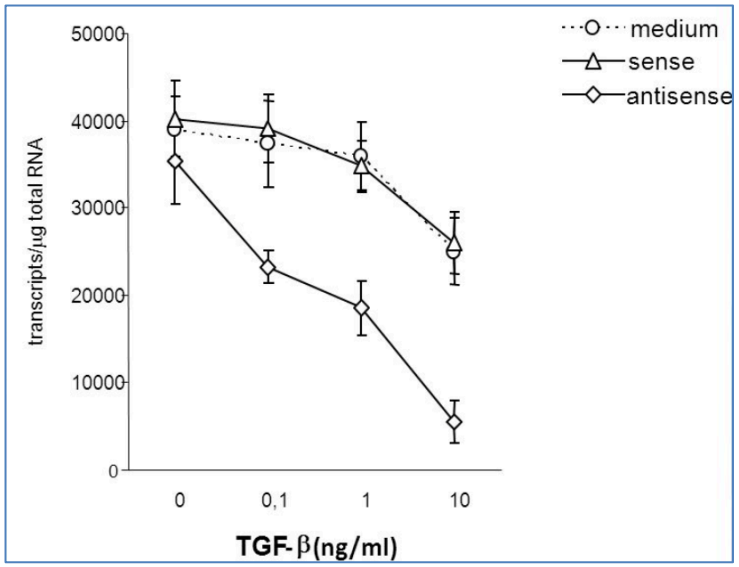
HLA Allel	Krankheiten mit erhöhtem Risiko	Relatives Risiko
HLA-B27	Ankylosierende Spondylitis	12
	Postgonokokkale Arthritis	14
	Akute anteriore Uveitis	15
HLA-B-47	21-Hydroxylase Mangel	15
HLA-DR2	SLE	2-3
HLA-DR3	Autoimmune Hepatitis	14
	Primäres Sjögren Syndrom	10
	Diabetes mellitus Typ 1	5
	Systemischer Lupus erythematodes	2-3
HLA-DR4	Rheumatode Arthritis	4
	Diabetes mellitus Typ 1	6
HLA-DR3 plus –DR4	Diabetes mellitus Typ 1	15
HLA-DQ2 und HLA-DQ8	Zöliakie	7

TGF-□1 Signalübertragung in normaler und Mukosa bei M. Crohn



- **Mongersen ist ein 21-Basen Oligonukleotid mit der Sequenz 5′-GTC GCC CCT TCT CCC CGC AGC-3′**

Mongerson Antisense Therapie bei Morbus Crohn



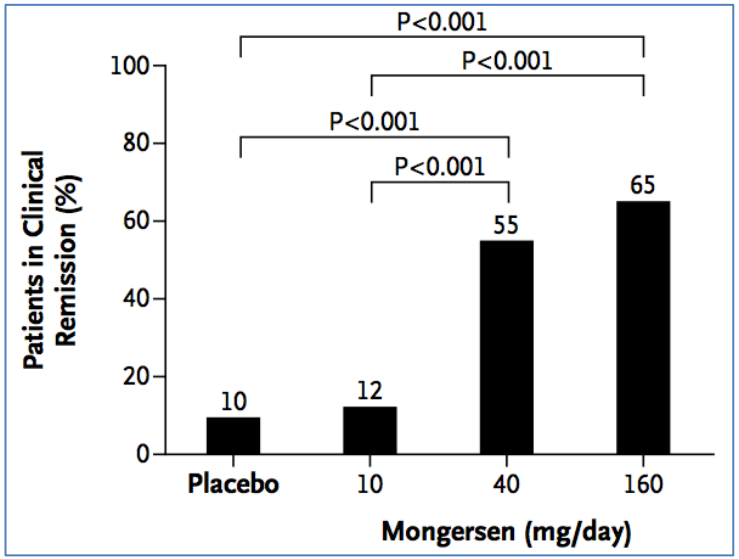
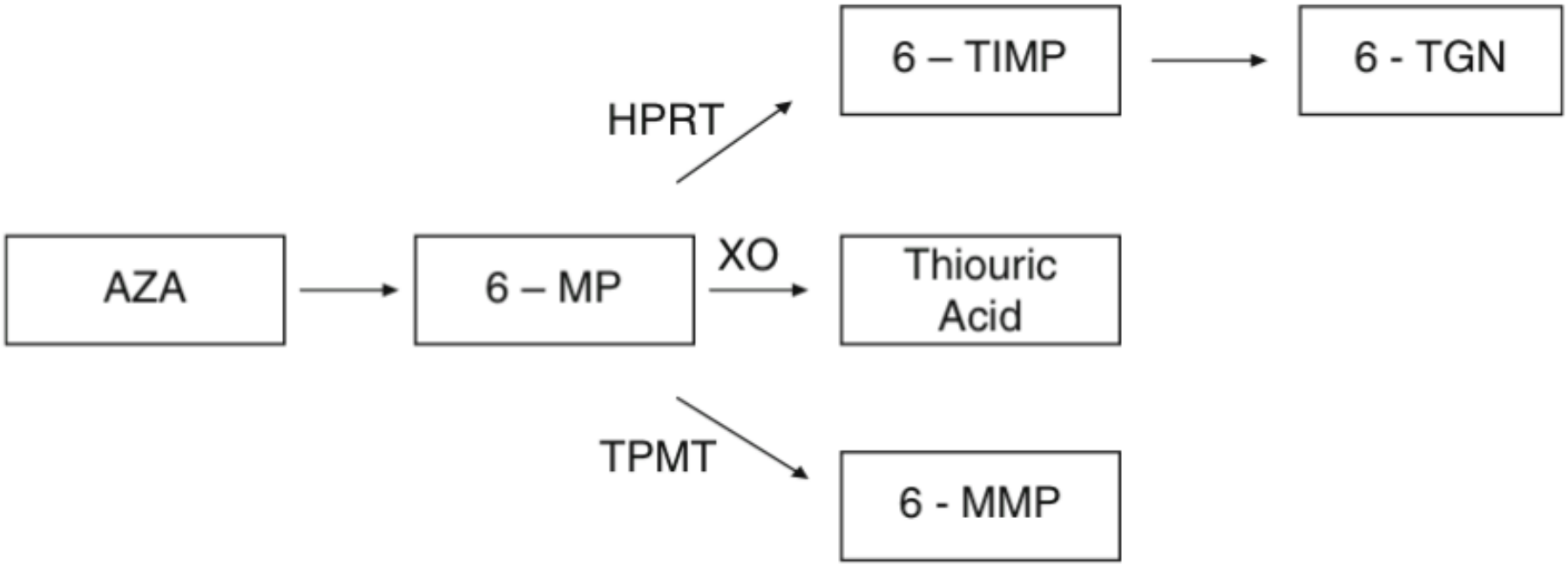


Table 3. Adverse Events Reported for 5% or More of Patients in Any Group.*

Variable	Placebo (N=42)	Mongersen		
		10 mg (N=41)	40 mg (N=40)	160 mg (N=43)
Patients with at least one adverse event — no. (%)	28 (67)	20 (49)	25 (62)	21 (49)
Adverse events — no.	64	39	50	47
Patients with adverse event — no. (%)				
Abdominal pain	6 (14)	4 (10)	4 (10)	5 (12)
Worsening of Crohn's disease	13 (31)	6 (15)	4 (10)	5 (12)
C-reactive protein level increased	4 (10)	2 (5)	2 (5)	4 (9)
Pyrexia	4 (10)	3 (7)	2 (5)	2 (5)
Abdominal mass	2 (5)	1 (2)	3 (8)	3 (7)
Diarrhea	1 (2)	0	2 (5)	3 (7)
Arthralgia	1 (2)	2 (5)	2 (5)	1 (2)
Urinary tract infection	1 (2)	6 (15)	2 (5)	2 (5)
Asthenia	1 (2)	0	2 (5)	1 (2)
Influenza-like illness	3 (7)	0	1 (2)	3 (7)
Headache	3 (7)	0	0	1 (2)
Increased aminotransferase levels	0	0	2 (5)	0

Monteleone G 2015, Moneleone G 2001

Thiopurin Metabolismus



TPMT Thiopurin Methyltransferase
XO Xanthin Oxidase
HPRT Hypoxanthine phosphorosyl Transferase
6-TIMP 6-Thiosin Monophosphate
6-MMP 6 Methylmerkaptopurin
6-TGN 6-Thioguanin Nukleotide
AZA Azathioprin
6-MP 6-Merkaptopurin

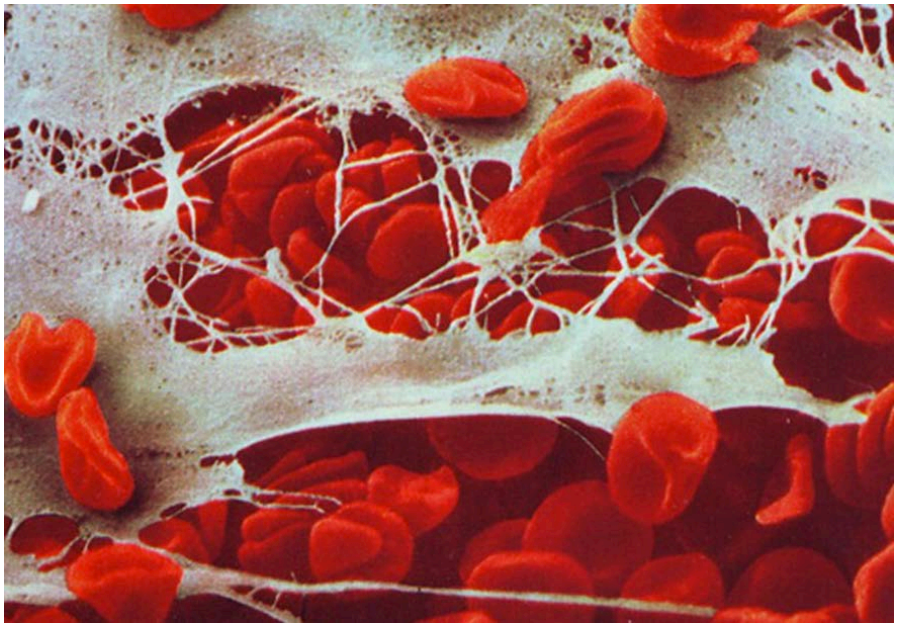
Genotyp und Adalimumab

Genotype distributions and allele frequencies of the *FcGR2A* (R>H) genetic variants in responder and nonresponder rheumatoid arthritis patients treated with adalimumab at 14 weeks

Subgroup (n)	Genotype, n (%)	Allele test, R allele frequency (%)	p-value	OR (95% CI)	p-value†	OR (95% CI)†
FcGR2A						
Good response (n = 162)	RR: 56 (35); RH: 75 (46); HH: 31 (19)	57.7	**0.026**	**1.43 (1.04–1.98)**	**0.017**	**1.53 (1.08–2.17)**
No good response (n = 140)	RR: 34 (24); RH: 68 (49); HH: 38 (27)	48.6				
Remission (n = 94)	RR: 33 (35.1); RH: 38 (40.4); HH: 23 (24.5)	55.3	0.54	1.11 (0.78–1.57)	0.56	1.18 (0.76–1.63)
No remission (n = 208)	RR: 57 (27.4); RH: 105 (50.5); HH; 46 (22.1)	52.6				

†Adjusted by age, gender, concomitant methotrexate and DAS28 at baseline.

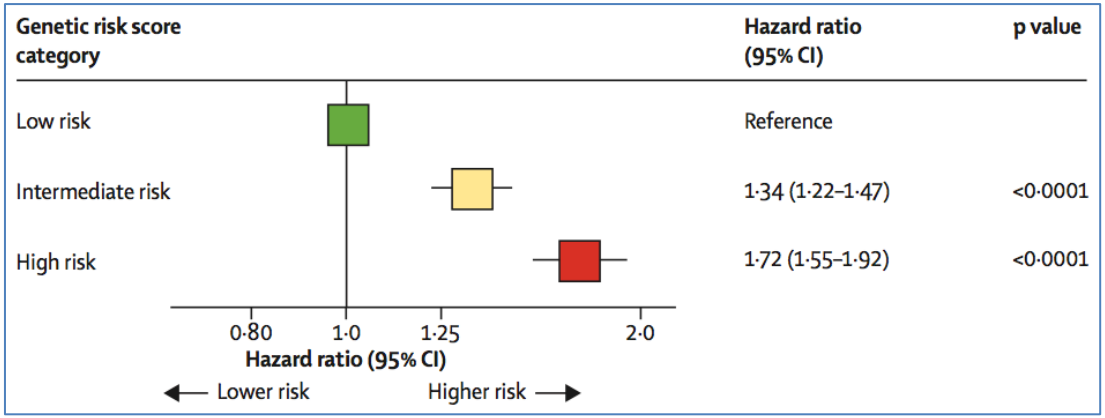
Davila-Fajardo CL 2014



HERZ-KREISLAUF/GERINNUNG

Multi-Lokus-genetischer Risiko-Score in der koronaren Herzkrankheit

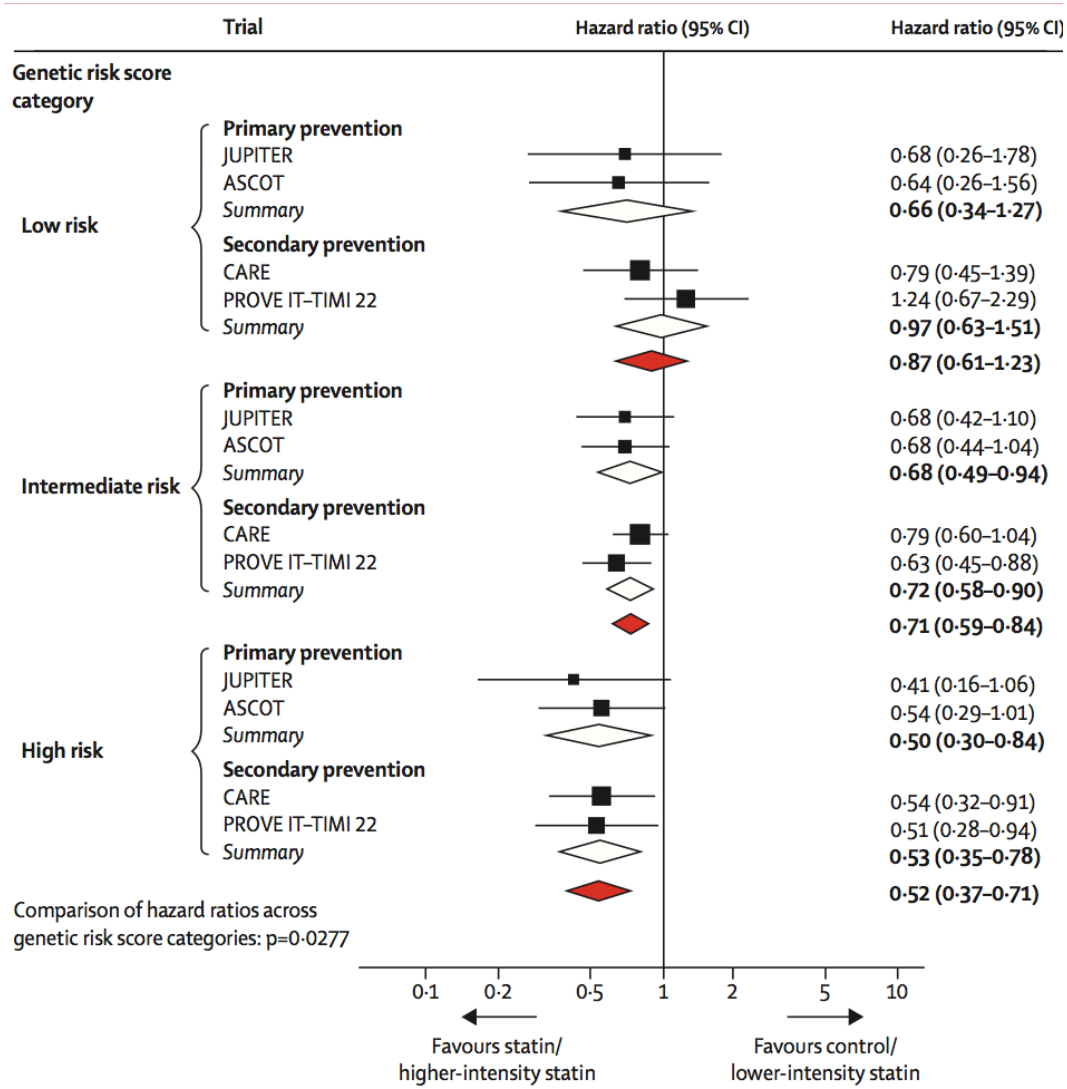
- **Erbliche Faktoren bestimmen 30-60% der Variabilität des koronaren Risikos**
- **Risikoscore mit 27 SNPs (assoziiert mit KHK in früheren GWAS)**



	Lead SNP	OR for coronary heart disease	Risk allele	Risk allele frequency
1p13.3 (*SORT1*)	rs646776	1·19	T	0·77
1p32.2 (*PPAP2B*)	rs17114036	1·17	A	0·92
1p32.3 (*PCSK9*)	rs11206510	1·15	T	0·82
1q41 (*MIA3*)	rs17465637	1·14	C	0·75
2q33.1 (*WDR12*)	rs6725887	1·17	C	0·13
3q22.3 (*MRAS*)	rs9818870	1·15	T	0·15
6p21.31 (*ANKS1A*)	rs17609940	1·07	G	0·79
6p24.1 (*PHACTR1*)	rs9349379	1·12	G	0·43
6q23.2 (*TCF21*)	rs12190287	1·08	C	0·63
6q25.3 (*LPA*)	rs3798220	1·47	C	0·01
6q25.3 (*LPA*)	rs10455872	1·70	G	0·07
7q32.2 (*ZC3HC1*)	rs11556924	1·09	C	0·64
9p21.3 (*CDKN2A*)	rs4977574	1·29	G	0·55
9q34.2 (*ABO*)	rs9411489	1·10	T	0·21
10q11.21 (*CXCL12*)	rs1746048	1·17	C	0·86
10q24.32 (*CYP17A1*)	rs12413409	1·12	G	0·90
11q23.3 (*APOA5*)	rs964184	1·13	G	0·13
12q24 (*HNF1A*)	rs2259816	1·08	T	0·35
12q24.12 (*SH2B3*)	rs3184504	1·13	T	0·48
13q34 (*COL4A1*)	rs4773144	1·07	G	0·41
14q32.2 (*HHIPL1*)	rs2895811	1·07	C	0·45
15q25.1 (*ADAMTS7*)	rs3825807	1·08	T	0·57
17p11.2 (*RASD1*)	rs12936587	1·07	G	0·53
17p13.3 (*SMG6*)	rs216172	1·07	C	0·64
17q21.32 (*UBE2Z*)	rs46522	1·06	T	0·48
19p13.2 (*LDLR*)	rs1122608	1·15	G	0·77
21q22.11 (*KCNE2*)	rs9982601	1·20	T	0·13

Mega JL 2015

Hazard ratio der koronaren Herzkrankheit unter Statinen je nach genetischem Risiko Score

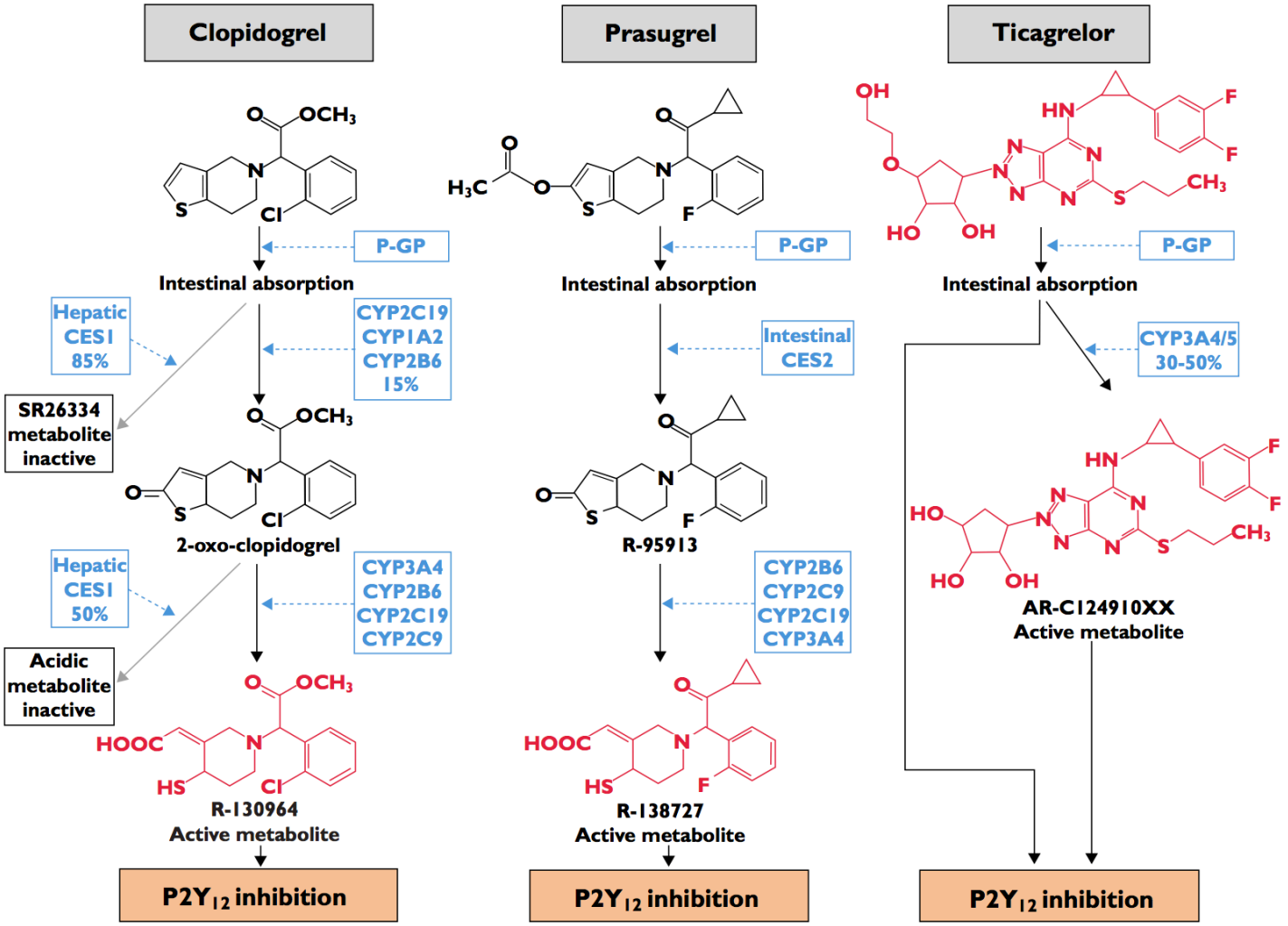


Relative Risikoreduktion der Statin Therapie

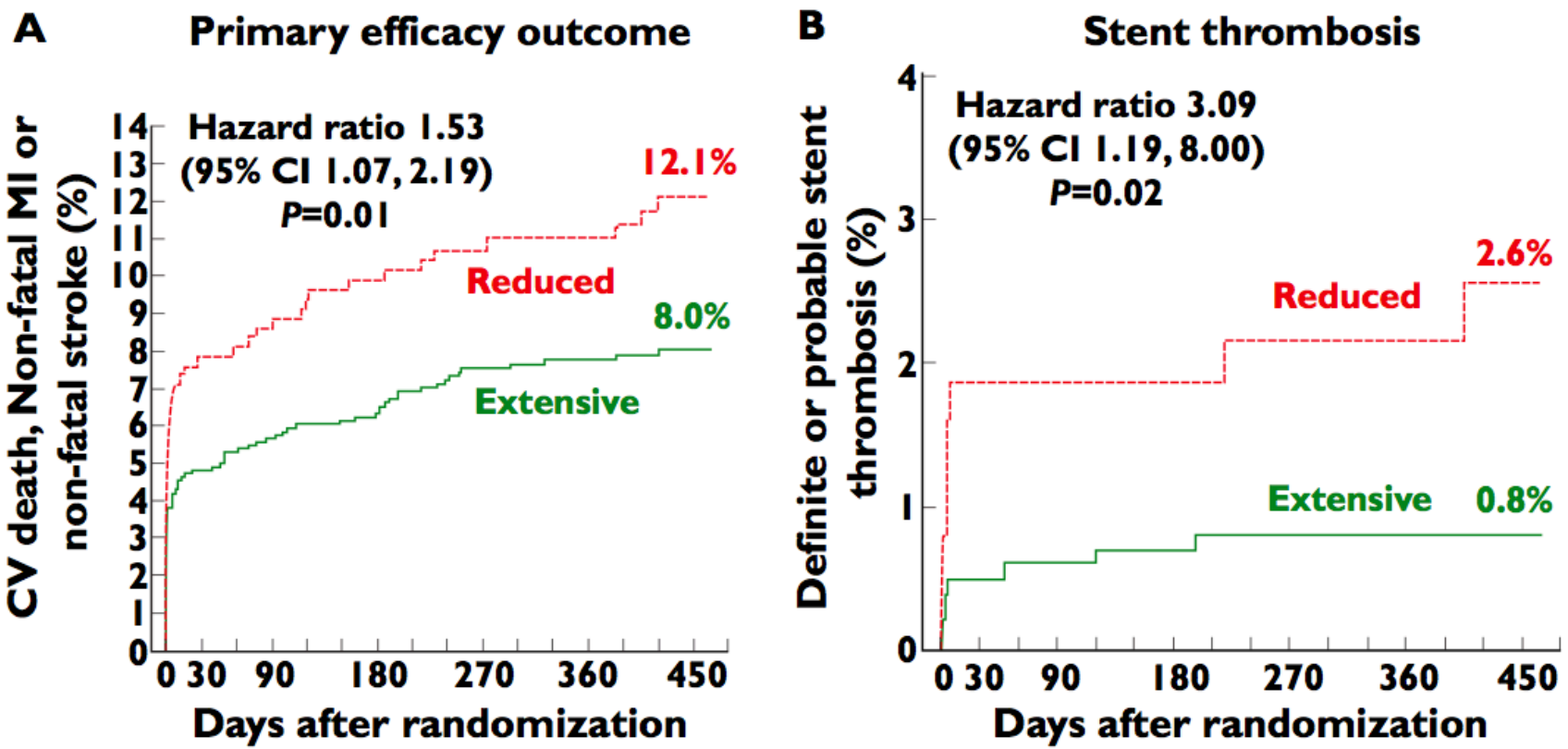
	1°	2°	1°+2°
Low	34%	3%	13%
Med	32%	28%	29%
High	50%	47%	48%

Mega JL 2015

Metabolismus von Clopidogrel, Prasugrel und Ticagrelor



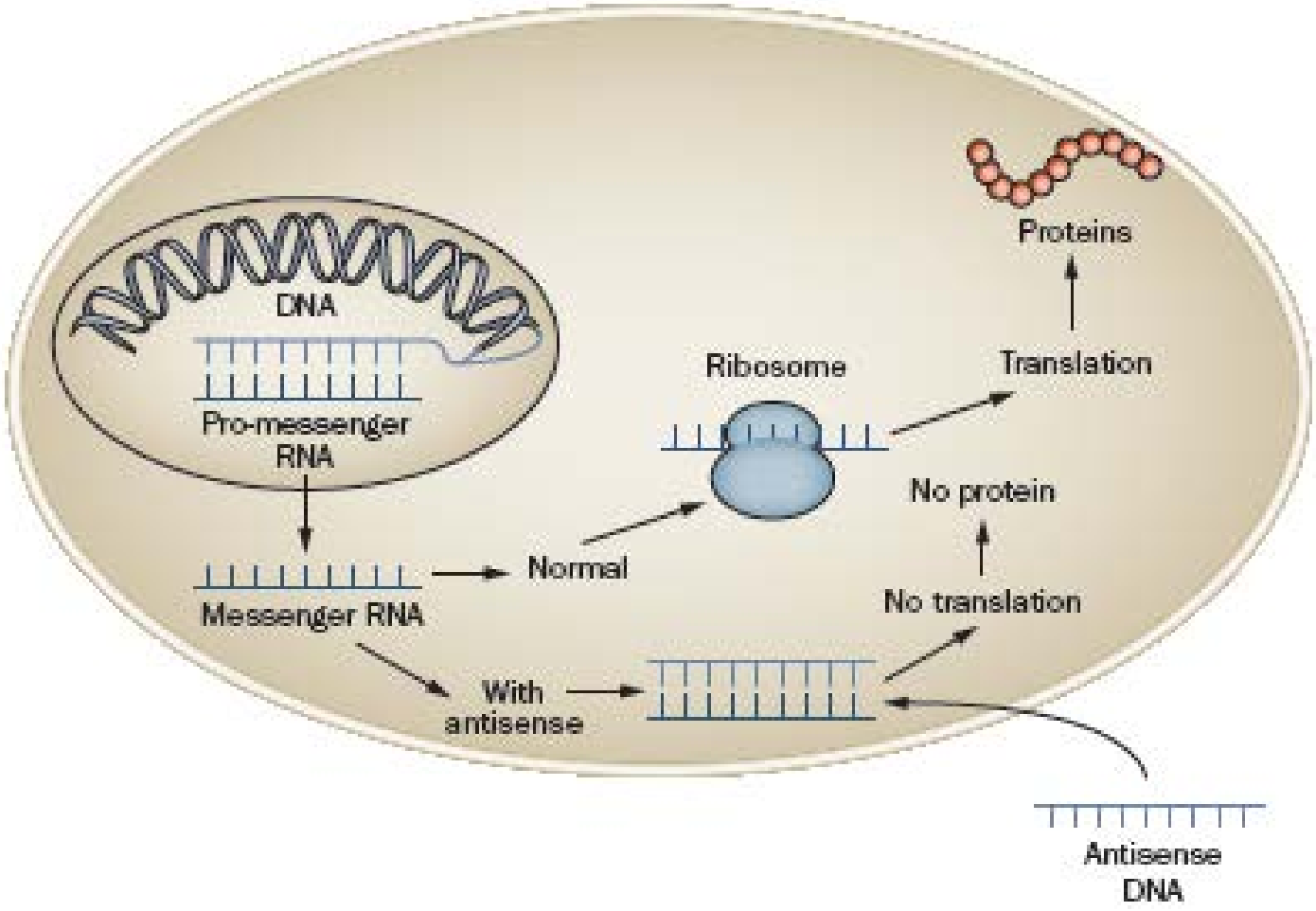
Clopidogrel Wirkung und CYP2C19 Genotyp



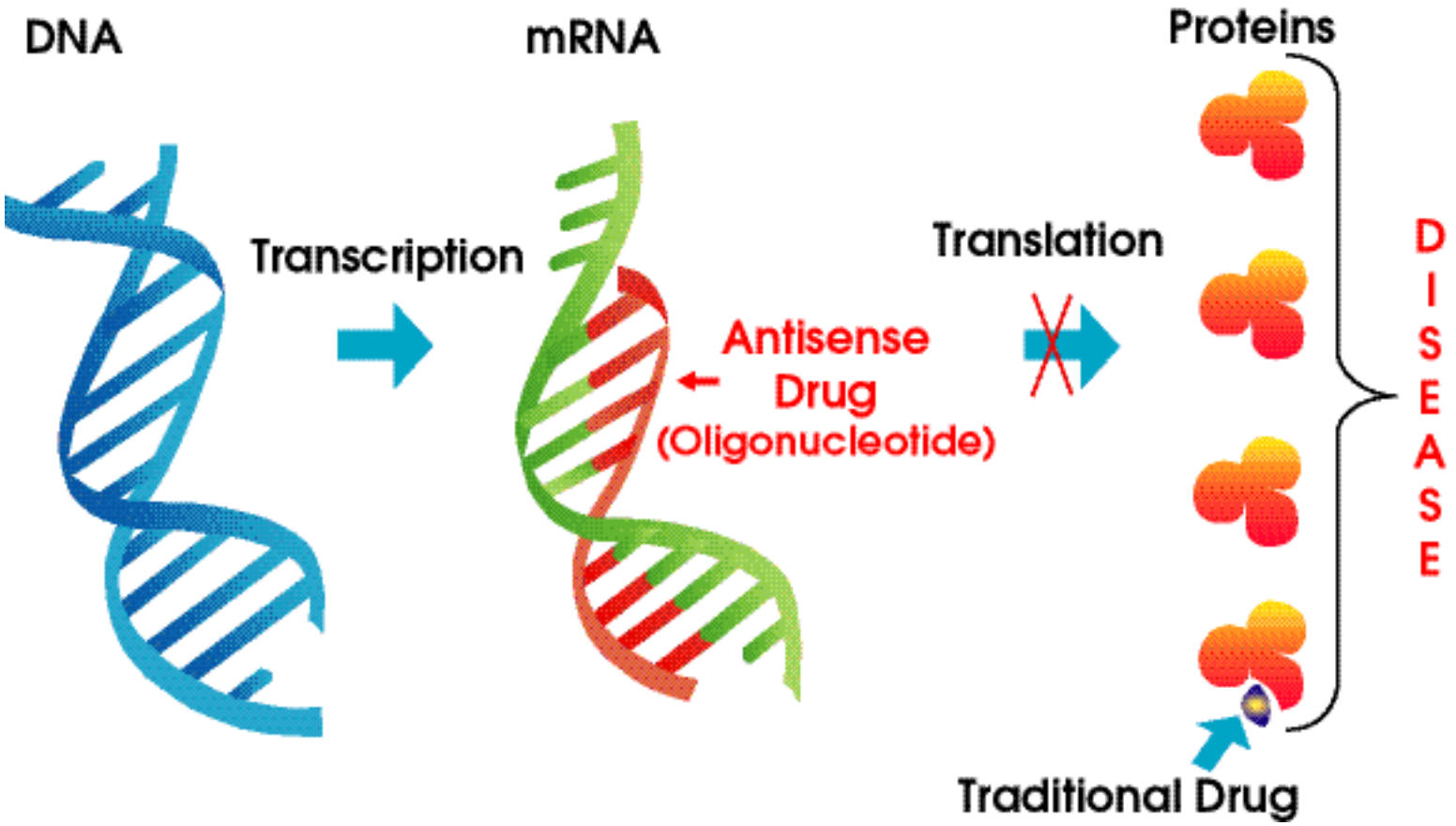
Nicht-Träger(CYP2C19*1/*1, *1/*17 und *17/*17) *vs*. Träger von CYP2C19 loss-of-function Allelen (Träger von *2, *3, *4,*5 oder *8 allele) behandelt in TRITON-TIMI 38 Studie mit Clopidogrel

Mega JK 2009

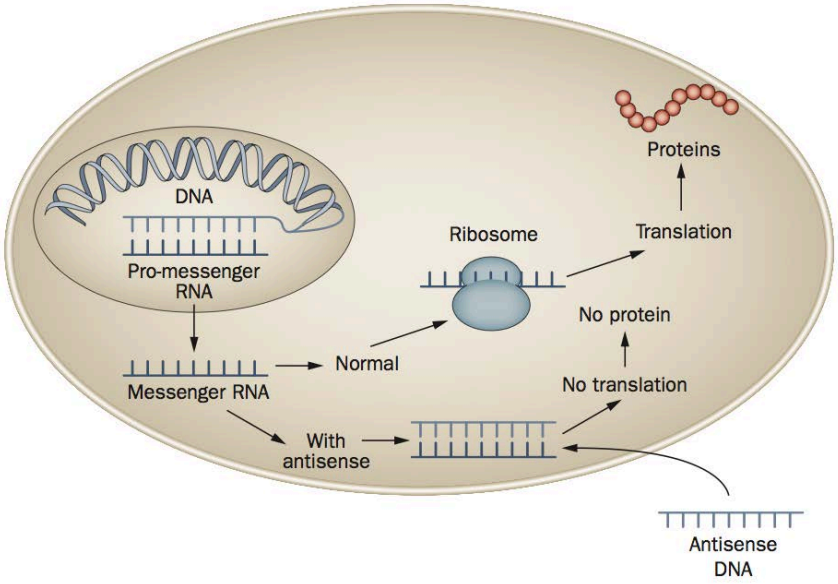
Wie Antisense funktioniert

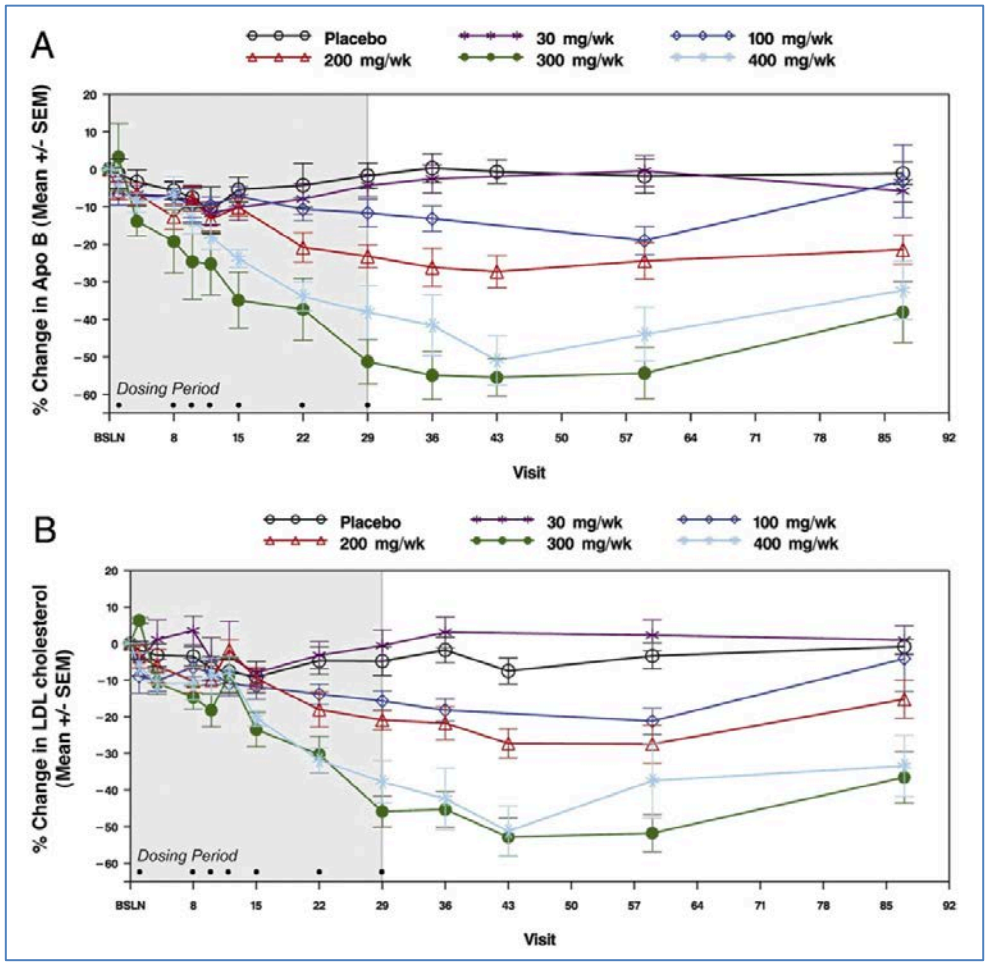


Wie funktioniert Mipomersen?



Antisense Nukleotide in der Behandlung der familiäre Hypercholesterinämie





Veränderungen der Lipide und Apolipoprotein B mit Mipomersen

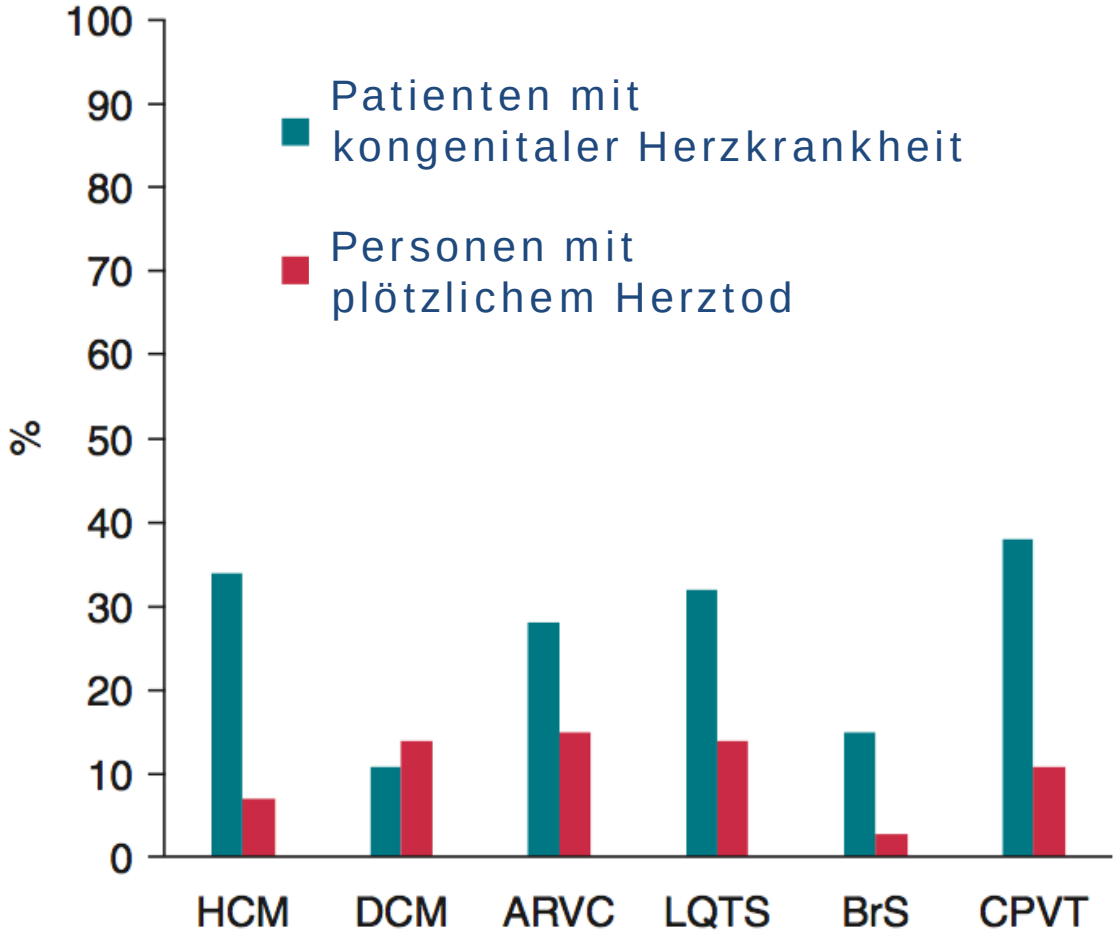
Lipid parameter	Mipomersen 200 mg per week				Mipomersen 300 mg per week	
	Total cholesterol <300 mg/dl[61] (*n* = 8); trial period 4 weeks	Concomitant statin therapy[63] (*n* = 10); trial period 13 weeks	Heterozygous FH[65] (*n* = 11); trial period 6 weeks	Homozygous FH[66] (*n* = 34); trial period 26 weeks	Concomitant statin therapy[63] (*n* = 8); trial period 5 weeks	Heterozygous FH[65] (*n* = 9); trial period 6 weeks
ApoB	−50.2±17.3	−35.7±14.1	−23±19	−26.8% (−32.7 to −20.8)	−54.4±19.2	−33±22
LDL-C	−30.6±15.9	−35.8±16.4	−21±23	−24.7% (−31.6 to −17.7)	−51.8±14.3	−34±18
VLDL-C	NR	−11.0±21.6	−14±28	−17.4% (−37.5 to −3.5)	−27.4±87.5	−6±61
Non-HDL-C	NR	−28.5±17.5	−21±19	−24.5% (−31.2 to −17.8)	−52.0±14.9	−31±20
HDL-C	NR	−1.1±8.5	−1±13	15.1% (3.2 to 27.1)	2.9±17.3	6±11
Total cholesterol	NR	−21.8±12.9	−16±15	−21.2% (−27.4 to −15.0)	−38.5±12.5	−25±17
Triglycerides	NR	−14.6	−23 (−48 to 48)	−17.4% (−36.0 to −4.2)	−40.5	−22 (−62 to 137)
Lp(a)	NR	NR	−17±19	−31.1% (−39.1 to −23.1)	NR	−24±26

Plötzlicher Herztod bei jungen Personen (1 - 40 Jahre)

Ursache	%
Atherosklerotische koronare Herzkrankheit	2-25
Koronare Vaskulitis	≈ 2
Kongenital Abnormalien der Koronarien	≈ 4
Hypertrophe Kardiomyopathie	4-36
Arrhythmogene rechtsventrikuläre Kardiomyopathie	4-13
Dilatiative Kardiomyopathie	3-5
Normales, gesundes Herz	20-40
Long QT Syndrom	**16-20**
Brugada Syndrom	**4-20**
Catecholaminerge polymorphe ventrikuläre Tachykardie (CPVT)	14-21
Myokarditis	1-1
Mitralklappen Prolaps	≈ 3
Angeborene Herzkrankheit (nicht koronar)	3-7
Aortendissekation	3-5
Andere	≈ 15
Unerklärliche Gründe	≈ 6

Lombardi R 2013

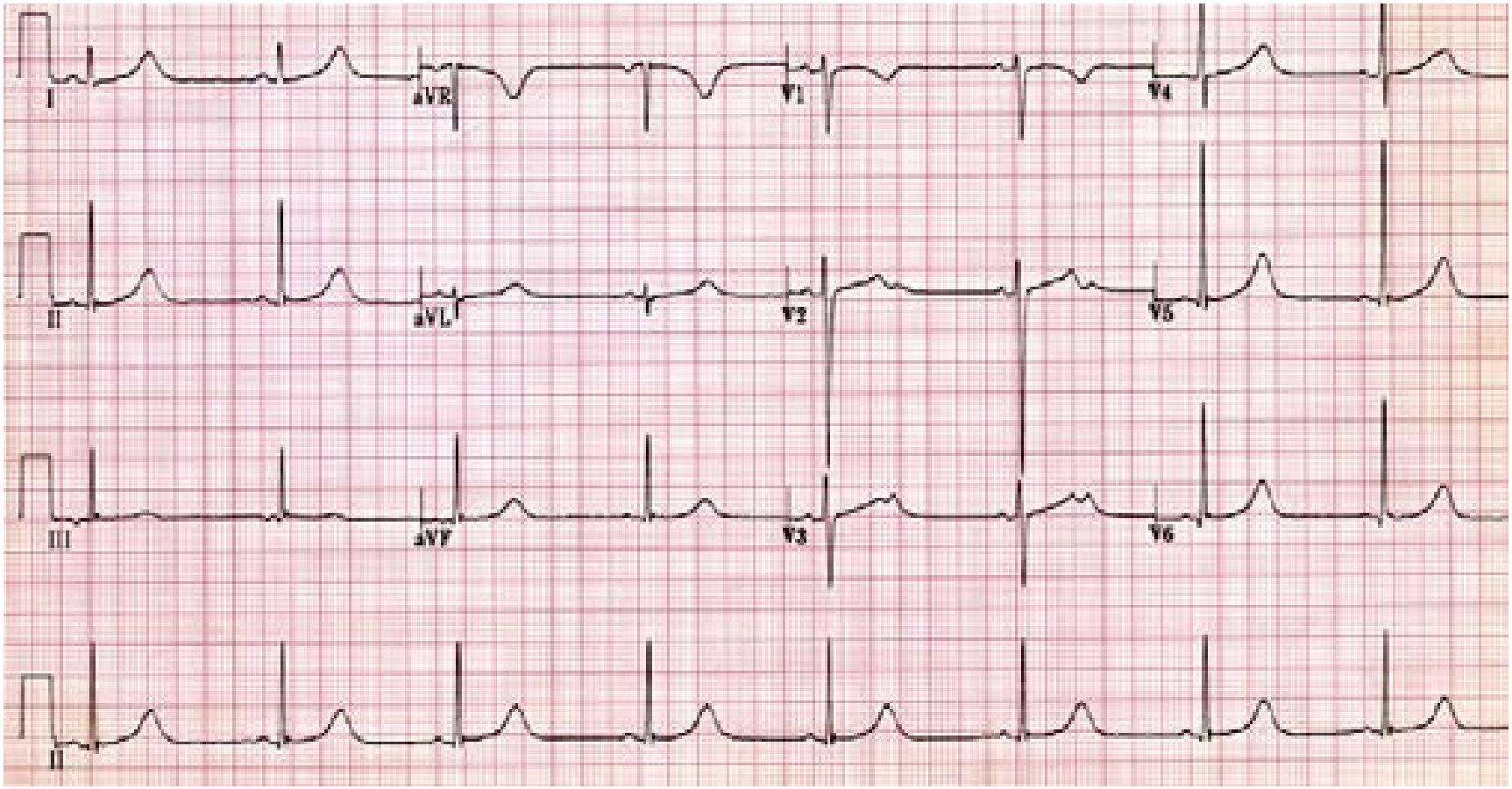
Mutationsraten von Genen bei kardiologischen Patienten und Patienten mit plötzlichem Herztod (SCD)



HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; ARVC, arrhythmogenic right ven- tricular cardiomyopathy; LQTS, long QT syndrome; BrS, Brugada syndrome; CPVT, cathecholaminergic polymorphic ventricular tachycardia.

Hertz CL 2014

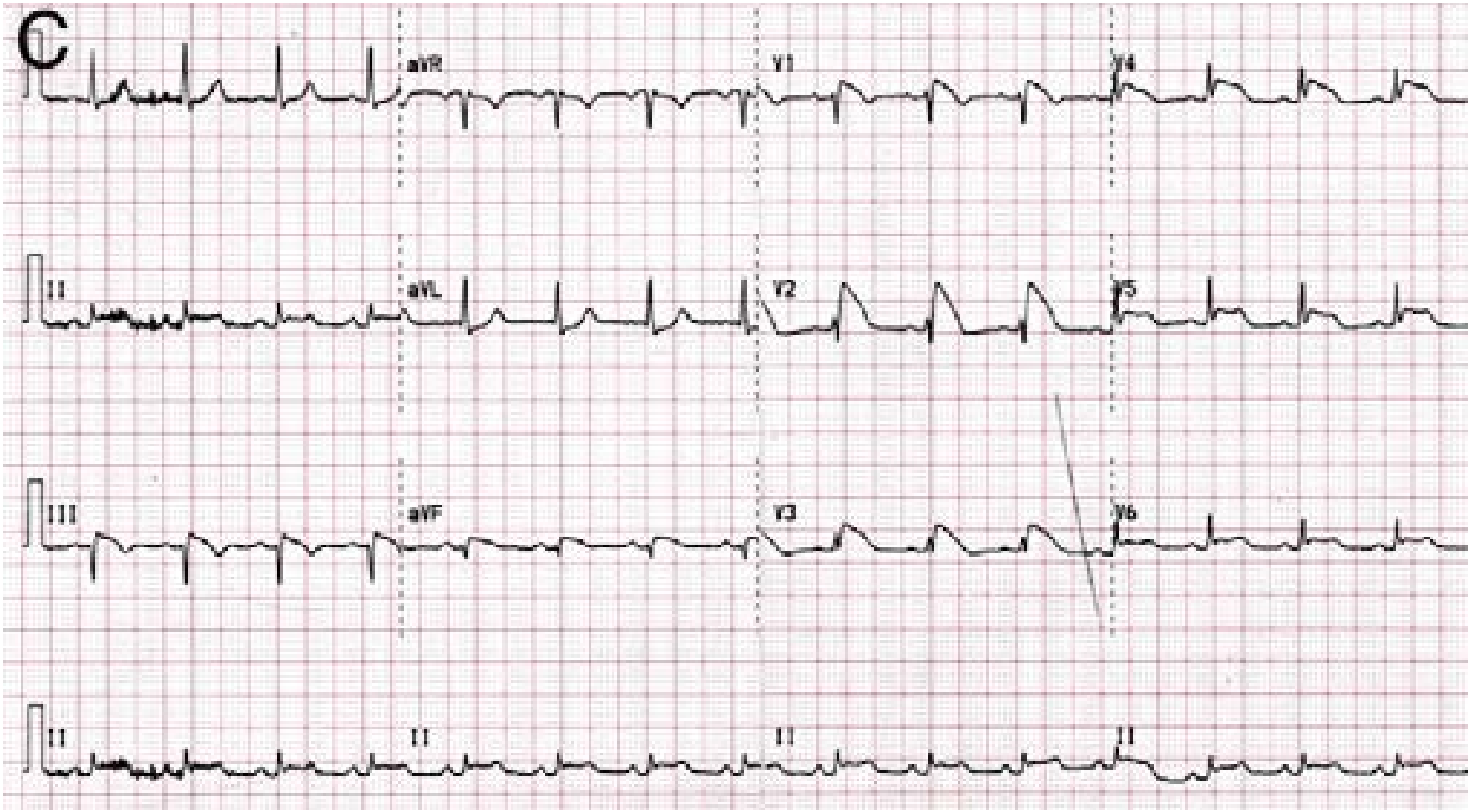
Kongenitales Long-QT Syndrom



QTc interval of > 460 ms

Chandra N 2013

Brugada Syndrome



Characteristic coved-type and down-sloping ST-segment elevation in leads V1 through V4 (type 1 electrocardiographic pattern)

Chandra N 2013

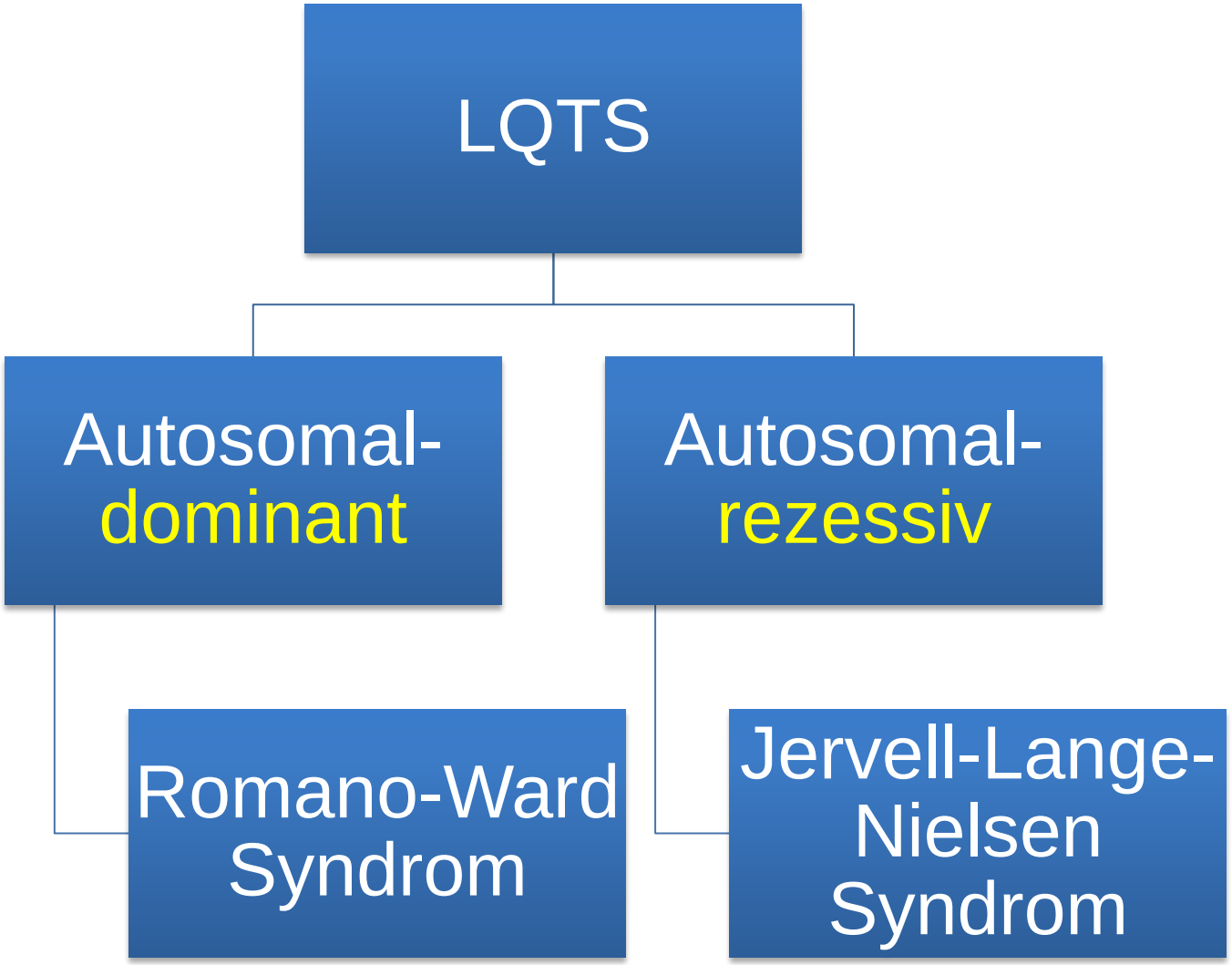
Genetische Ursachen des Brugada Syndroms

Syndrom	Lokalisation	Gen	Genprodukt
BRGDA1	3p21	*SCN5A*	Natriumkanal (Ina)
BRGDA2	3p22.3	*GPD1L*	Glycerol-3-Phosphat Dehydrogenase 1-like
BRGDA3	12p13.3	*CACNA1C*	Kalzium Kanal, Voltage-abhängig, L-Typ, Alpha 1c Untereinhaeit (Cav1.2)
BRGDA4	10p12	*CACNB2*	Kalzium Kanal, Voltage-abhängig, L-Typ, Beta-1 Untereinheit
BRGDA5	19q13.1	*SCN1B*	Natriumkanal Untereinheit Beta-1
BRGDA6	11q13-q14	*KCNE3*	Kaliumkanal, Voltage-gated, Isk-Familie 3
BRGDA7	11q23.3	*SCN3B*	Natriumkanal, Untereinheit Beta-3
BRGDA8	15q24-q25	*HCN4*	Kalium/Natrium Hyperpolarisation-aktivierte, zyklisches Nukleotid-gated Kanal 4

Genetische Testung des Brugada Syndroms

- **Wenig sinnvoll**
- **Nur in 20% ein positives Ergebnis**
- **Genetischer Befund erlaubt keine Risikostratifizierung**
- **Goldstandard = pharmakologische Testung**

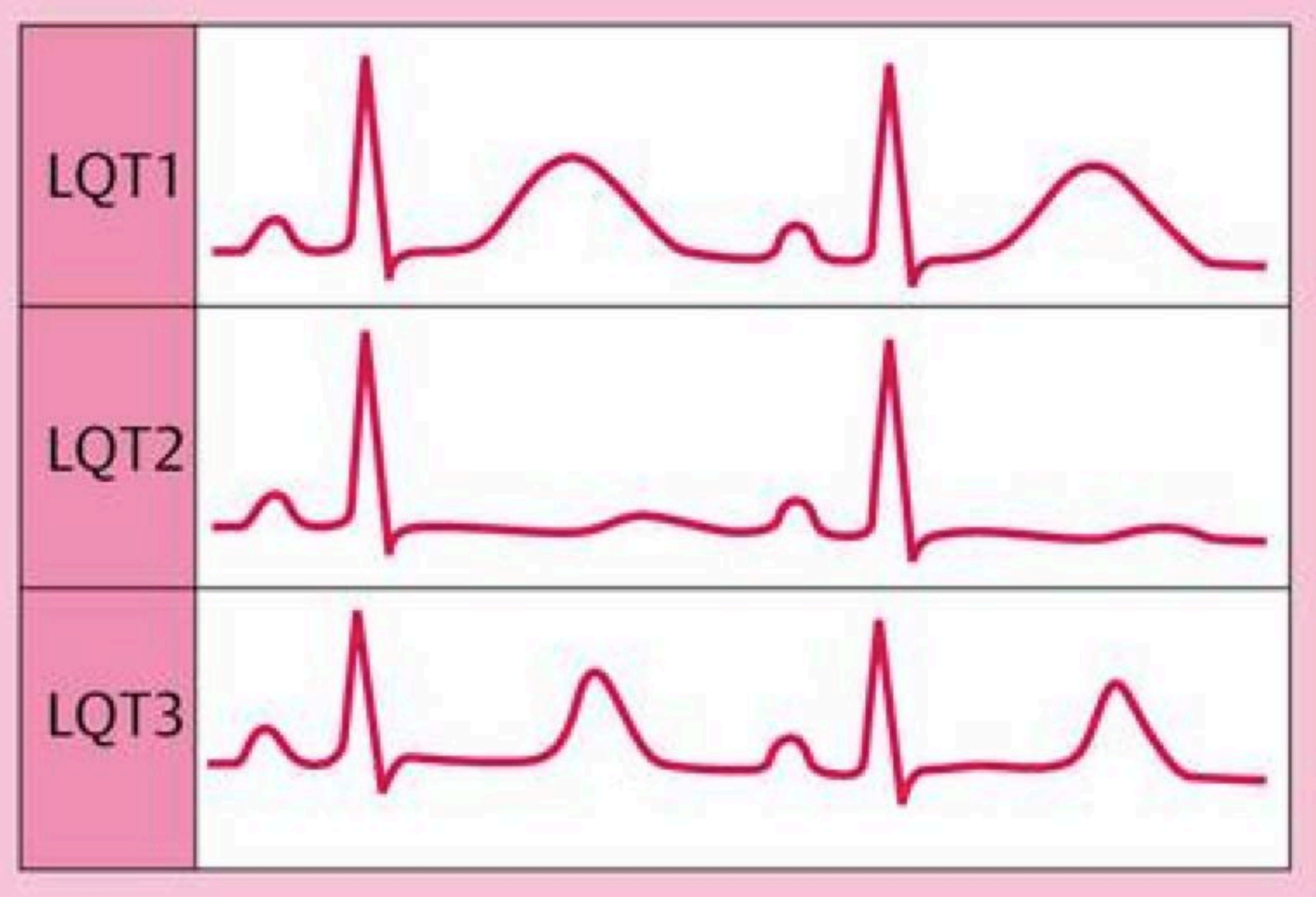
Long-QT Syndrom (LQTS)



Genetische Testung des LQTS

- **Paradebeispiel für Nutzen der Gendiagnostik**
- **Kenntnis des Genotyps erlaubt Vorhersage des Phänotyps und spezifische Handlungs-empfehlungen**
- **In einzelnen Fällen Ableitung des Genotyps anhand des EKGs**

LQTS Typen



KCNQ1

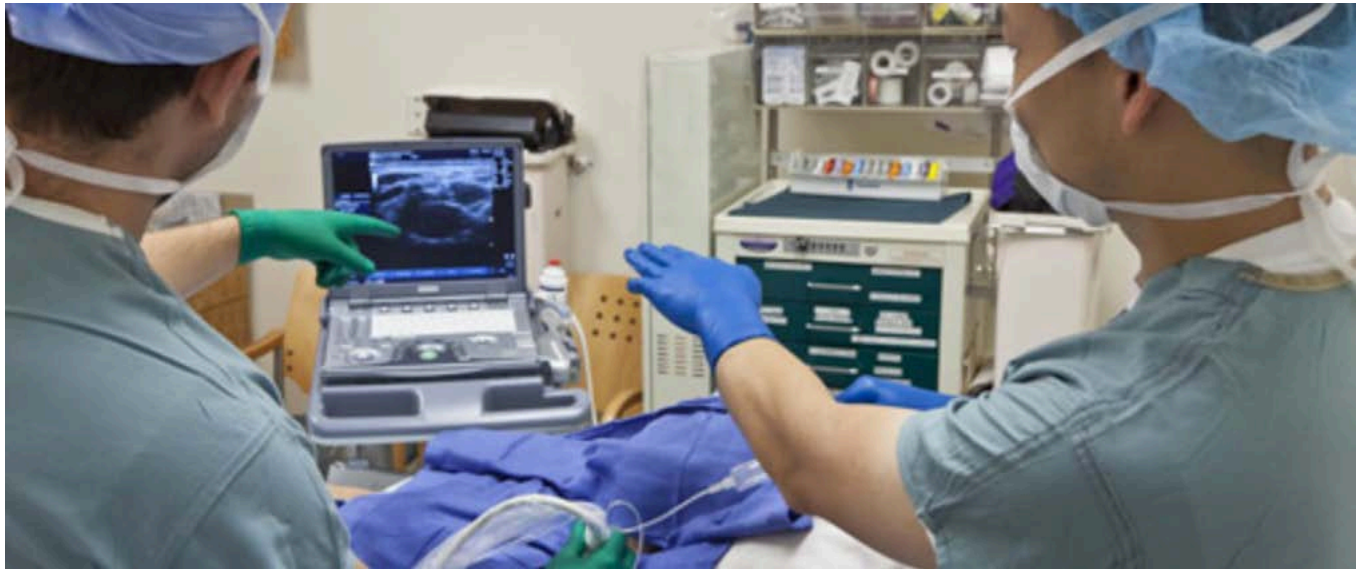
KCHN2

SCN5A

Risikostratifizierung für den plötzlichen Herztod

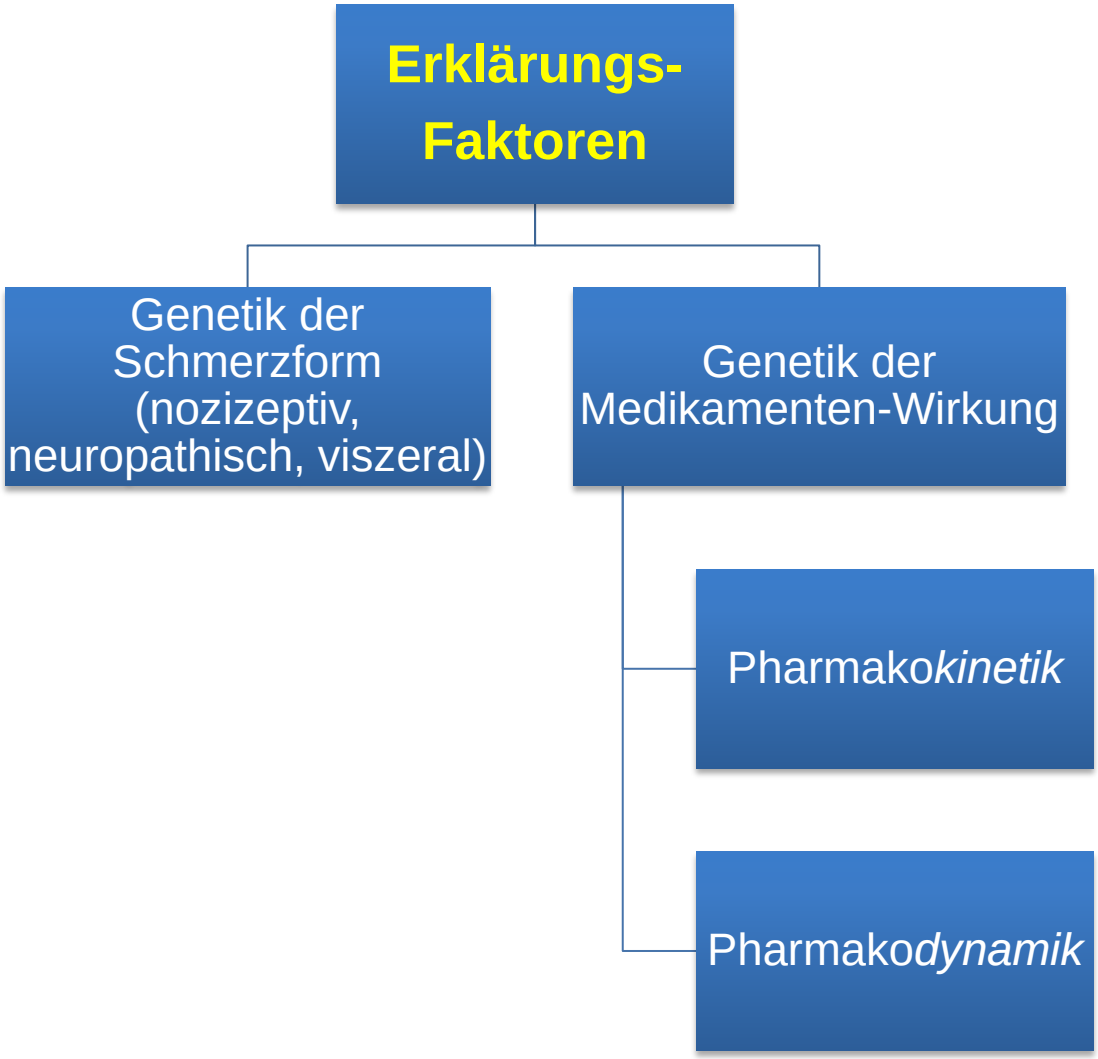
Risiko für Event (Synkope, Herzstillstand, Tod) vor dem 40. Lebensjahr	QTc-Zeit in Abhängigkeit von Genotyp und Geschlecht
> 50%	QTc ≥ 500 ms: LQT1 (m/w), LQT2 (m/w), LQT3 (m)
30–50%	QTc ≥ 500 ms: LQT3 (w)
	QTc < 500 ms: LQT2 (w), LQT3 (m/w)
< 30%	QTc < 500 ms: LQT1 (m/w), LQT2 (m)

- **LQTS1: 40% (Auslöser: körperliche Belastung)**
- **LQTS2: 40% (Auslöser: auditorische Stimuli im Schlaf)**
- **LGTS3: 5% (Auslöser: Bradykardien, zB Betablocker)**



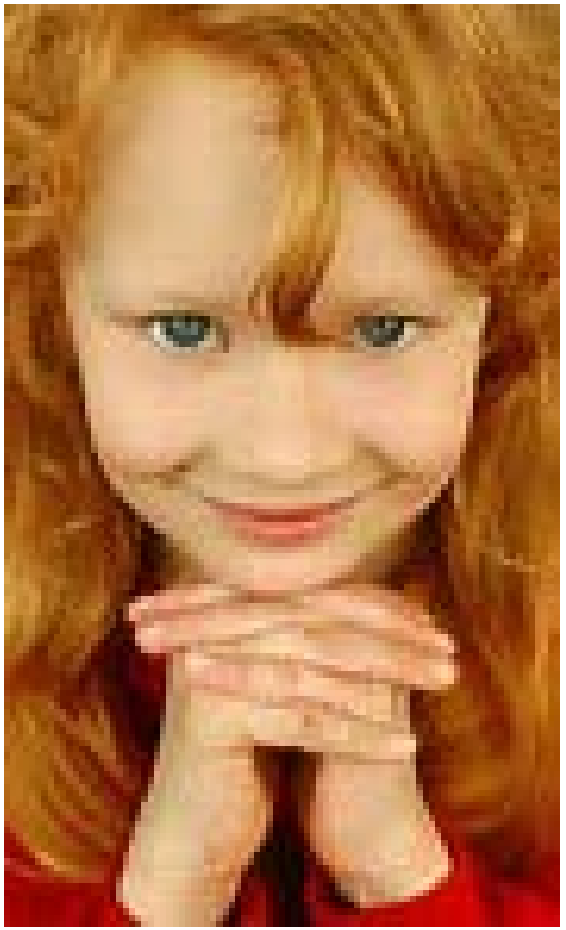
PERIOPERATIVE MEDIZIN/ANÄSTHESIE

Genetik der Analgesie

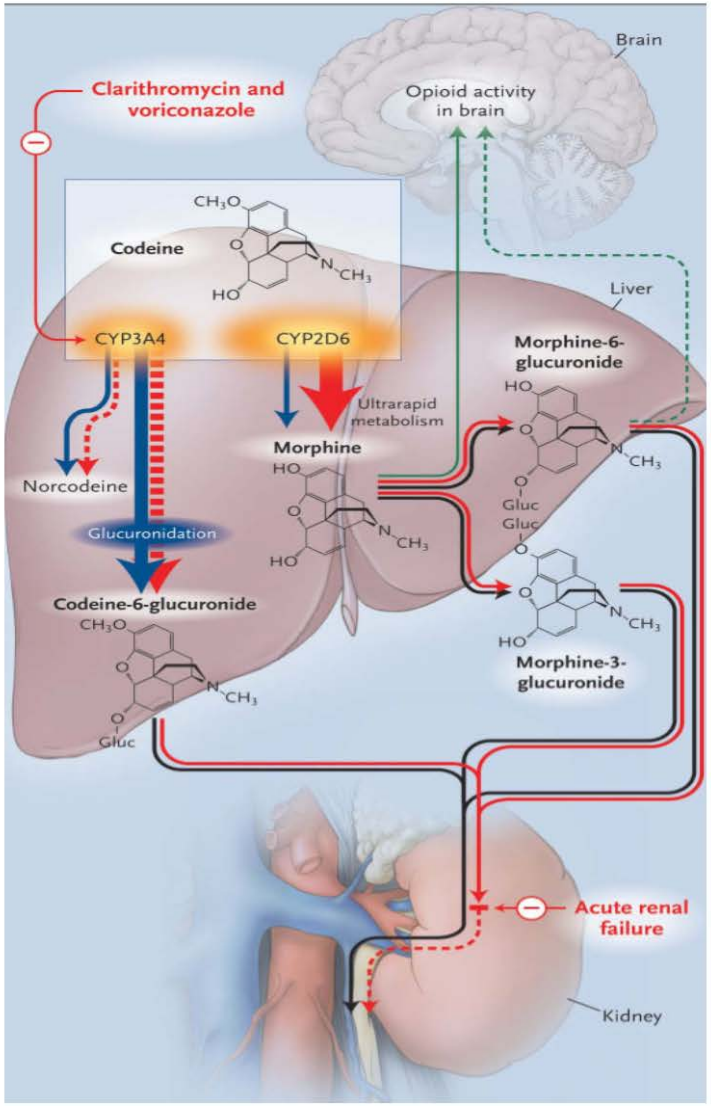


Melanocortin-1-Rezeptor

Rot-haarige benötigen 20% mehr Anästhetika



Codeine Toxizität



Codeine toxicity and CYP2D6 Ultrarapid Metabolizer Genotype

62-y.o.man with pneumonia received codeine 25 mg tid, developed life-threatening opioid intoxication.

Retrospectively, it turned out that he had duplicated CYP2D6 genes and transformed more codeine to morphine.

Gasche et al. 2004
NEJM 351:2827-2831

Postoperatives Erbrechen (PONV)

- **Ultraschnelle Metabolisierer CYP2D6 ➔ PONV↑**
- **HTR3A Variante c1377A>G ➔ PONV↑**
- **HTR3B Variante ➔ PONV↓**

Propofol

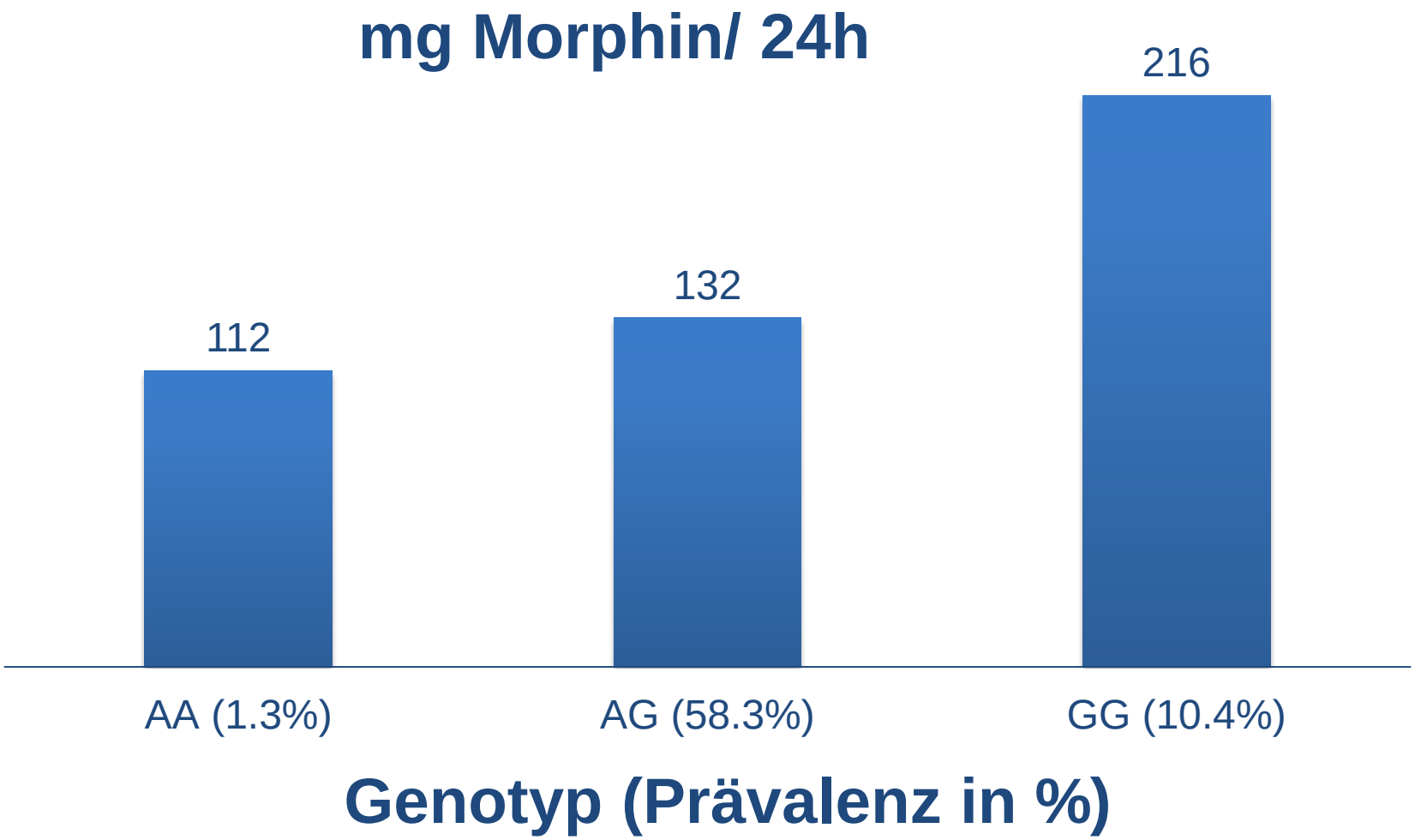
- **Hydroxylierung via CYP2B6**
- **O-Glukuronidierung via UGT1A9**
- **Bisher einziger SNP: UGT1A1 766G>A ➔ unerwünschte Nebenwirkungen ↑**

Hauptsächliche CYP Enzyme und ihre Substrate in der Anästhesie

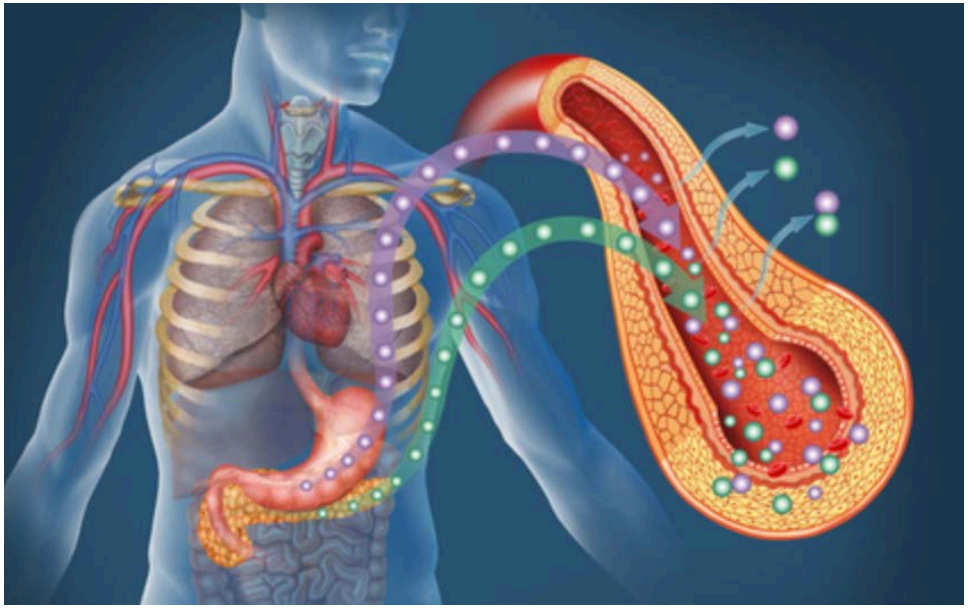
CYP2B6	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A4	CYP3A5
Propofol	Propofol Parecoxib	Diazepam Barbiturates Omeparzole Pantoprazole	Codein	Sevofluran Halothane Isoflurane Paracetamol	Diazepam Midazolam Temazepam Fenatalyn Alfentanil Lignocaine Vecuronium	Diazepam

Bhasker et al.

Morphinverbrauch und OPRM1 Genotyp



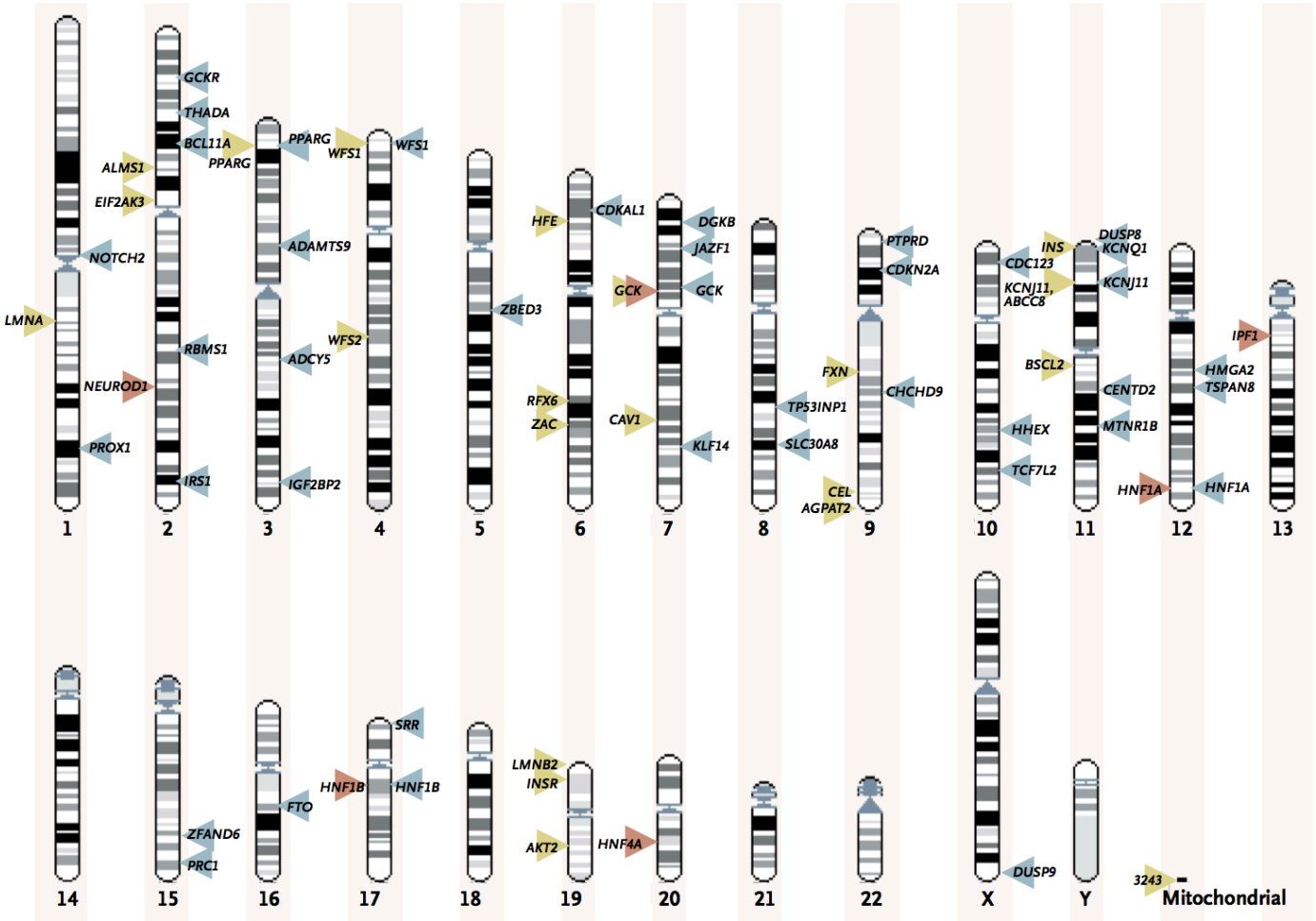
Reyes-Gibby CC 2007



ENDOKRINOLOGIE/STOFF-WECHSEL

Genomik, Typ2 Diabetes und Adipositas

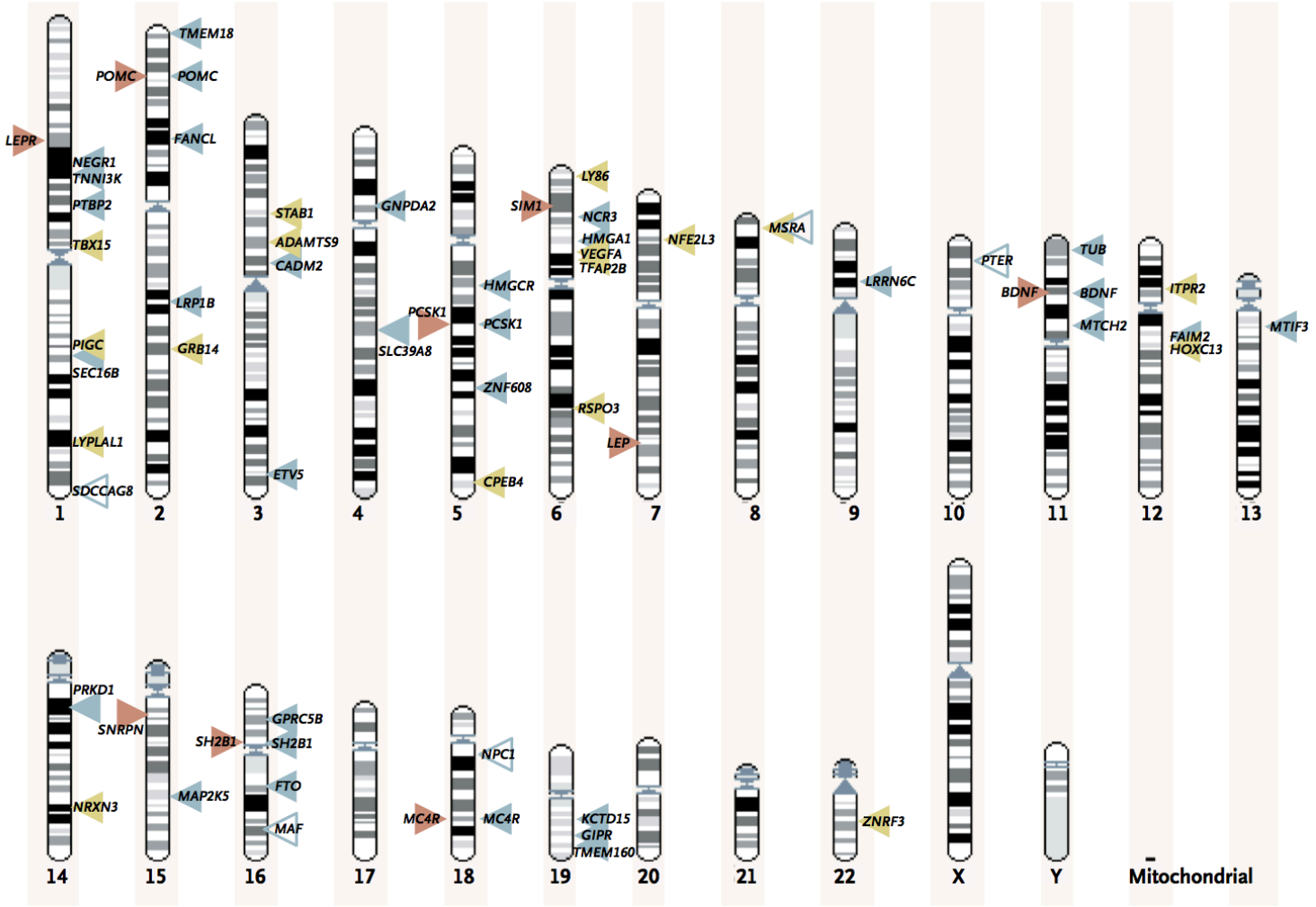
Genomische Lokalisation von bewiesenen Signalen nicht autoimmuner Formen von Diabetes



McCarthy MI 2010

Genomik, Typ2 Diabetes und Adipositas

Genomische Lokalisation von bewiesenen Signalen des BMI



McCarthy MI 2010

Genvarianten assoziiert mit Typ 2 Diabetes mellitus

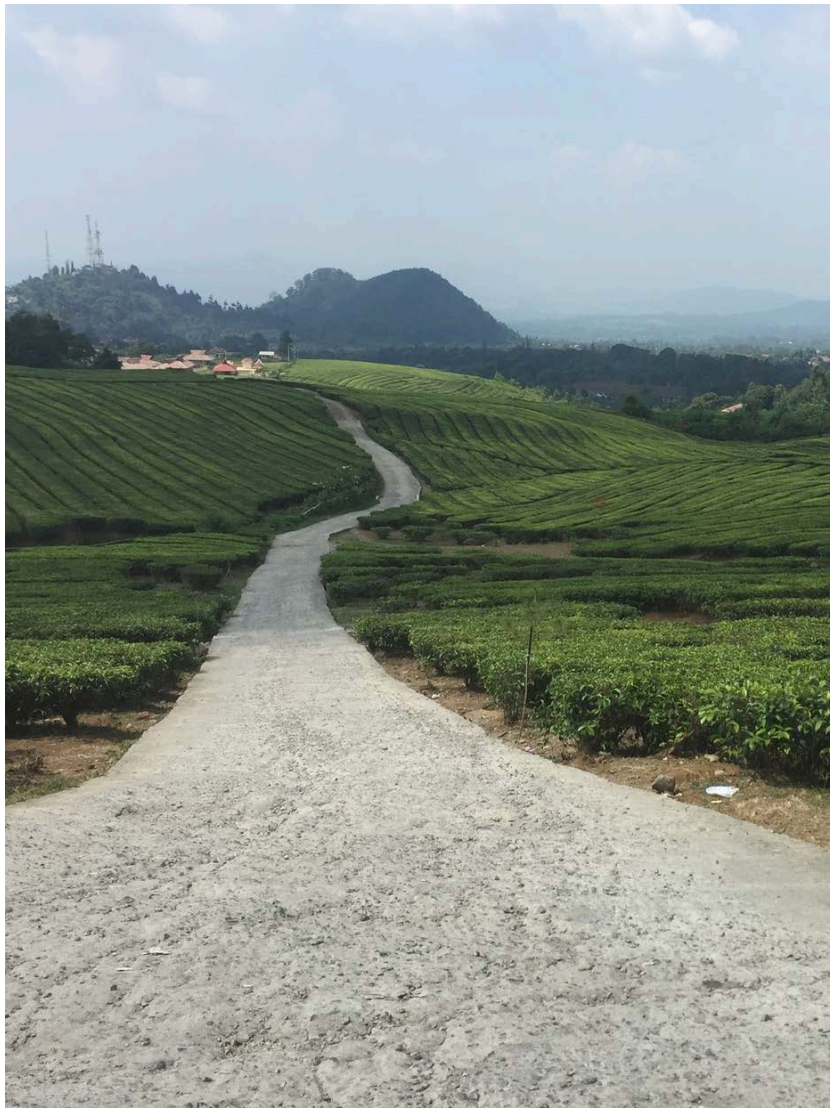
bekannte Variante	(nächstgelegenes) Gen	Odds Ratio (Effektgröße)	Jahr der Entdeckung
rs3792267 (SNP43), rs2975760 (SNP44)	CAPN10	1,2	1996
rs1801278 (G972R)	IRS1		1993
rs1801282 (P12A)	PPARγ	1,14	2000
rs5215 (E23K)	KCNJ11	1,14	2003
rs7901695, rs7903146	TCF7L2	1,37	2006
rs4430796	TCF2	1,10	2007
rs10010131	WSF1	1,11	2007
rs1111875	HHEX-IDE	1,15	2007
rs13266634	SLC30A8	1,15	2007
rs10946398	CDKAL1	1,14	2007
rs10811661	CDKN2A-2B	1,20	2007
rs4402960	IGF2BP2	1,20	2007
rs8050136	FTO	1,17	2007

Kleine Effektgrössen!

Fragen?

Übersicht

- **Gezielte Therapie und Prävention**
- **Einfluss auf Compliance, Medikamentensicherheit, Versorgungsqualität**
- **Ökonomische Aspekte**
- **Ausblick in die Zukunft**



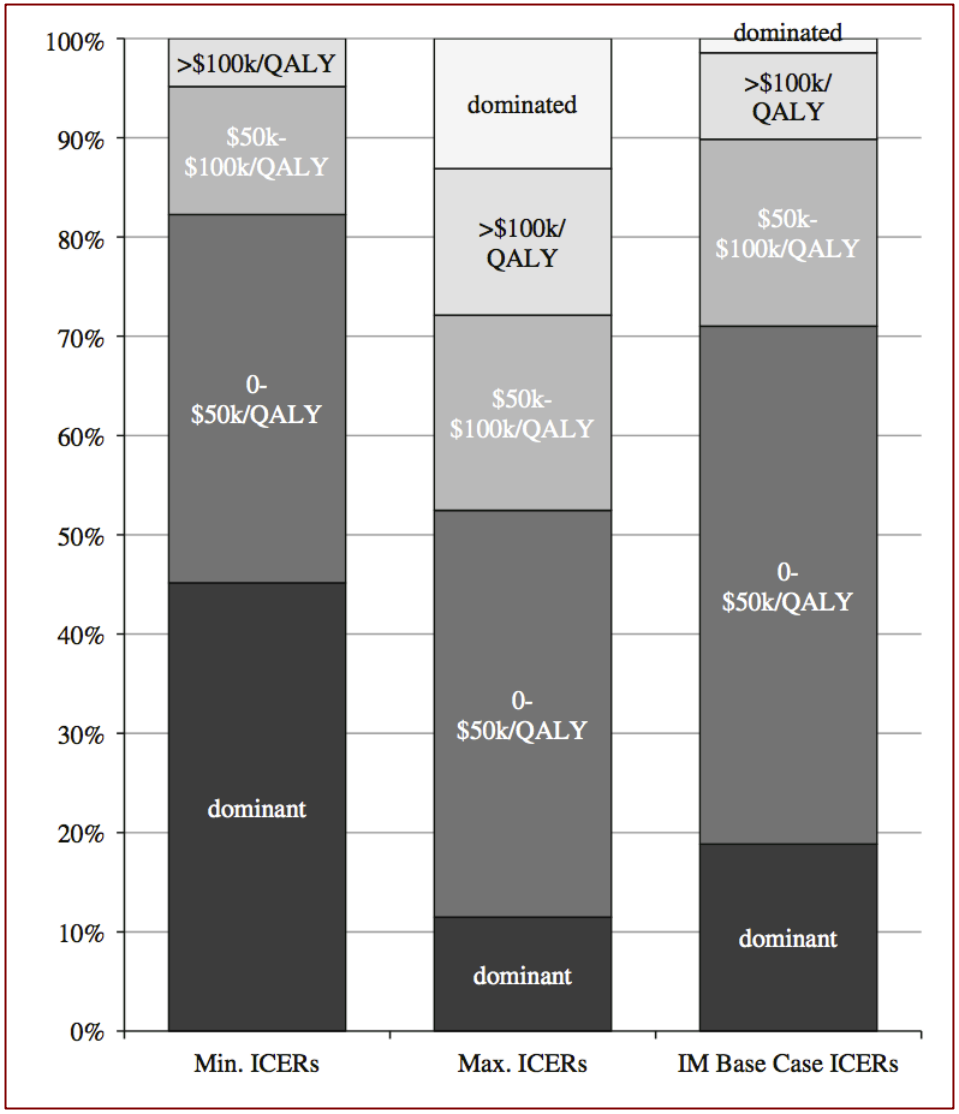
Cost-effectiveness ratios according to type of tests used in PHC

Type of test used	Base case ICER (USD/QALY gained)
Test to stratify for patients with potential adverse reactions	39‘196
Test to stratify for responders/non-responders	37‘308
Test for disease prognosis	10‘150
Test for screening	8‘497

Hatz MHM, 2013

Distribution of ICER‘s in 84 PHC studies

Condition	*n*	%
Breast cancer	18	21
HIV	10	12
HNPCC	9	11
Chronic hepatitis C	5	6
Atrial fibrillation	4	5
Vein thrombosis	4	5
Familial hypercholesterolemia	3	4
Hereditary breast and ovarian cancer	2	2
Cervical cancer	2	2
Hypertrophic cardiomyopathy	2	2
Long QT syndrome	2	2
Non-small-cell lung cancer	2	2
Colorectal cancer	2	2
Smoking cessation	2	2
Acute coronary syndrome	1	1
Nephropathies	1	1
Major depressive disorder	1	1
Schizophrenia	1	1
Periodontal disease	1	1
Cystic fibrosis	1	1
Lung cancer	1	1
Acute lymphoblastic leukemia	1	1
MAP	1	1
Epilepsy	1	1
Thromboembolic events	1	1
Idiopathic pulmonary fibrosis	1	1
Prostate cancer	1	1
Kidney failure	1	1
Cardiovascular disease	1	1
Hypercholesterolemia	1	1
Hypertension	1	1
Sum	84	100



Hatz MHM, 2013

League-table of pharmacogenetic screening programs

Study	Gene	Drug	ICER
You (2004)	CYP2C9	Coumadin	EUR 7‘326/bleeding avoided
Schafekamp (2006)	CYP2C9	Coumadin	EUR 4‘233/bleeding avoided
Desta (2002)	CYP2C19	PPI	Favourable
Lehman (2003)	CYP2C19	PPI	**Dominant**
Furuta (2007)	CYP2C19	PPI	**Dominant**
Chou (2000)	CYP2D6	Antipsychotics	Undetermined
Marra (2002)	TPMT	AZA	**Dominant**
Oh (2004)	TPMT	AZA	**Dominant**
Winter (2004)	TPMT	AZA	GBP487/LYG
Dubinskiy (2005)	TPMT	AZA	**Dominant**
Priest (2005)	TPMT	AZA	**Dominant**
Tavadia (2000)	TPMT	AZA	Favourable
Van den Akkeren (2006)	TPMT	6-MP	EUR 4‘800/LYG
Pedis (2005)	Multiple	Clozapine	EUR 36‘186/QALY
Meckley (2006)	α-adductin	Thiazide	**Dominant**
Maitland van der Zee (2004)	ACE	Statins	**Dominant**
Costa (2007)	ACE	ACE inhibitors	**Dominant**
Kim (2006)	MTHFR	MTX	**Dominant**
Hughes (2004)	HLA	Abacavir	**Dominant** to EUR 22‘811/hypersensitivity reaction avoided
Veenstra (2007)	A1555G	Aminoglycosides	EUR 59759/QALY

Vegter S et al. Pharmacoeconomics 2008; 26: 569

Cost-effectiveness of high profile drugs and companion diagnostics

Drug	Results
Trastuzumab	≈ 12 Peer-reviewed clinical- and/or cost-effectiveness studies with varied results: Cost-per-QALY* ranged from $18‘000 to $125‘000
Cetuximab	Two peer-reviewed clinical- and/or cost-effectiveness studies: Both > $120‘000 cost-per-QALY
Imatinib	≈12 Peer-reviewed clinical- and/or cost-effectiveness studies with varied results: Cost-per-QALY ranged from $15‘000 to $120‘000
Abacavir	Four peer-reviewed clinical- and/or cost-effectiveness studies with varied results Cost-per-QALY ranged from <0 or cost-saving to $37‘000
Irinotecan	Six peer-reviewed clinical- and/or cost-effectiveness studies with varied results All over $50‘000 cost-per-QALY
Erlotinib	Five peer-reviewed clinical- and/or cost-effectiveness studies with varied results Cost-per-QALY ranged from <0 or cost-saving to $170‘000

Cohen J 2013

Übersicht

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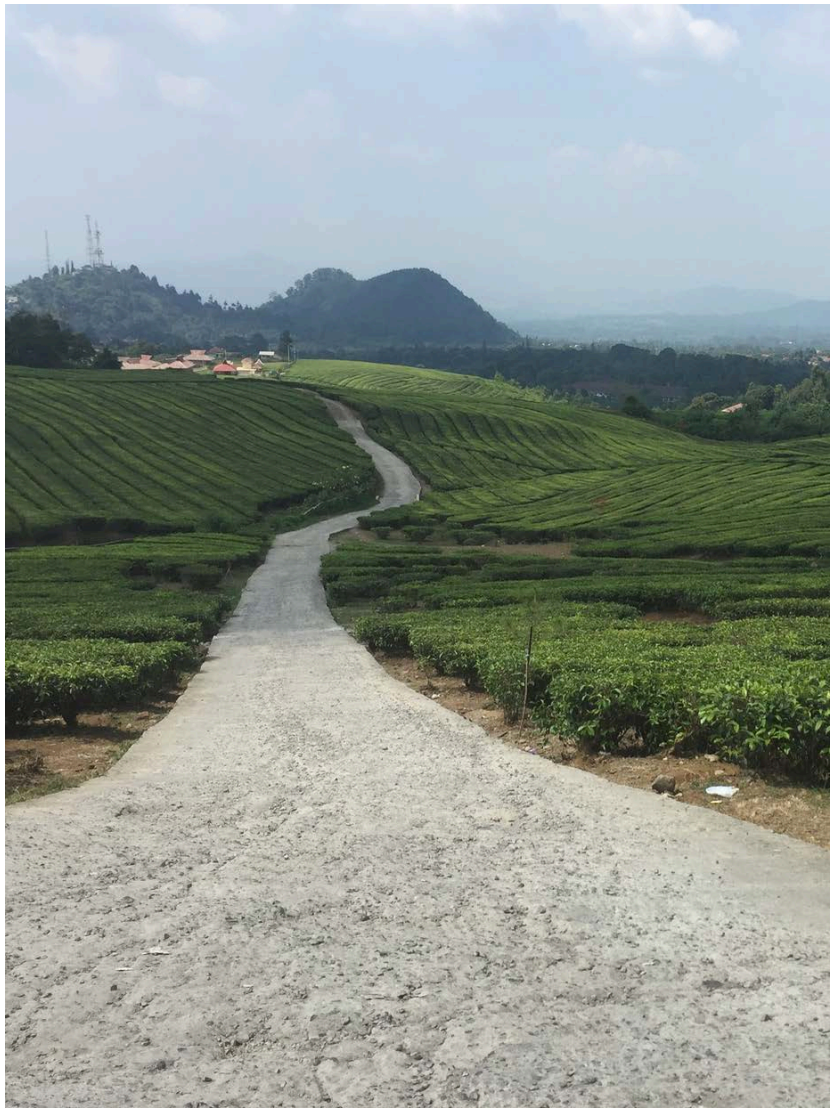
- **Ökonomische Aspekte**
- **Ausblick in die Zukunft**

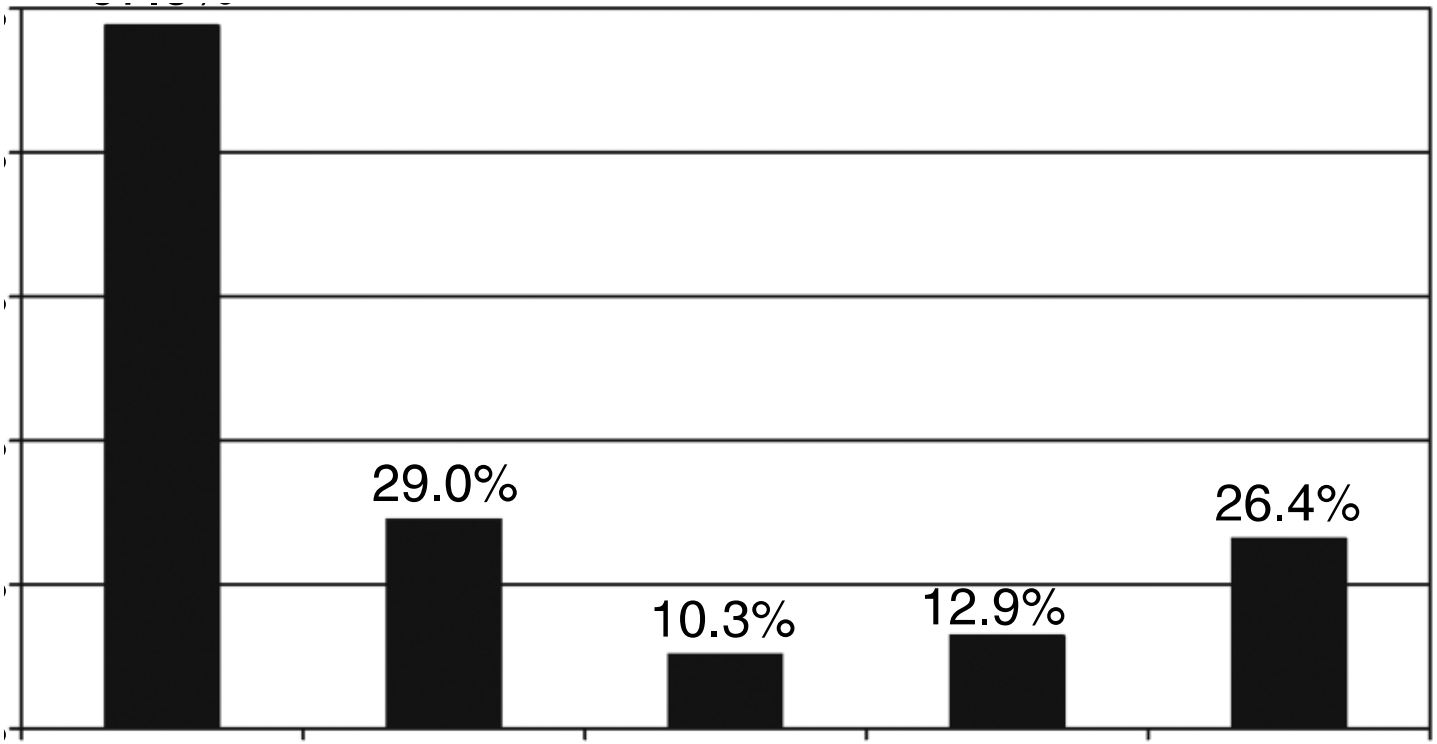


Education and training

„A lot of clinicians don‘t know how to interpret genetic results. They know how to look at a graph of chemistry results. They know how to read a pathology report. But they actually don‘t know how to look at this data and to make decisons based on it.“

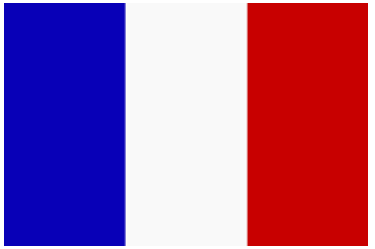
John Glaser, Chief Information Officer, Partners Healthcare

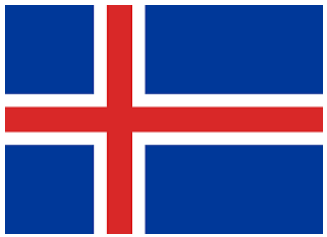
Survey on physician knowledge of pharmacogenomics



Stanek EJ et al 2011

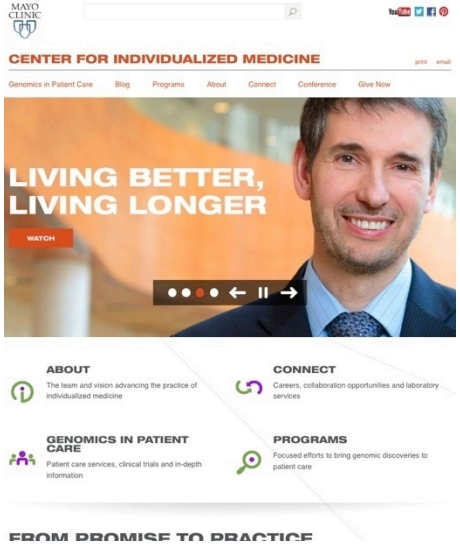
Länder mit nationalen Genomstrategien (public health genomics)

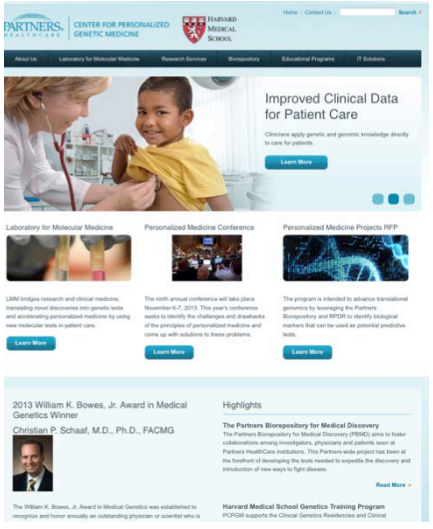




Die Zukunft ist schon heute

MAYO CLINIC



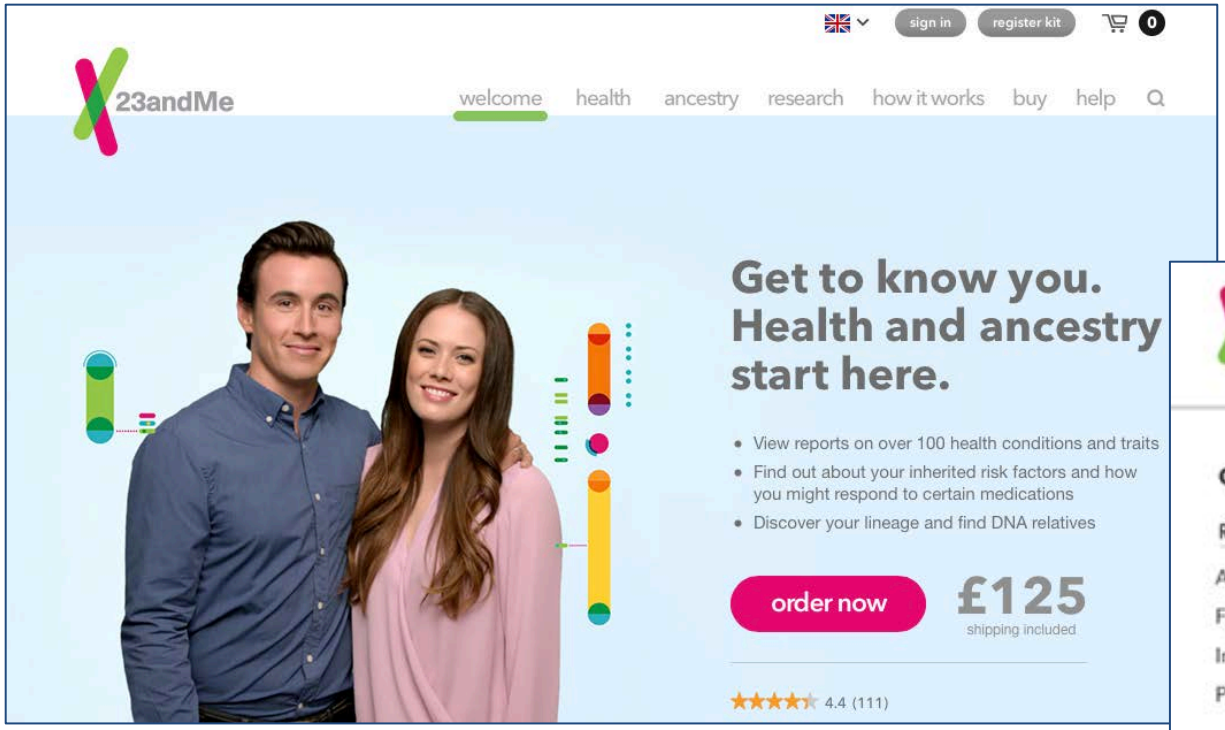


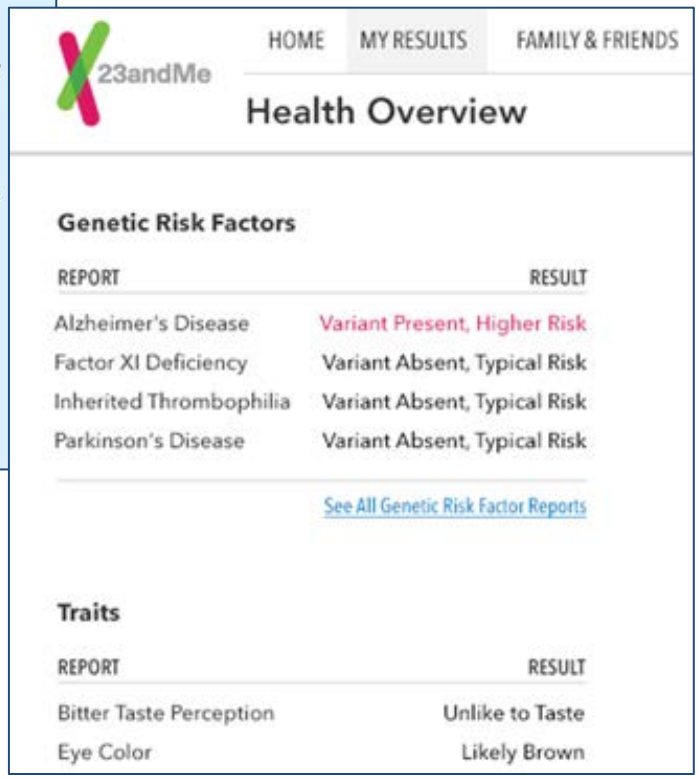
A Medicine Safety Code

Training for the London Marathon? It's now as simple as DNA

- ·VO2 max potential
- · Ability to recover from training
- · Ideal nutrition and training recommendations
- · Carbohydrate & Saturated Fat Sensitivity
- · Lactose & Gluten Intolerance Risk
- · Detox Ability
- · Anti-Oxidant Needs
- · Recommended vitamin & micronutrient Intake
- · Salt and Caffeine Sensitivity

23andme ist zurück (in UK)





Zukünftiger Ausblick der personalisierten Medizin

- **Personalisierte Medizin hat ein riesiges Potenzial und wird von den neuen Sequenzierungs Technologien profitieren**
- **Entwicklung ist unumkehrbar und die medizinische und wissenschaftliche Gesellschaft ist in der Verantwortung, den zu erwartenden Nutzen sowie die potenziellen Risiken zu antizipieren.**
- **Beträchtliche Investitionen werden notwendig sein, aus diesem Potenzial eine Realität werden zu lassen und die personalisierte Medizin zur Reife zu bringen. Damit ist auch ein Paradigmenwechsel bei der Durchführung der klinischen Forschung notwendig.**

Die Zukunft ist da

Nature 2011


KEEP
CALM
AND
LOVE
DNA

Fragen?

Kontakte

Prof. Dr. med. Thomas D. Szucs

Institut für Pharmazeutische Medizin
Universität Basel
Klingelbergstrasse 61
CH-4056 Basel
T +41 61 267 19 50
E thomas.szucs@unibas.ch