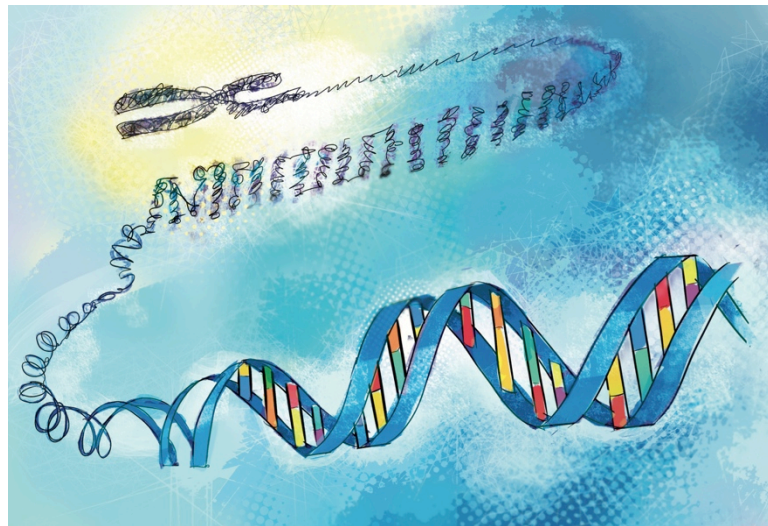


# Personalisierte Medizin

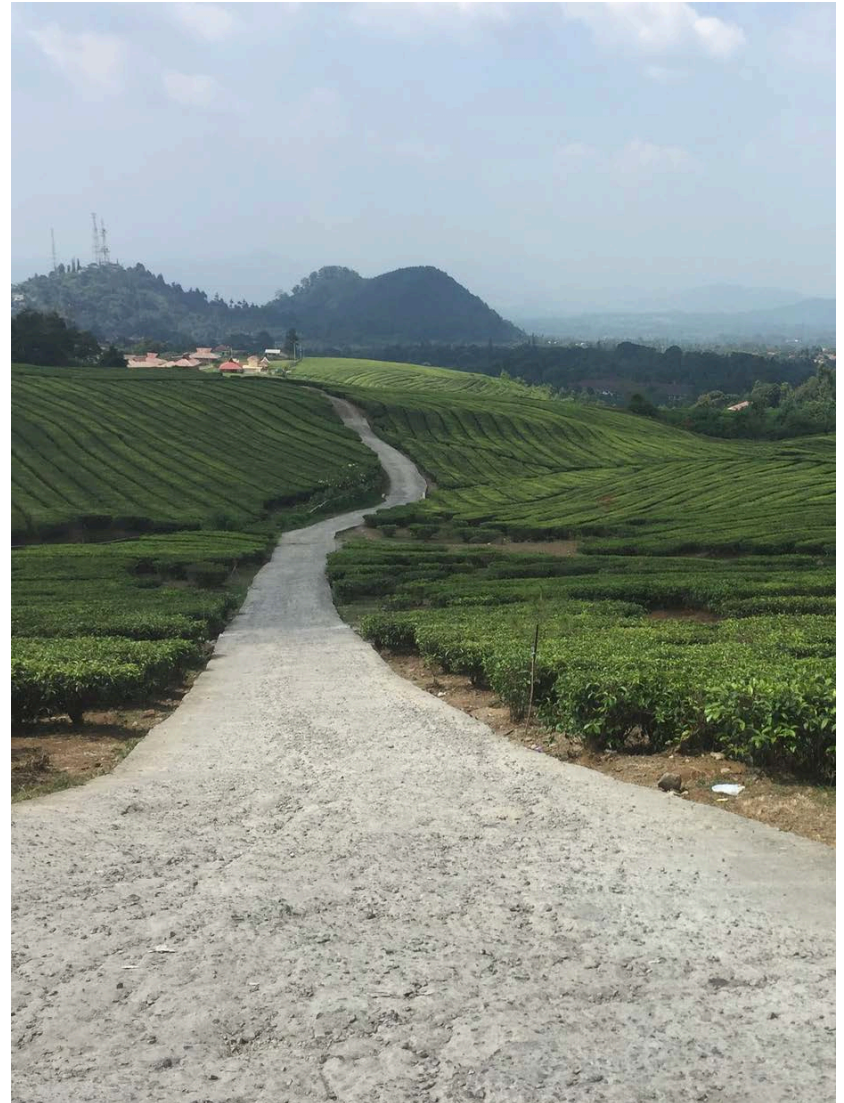


Thomas D. Szucs

Universität Basel & Klinik Hirslanden

# Übersicht

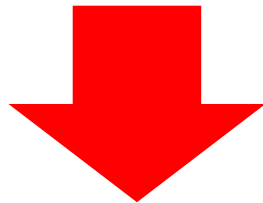
- **Gezielte Therapie und Prävention**
- **Einfluss auf Compliance, Medikamentensicherheit, Versorgungsqualität**
- **Ökonomische Aspekte**
- **Ausblick in die Zukunft**



# Personalisierte Medizin

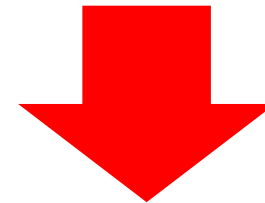
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**Identifikation  
von  
Risikofaktoren**



**Prävention**

**Identifikation  
genetischer Marker  
oder  
molekulare Basis von  
Krankheitsfaktoren**



**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

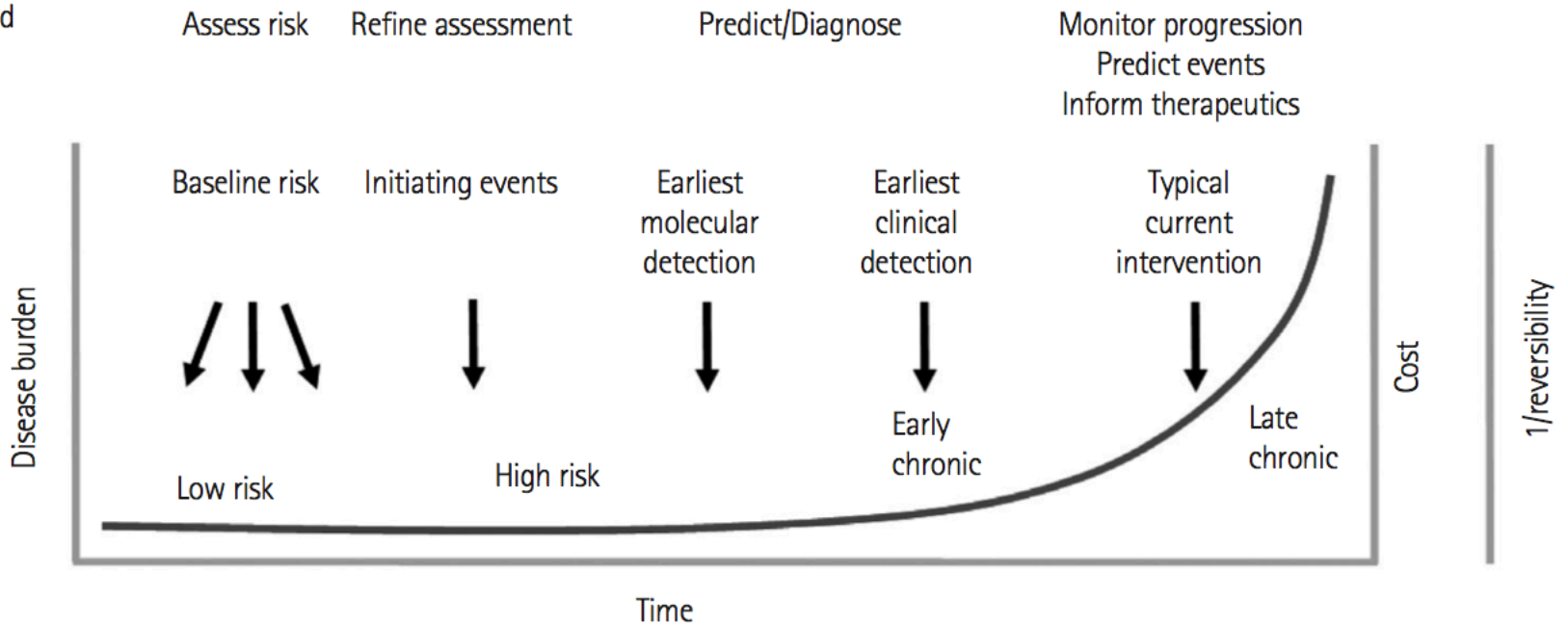
The use of combined knowledge (genetics, or otherwise) about a person to predict **disease prognosis or treatment response** and thereby improve that person's health

## Definition 3

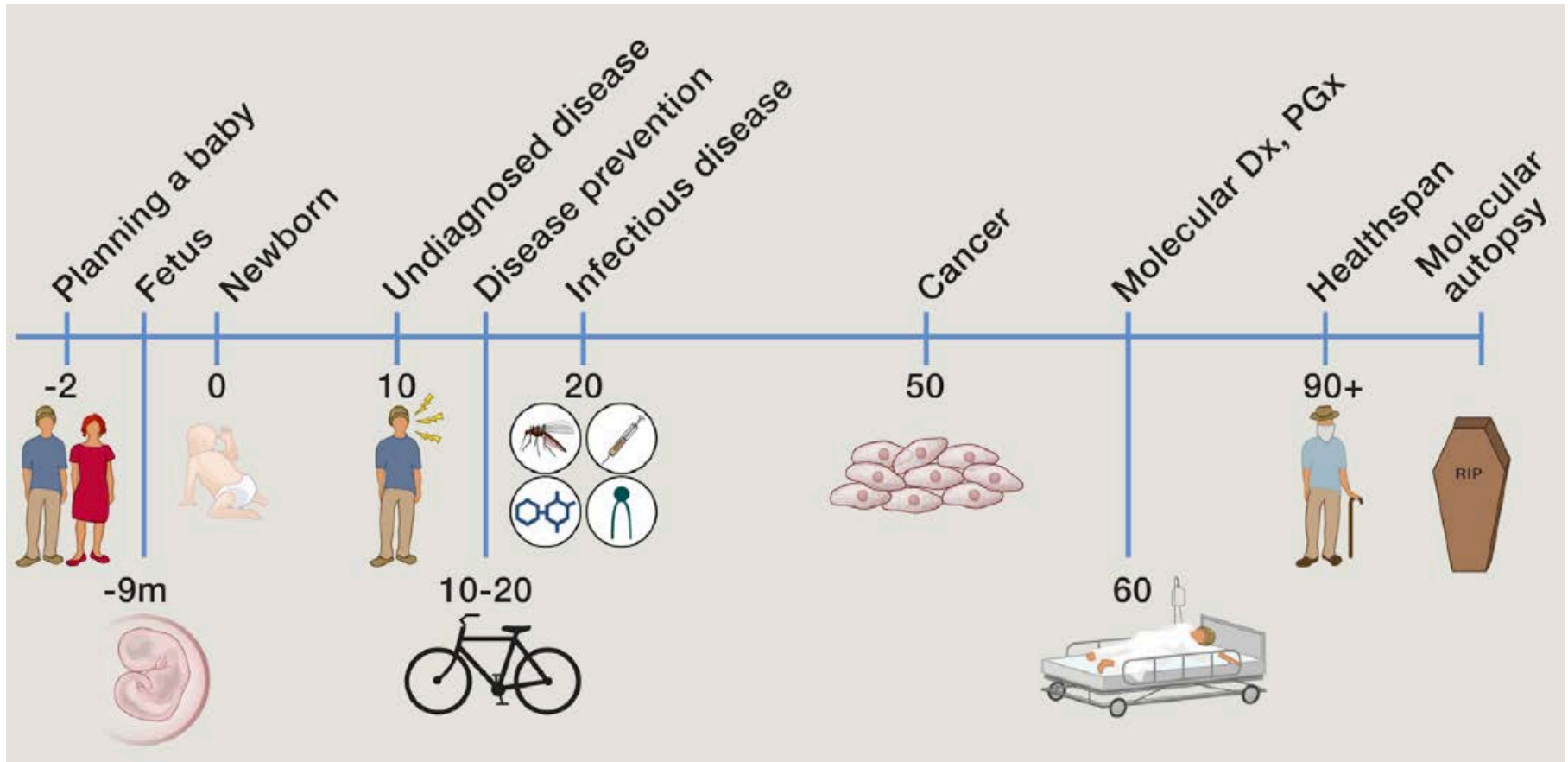
The use of combined knowledge (genetics, or otherwise) about a person to predict **disease susceptibility, disease prognosis or treatment response** and thereby improve that person's health

# Kontinuum von Gesundheit/Krankheit

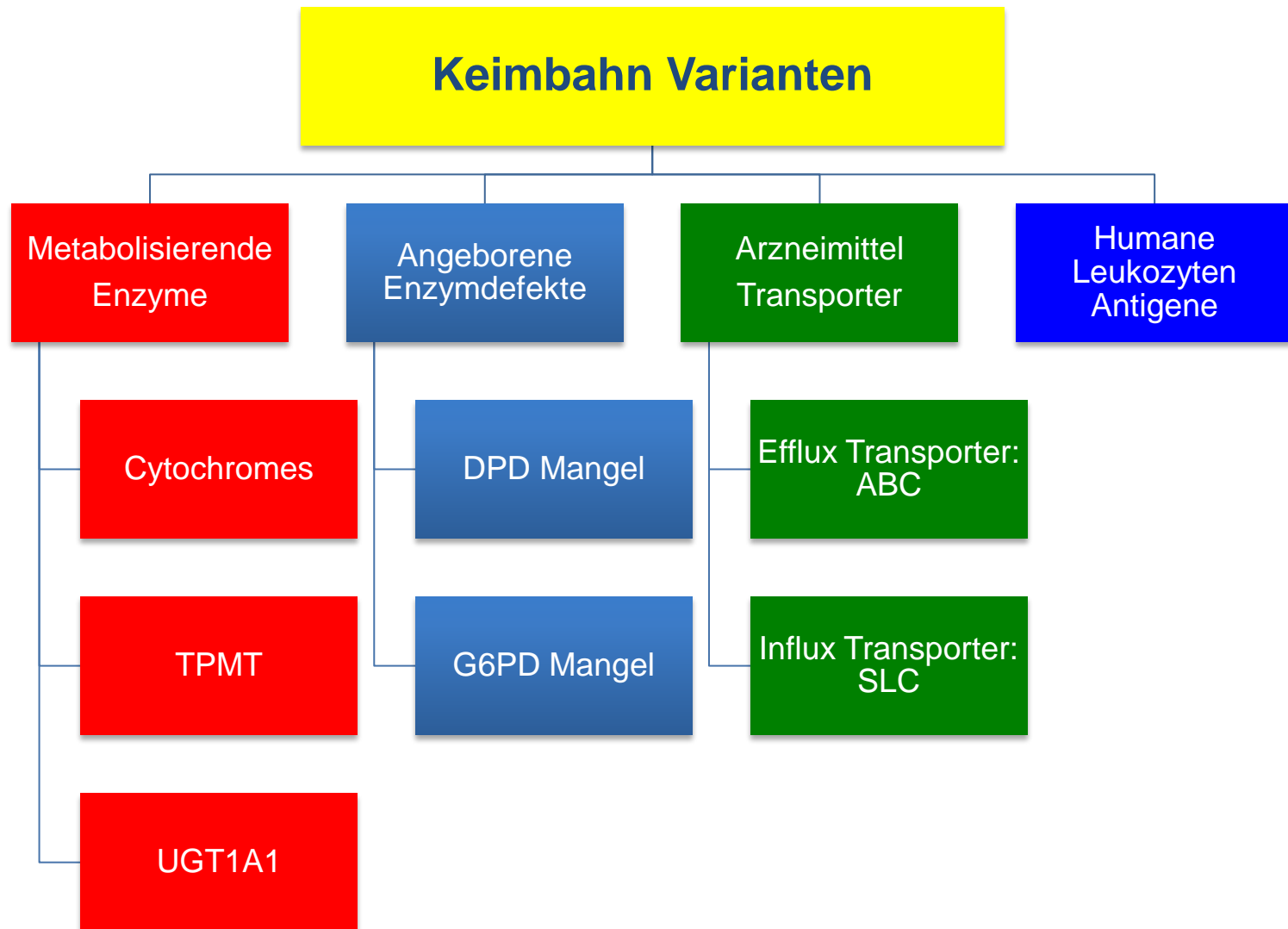
Risk  
Assessment and  
Decision  
Support Tools:



# Personalisierte Medizin: Von der Empfängnis zur Bahre

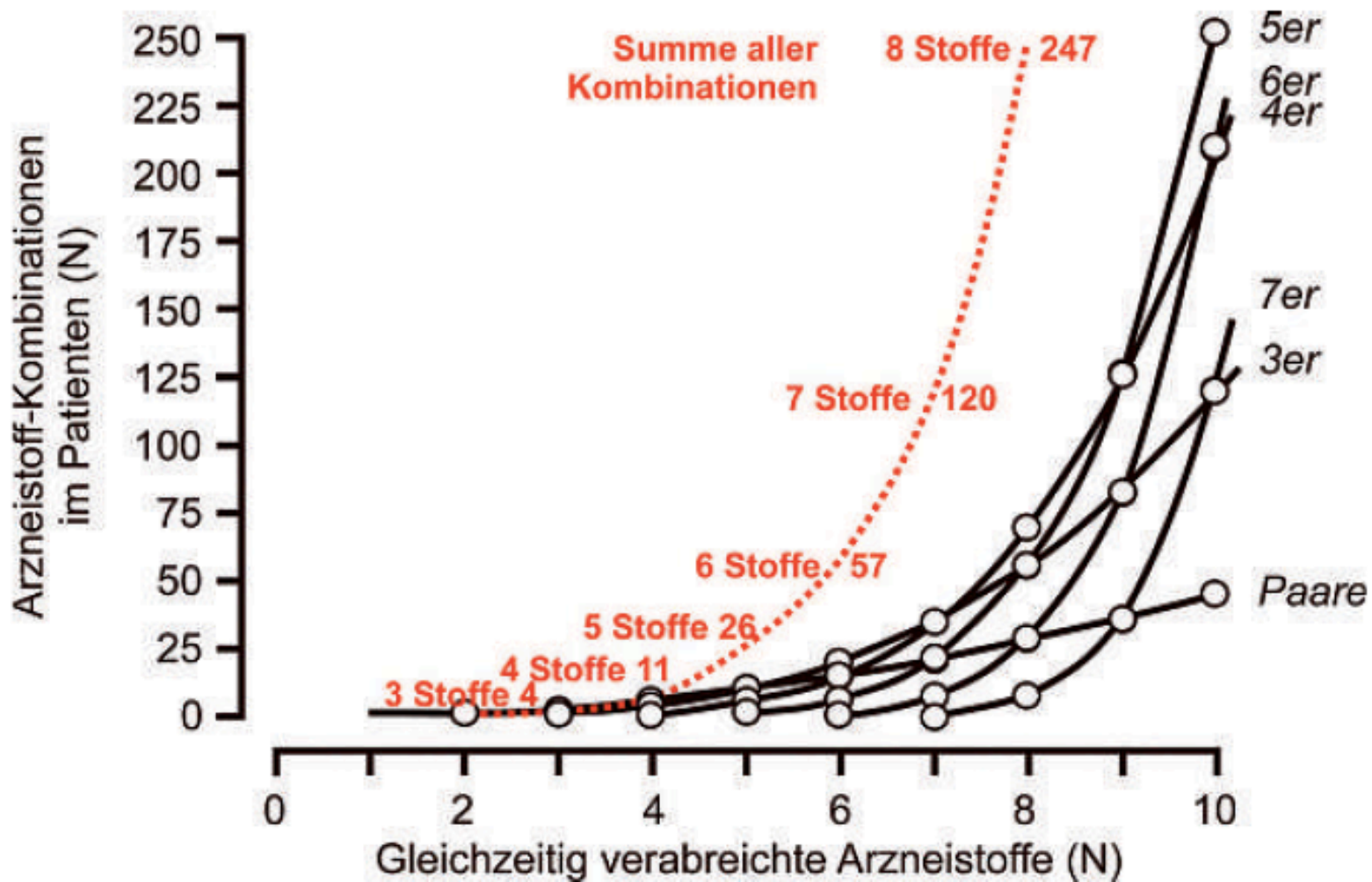


# Pharmakogenomik unerwünschter Arzneimittelwirkungen





# Polypharmazie - Anzahl Kombinationspaare





# 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

# Nutzen der Pharmakogenetik

<b>Individuelle Probleme mit Arzneimitteln</b>	<b>Pharmakogenetische Lösungen und Ziele</b>
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?!



"Here's my  
sequence..."

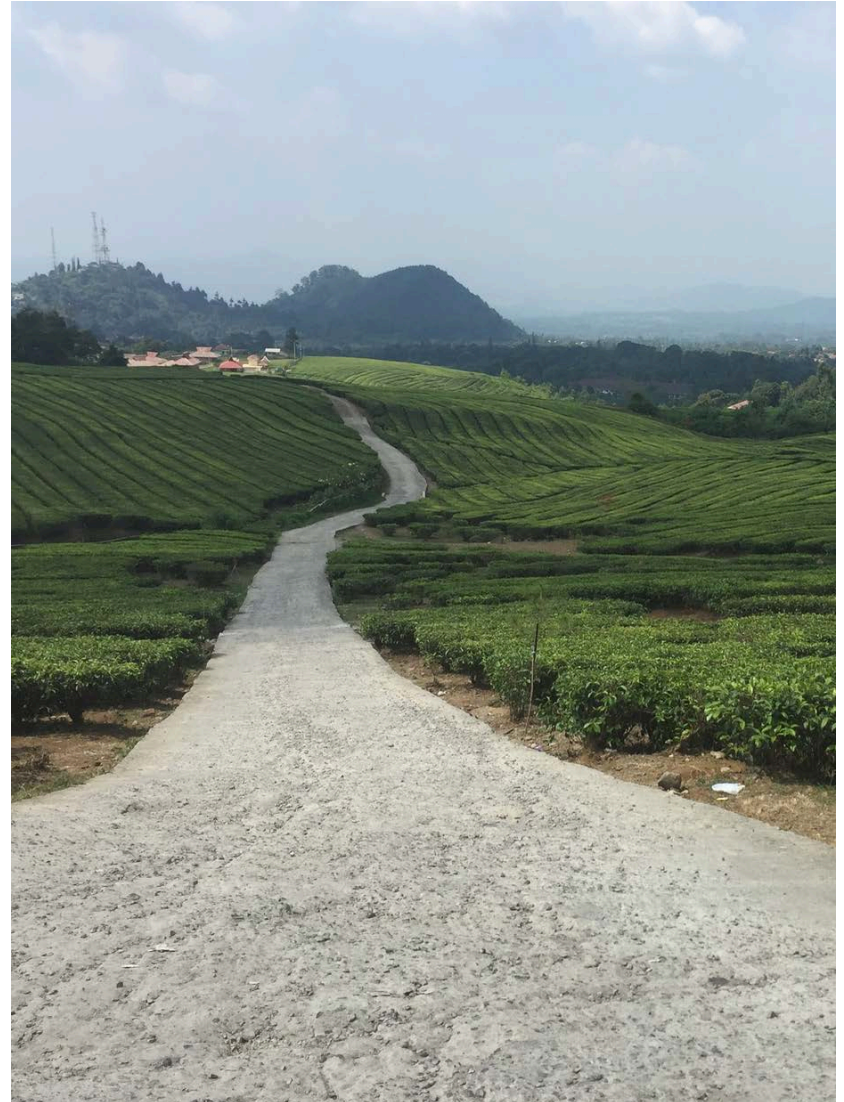
*New Yorker*

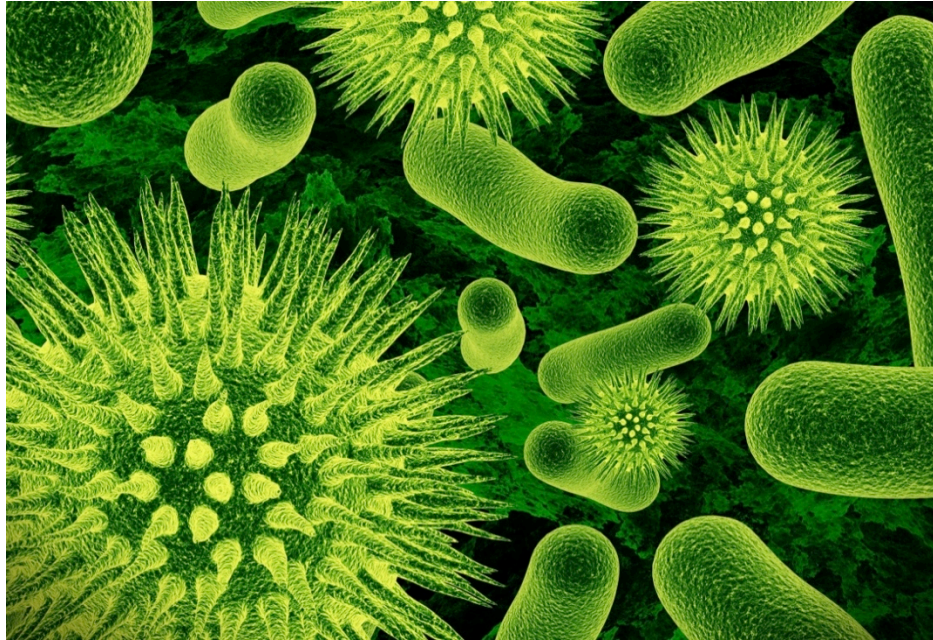
# Fragen?



# Übersicht

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





# INFEKTILOGIE



The  
Economist

AUGUST 18TH - 24TH 2012

Economist.com

The Catholic church's unholy mess

Paul Ryan: the man with the plan

Generation Xhausted

China, victim of the Olympics?

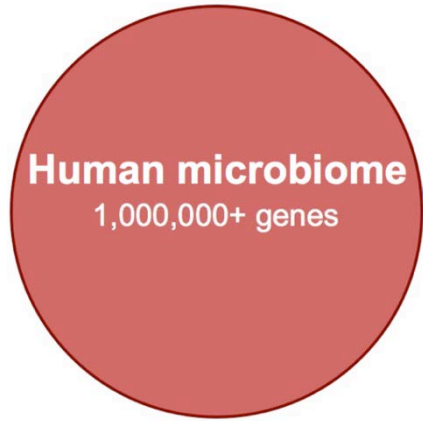
On the origin of specie

# Microbes maketh man





# Mikrobiom: 10'000 Spezies (2kg)



**Körperzellen:  $1 \cdot 10^{13}$**

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

Bacteria, fungi, and viruses outnumber human cells in the body by a factor of 10 to one. The microbes synthesize key nutrients, fend off pathogens and impact everything from weight gain to perhaps even brain development. The Human Microbiome Project is doing a census of the microbes and sequencing the genomes of many. The total body count is not in but it's believed over 1,000 different species live in and on the body.

**Mund/Lunge**  
**600 +Spezies**

in the **mouth, pharynx and respiratory system** include:

- Streptococcus viridans
- Neisseria sicca
- Candida albicans
- Streptococcus salivarius

**Magen**  
**25 Spezies**

in the **stomach** include:

- Helicobacter pylori
- Streptococcus thermophilus

**Darm**  
**500- 1'000 Spezies**

in the **intestines** include:

- Lactobacillus casei
- Lactobacillus reuteri
- Lactobacillus gasseri
- Escherichia coli
- Bacteroides fragilis
- Bacteroides thetaiotaomicron
- Lactobacillus rhamnosus
- Clostridium difficile

**Haut**  
**1'000 Spezies**

in the **skin** include:

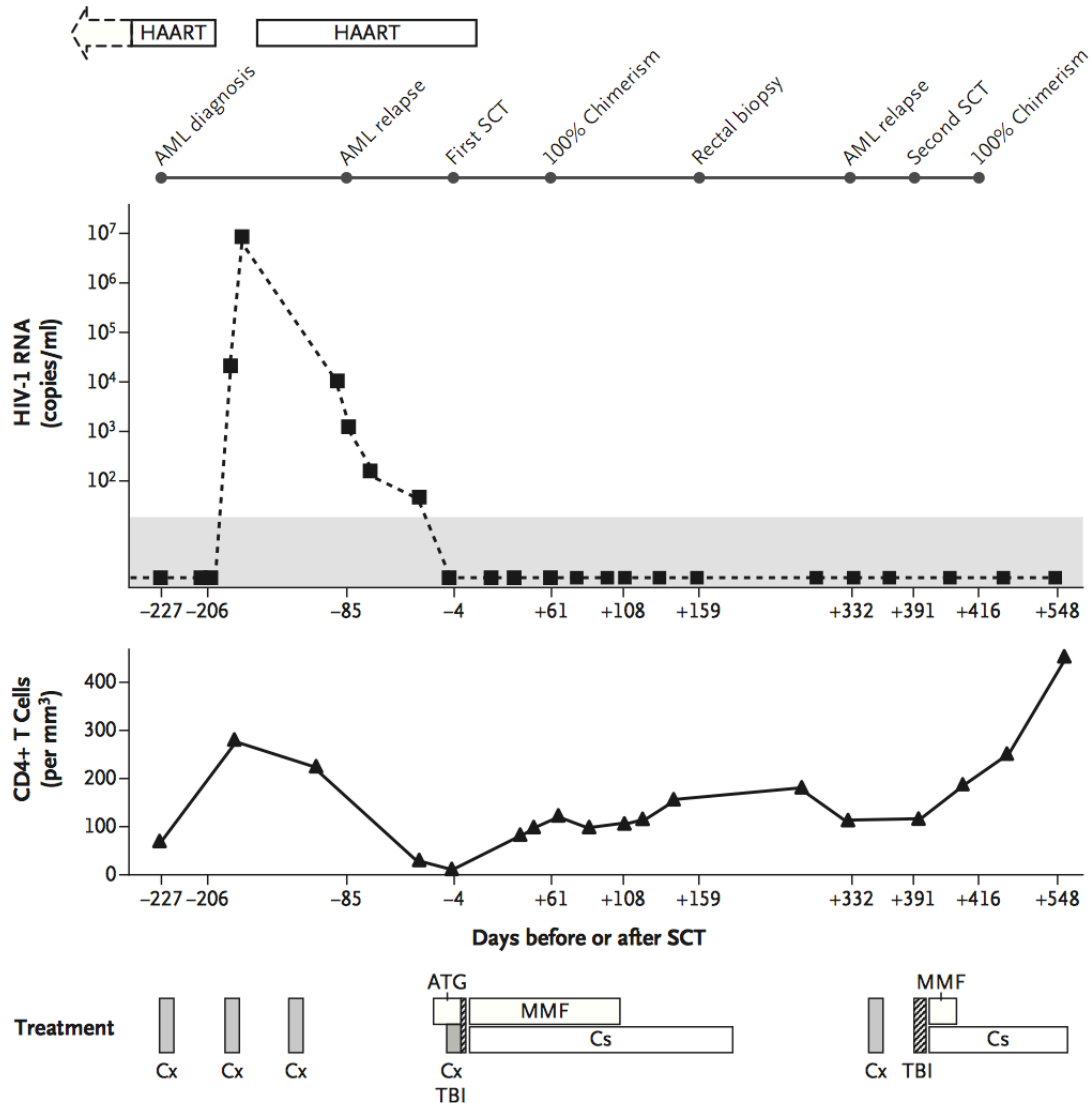
- Pityrosporum ovale
- Staphylococcus epidermidis
- Corynebacterium jeikeium
- Trichosporon
- Staphylococcus haemolyticus

**Urogenital**  
**60 Spezies**

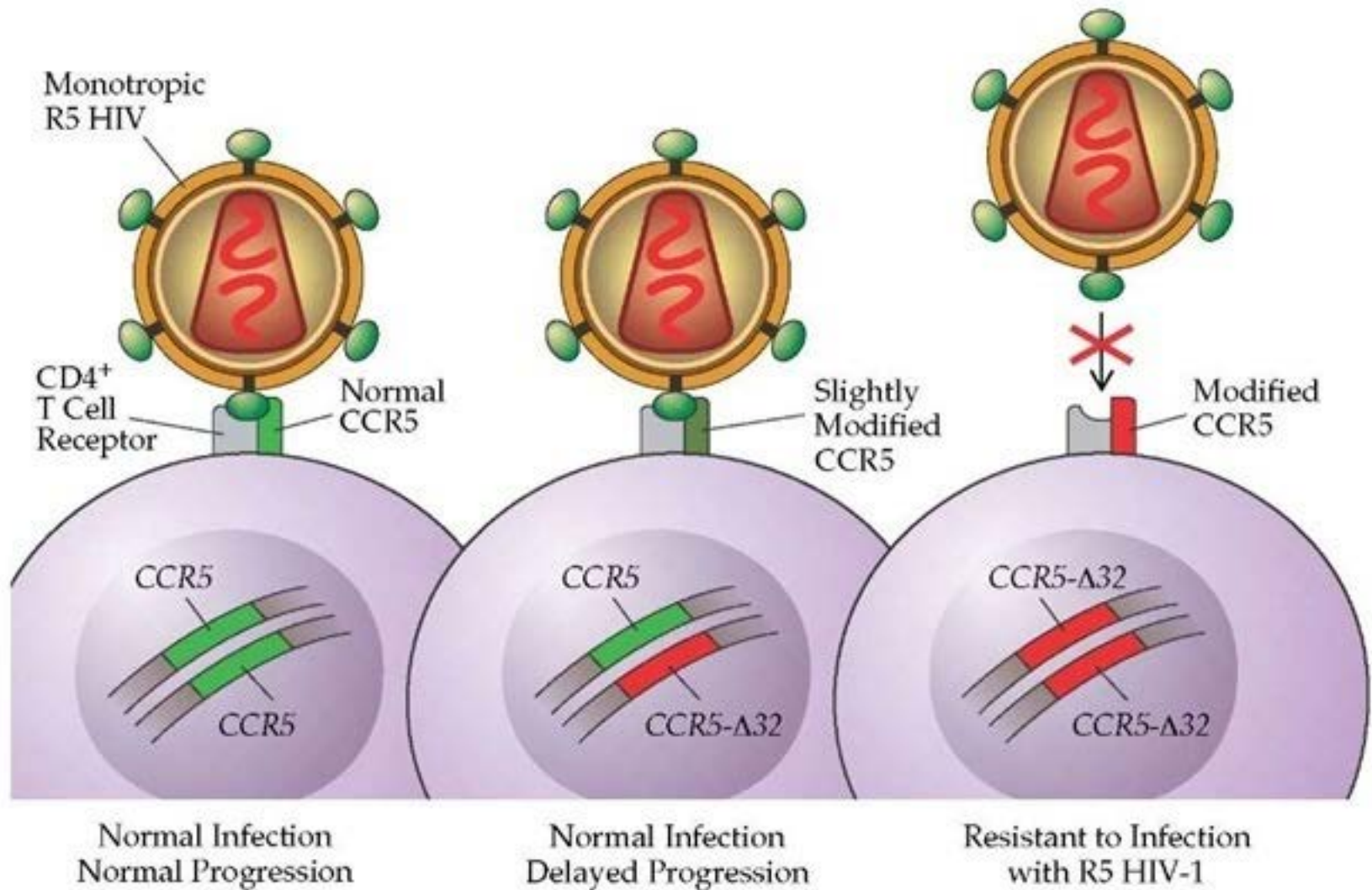
in the **urogenital tract** include:

- Ureaplasma parvum
- Corynebacterium aurimucosum

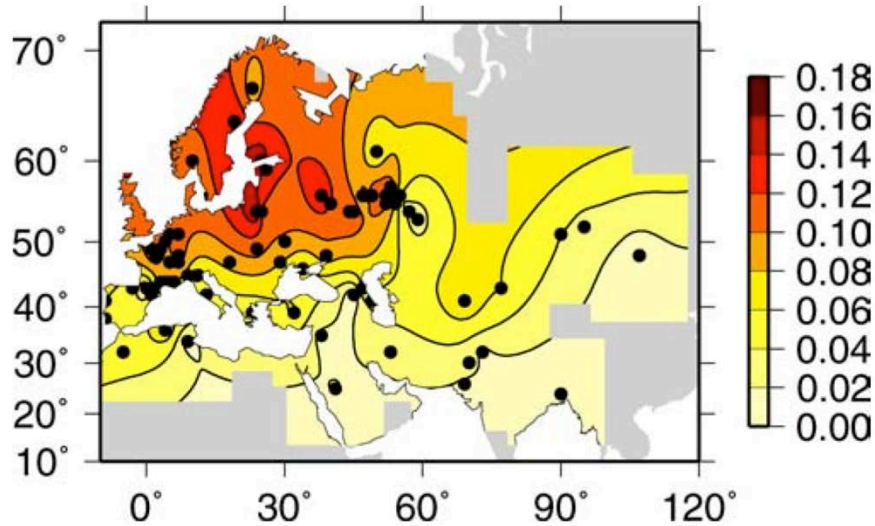
# Der „Berliner Patient“ Timothy Brown



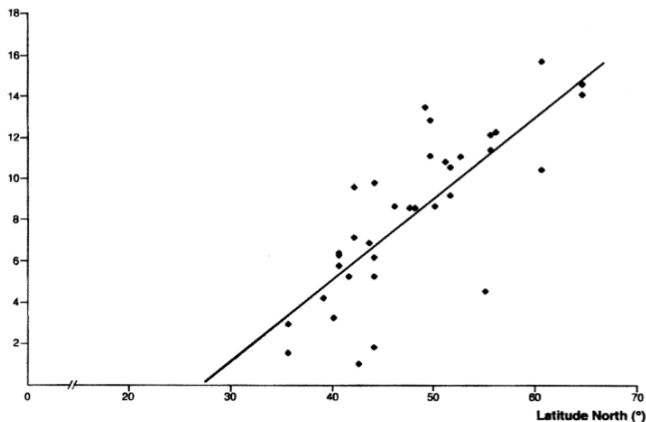
# CCR5-Rezeptor Mutationen



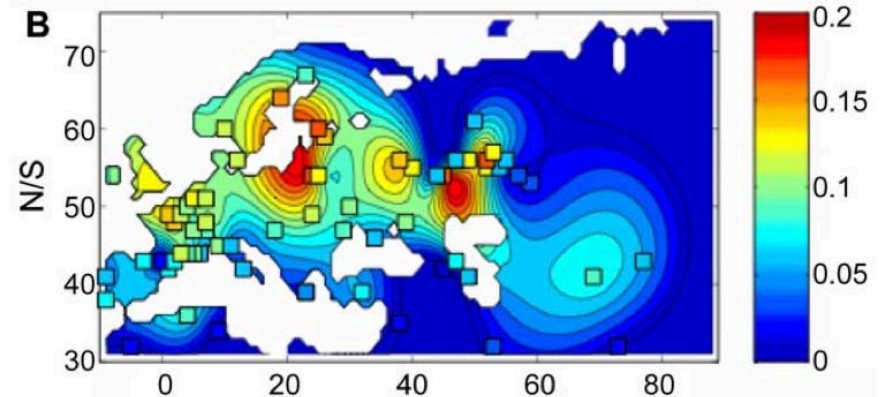
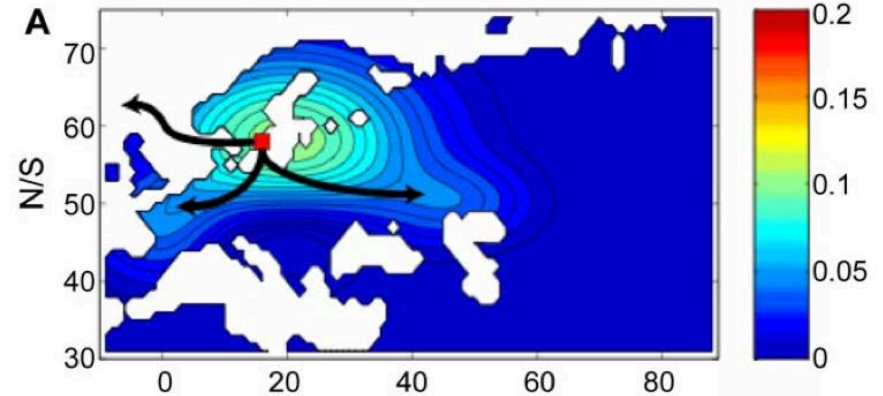
# Geographische Verteilung der $\Delta 32$ Allel Frequenz



$\Delta 32$  frequency (%)



Viking hypothesis



Modern-day observed allele frequencies.

*CCR5-D32* is at average allele frequency of 10% across Europe, translating into a homozygote frequency of about 1%

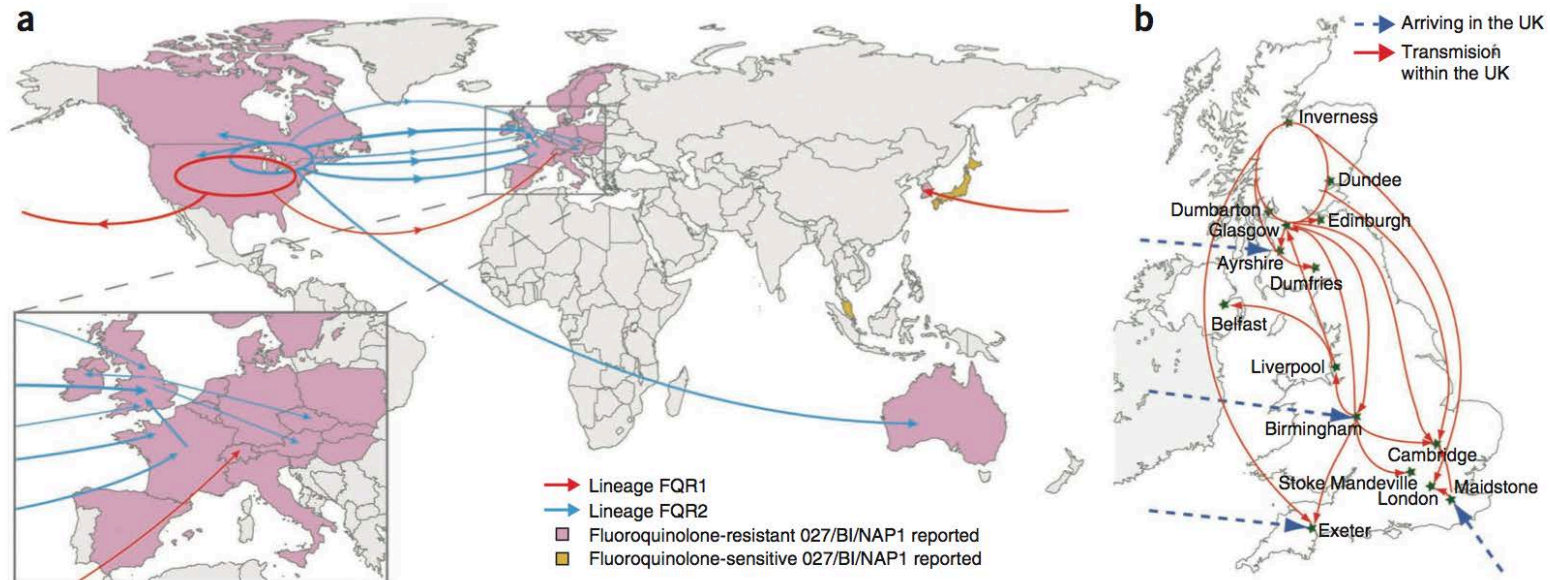


# Genomik zur Analyse bakterieller Übertragungsmechanismen

---

- **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 <sup>a</sup>
5420	DNA gyrase subunit B ( <i>gyrB</i> )	c.1276G>A	p.Asp426Asn	Fluoroquinolone
6310	DNA gyrase subunit A ( <i>gyrA</i> )	c.245C>T	p.Thr82Ile	Fluoroquinolone
95412	DNA-directed RNA polymerase $\beta$ chain ( <i>rpoB</i> )	c.1504C>A	p.His502Asn	Rifampicin
95422	DNA-directed RNA polymerase $\beta$ chain ( <i>rpoB</i> )	c.1514G>A	p.Arg505Lys	Rifampicin
103867	Translation elongation factor G ( <i>fusA</i> )	c.1363C>A, c.1363C>T	p.His455Asn, p.His455Tyr	Fusidic acid
104117	Translation elongation factor G ( <i>fusA</i> )	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 ( <i>slpA</i> )	c.467G>A, c.467G>T	p.Pro156Leu, p.Pro156Gln	
3170482	S-layer precursor protein ( <i>slpA</i> )	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.

<sup>a</sup>Antibiotic to which the substitution confers resistance.

# HGT in *S. aureus*



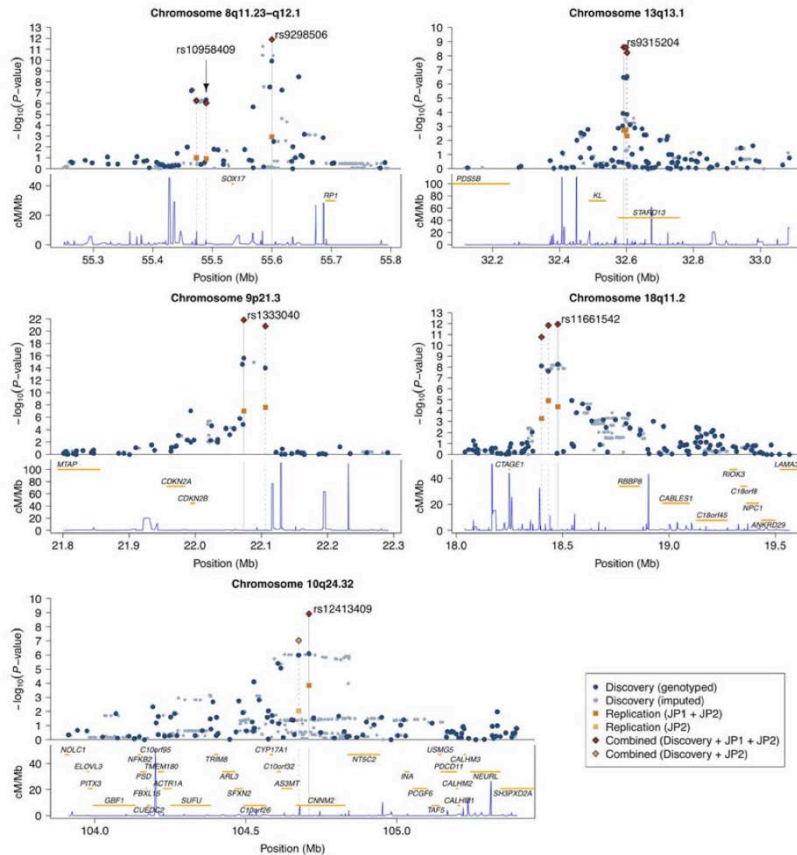
- Akquisition von Virulenzgenen
- Phagen-bezogene Chromosomen Inseln
- Kodieren Superantigene (Enterotoxin B, Resistenz, etc.)





NEUROLOGIE/PSYCHIATRIE

# GWAS Risiko Loci für intrakranielle Aneurysmen

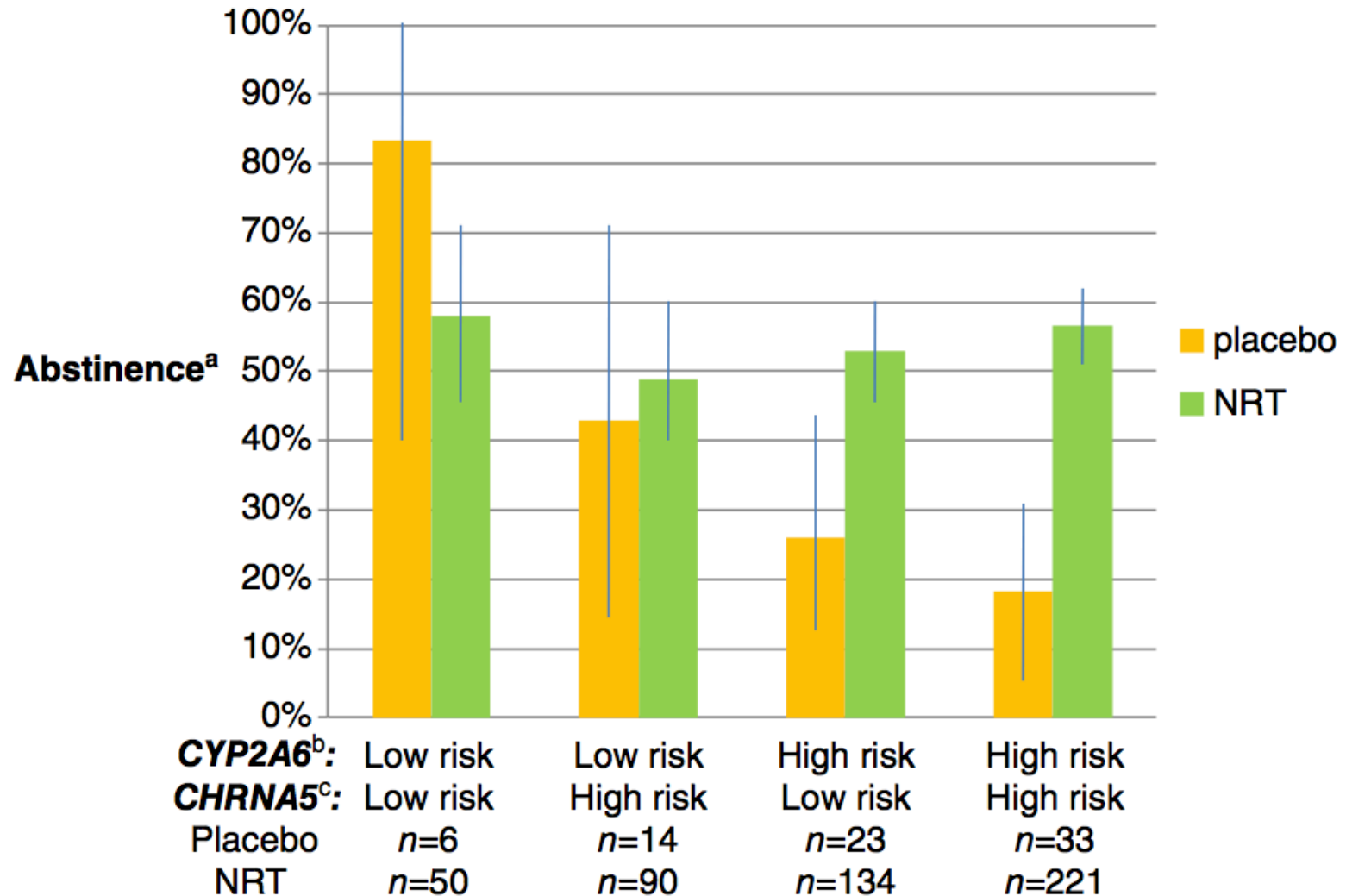


Locus	SNP	Position	Genes	Risk Allele	Cohort	P-value	log <sub>10</sub> (BF)	PPA	Per-allele OR (95% CI)	Control RAF	Case RAF
8q11.23	rs10958409	55,489,644	<i>SOX17</i>	A	Discovery	4.2x10 <sup>-07</sup>	4.64	0.8128	1.24 (1.14-1.35)	0.15, 0.19	0.18, 0.22
					Replication	0.12	-0.11	1.08 (0.98-1.20)	0.28	0.29	
					Combined	9.0x10 <sup>-07</sup>	4.30	0.6685	1.17 (1.10-1.25)		
8q12.1	rs9298506	55,600,077	<i>SOX17</i>	A	Discovery	1.2x10 <sup>-10</sup>	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	1.3x10 <sup>-12</sup>	9.85	1.0 - 1.4x10 <sup>-06</sup>	1.28 (1.20-1.38)		
9p21.3	rs1333040	22,073,404	<i>CDKN2A</i> , <i>CDKN2B</i>	T	Discovery	2.5x10 <sup>-14</sup>	13.41	1.0 - 3.9x10 <sup>-10</sup>	1.32 (1.24-1.41)	0.56, 0.45	0.63, 0.53
					Replication	1.0x10 <sup>-07</sup>	5.18	1.31 (1.19-1.45)	0.66	0.72	
					Combined	1.5x10 <sup>-22</sup>	19.48	1.0 - 3.3x10 <sup>-16</sup>	1.32 (1.25-1.39)		
10q24.32	rs12413409	104,709,086	<i>CNNM2</i>	G	Discovery	7.9x10 <sup>-07</sup>	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	1.2x10 <sup>-09</sup>	7.00	0.9990	1.29 (1.19-1.40)		
13q13.1	rs9315204	32,591,837	<i>KL</i> , <i>STARD13</i>	T	Discovery	3.3x10 <sup>-07</sup>	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	2.5x10 <sup>-09</sup>	6.72	0.9981	1.20 (1.13-1.28)		
18q11.2	rs11661542	18,477,693	<i>RBBP8</i>	C	Discovery	5.6x10 <sup>-09</sup>	6.39	0.9959	1.21 (1.14-1.30)	0.49, 0.44	0.54, 0.47
					Replication	4.5x10 <sup>-05</sup>	2.79	1.22 (1.11-1.34)	0.61	0.65	
					Combined	1.1x10 <sup>-12</sup>	9.92	1.0 - 1.2x10 <sup>-06</sup>	1.22 (1.15-1.28)		

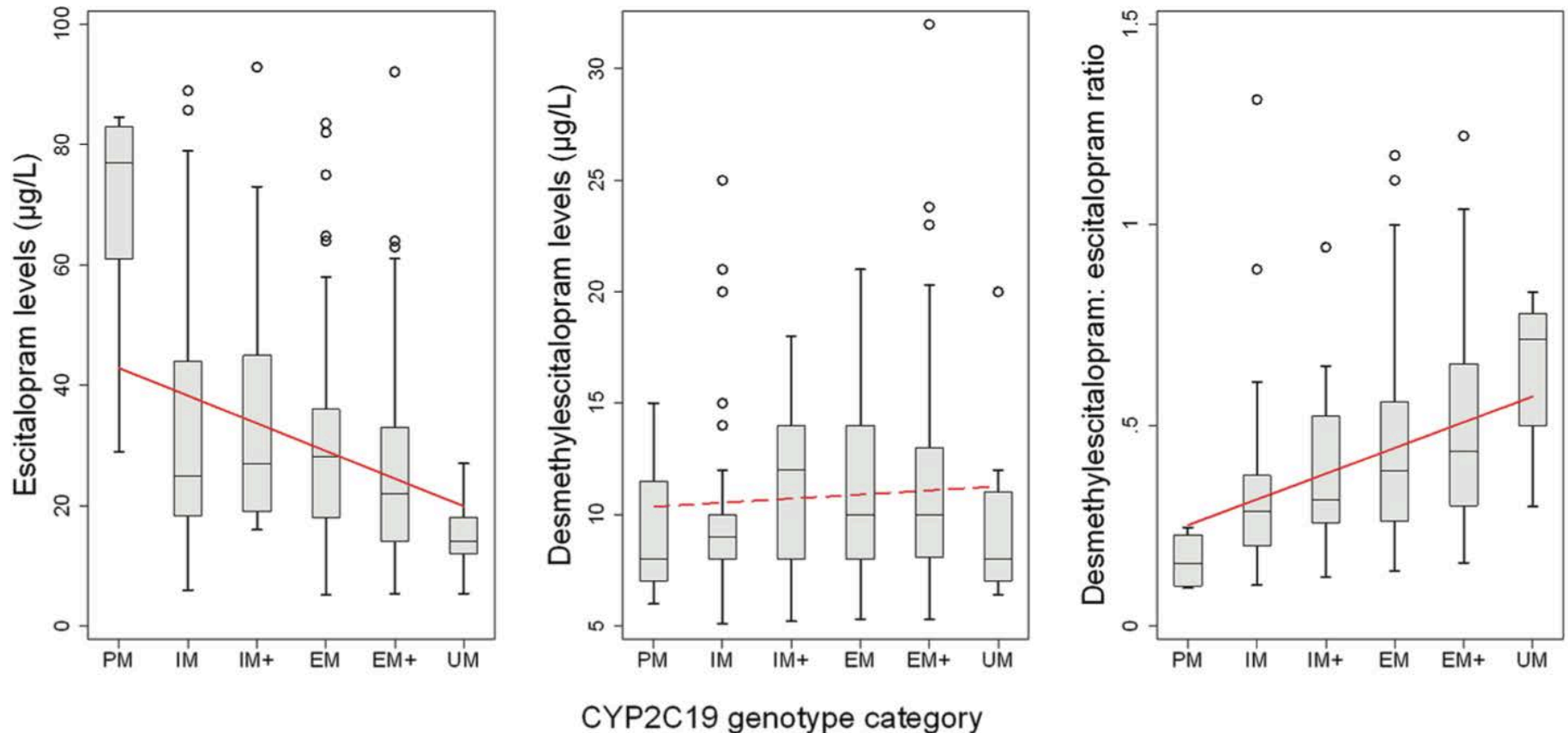
## 3 neue Risiko Loci:

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

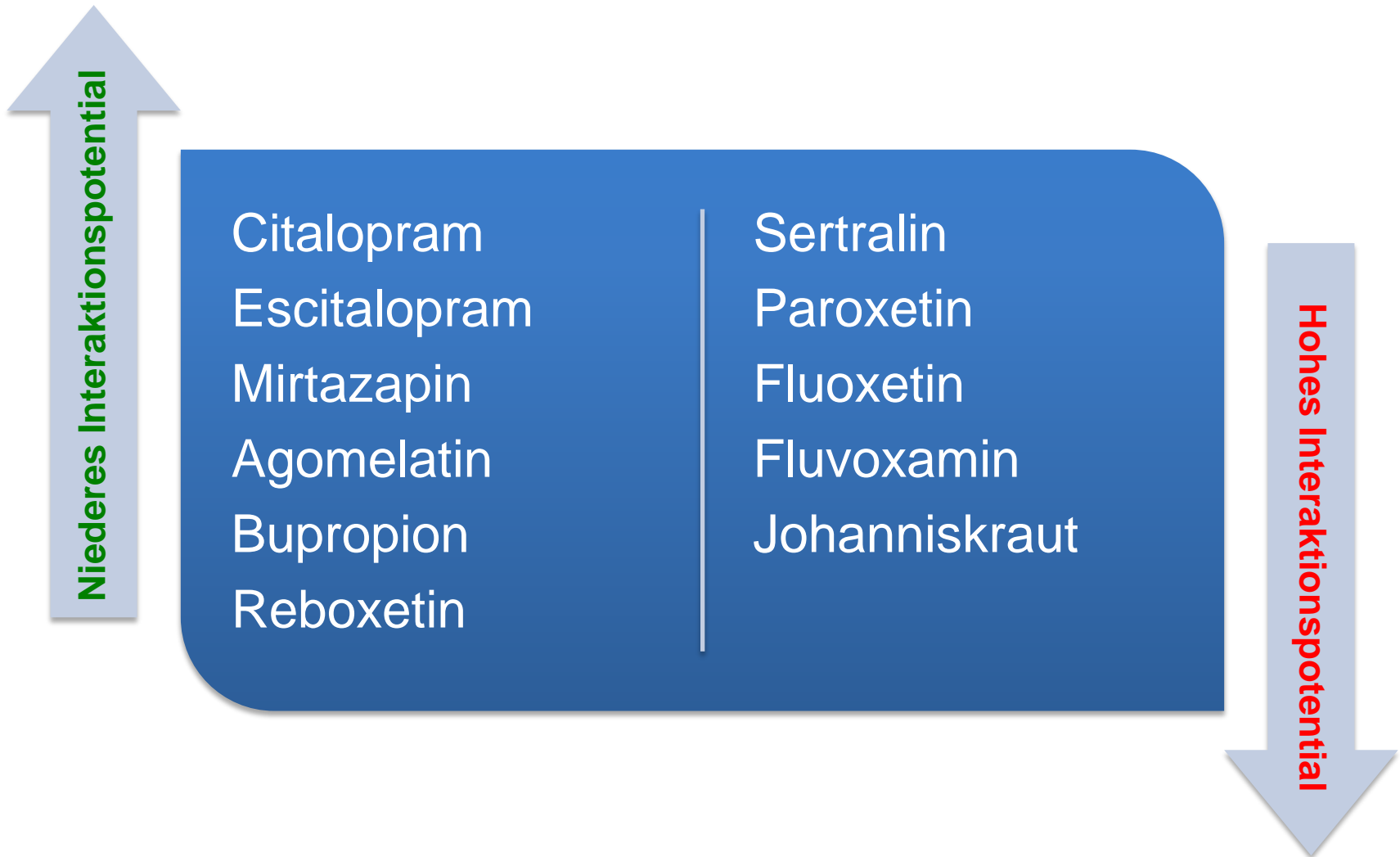
# Genetische Determinanten bestimmen Ansprechen auf Nikotinersatztherapie



# Beziehung zwischen CYP2D6/CYP2C19 Genotyp und Antidepressiva Blutspiegel



# 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

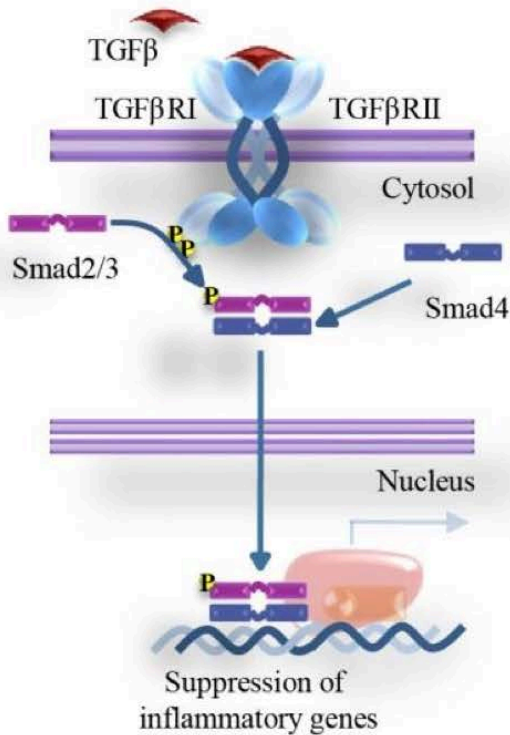


# HLA und Autoimmun-Krankheiten

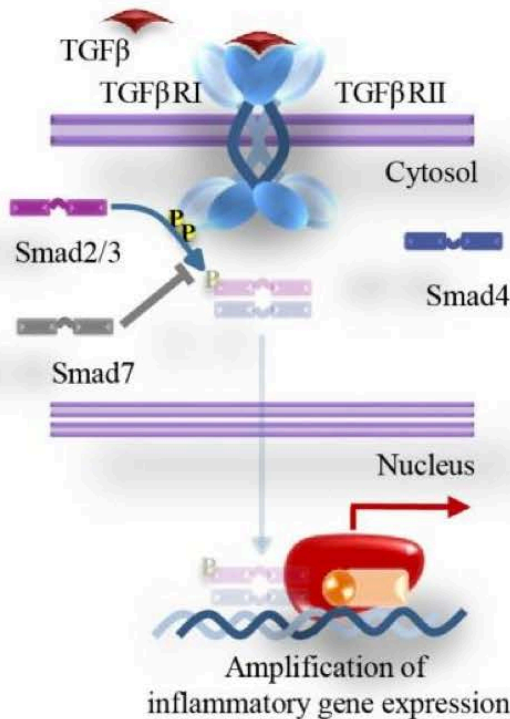
HLA Allel	Krankheiten mit erhöhtem Risiko	Relatives Risiko
HLA-B27	Ankylosierende Spondylitis	12
	Postgonokokkale Arthritis	14
	Akute anteriore Uveitis	15
HLA-B-47	21-Hydroxylase Mangel	15
HLA-DR2	SLE	2-3
HLA-DR3	Autoimmune Hepatitis	14
	Primäres Sjögren Syndrom	10
	Diabetes mellitus Typ 1	5
	Systemischer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

# TGF- $\beta$ 1 Signalübertragung in normaler und Mukosa bei M. Crohn

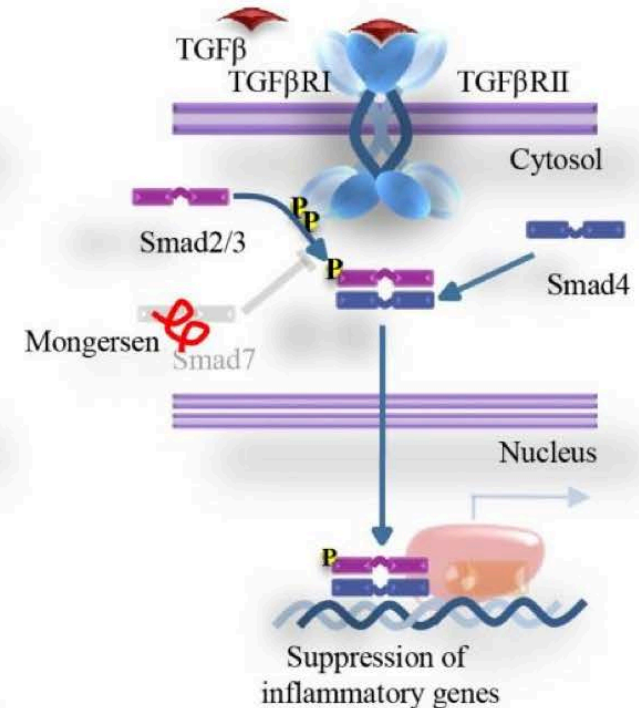
Normal



CD

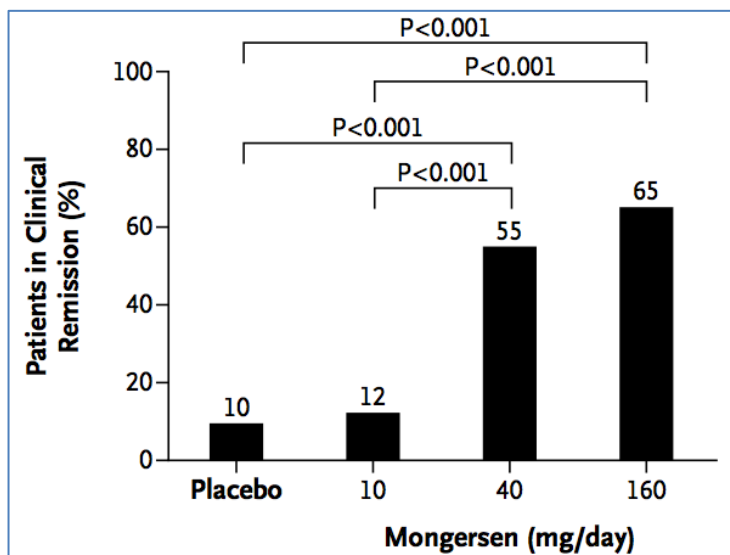
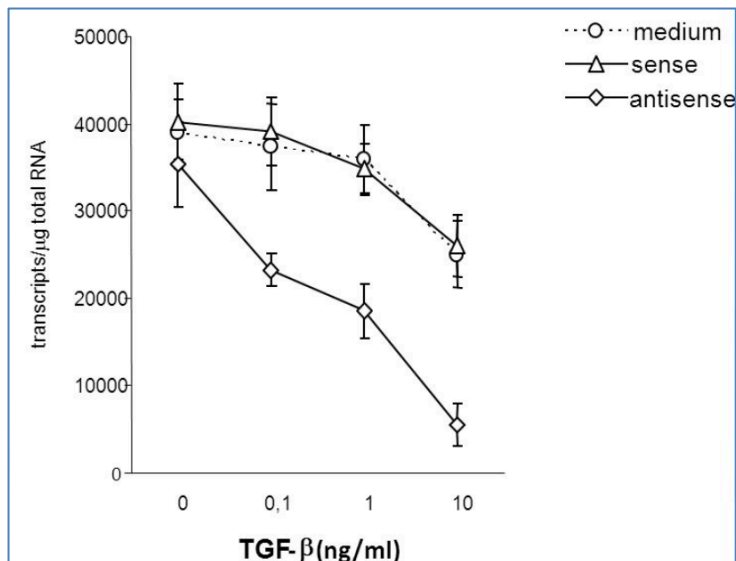


CD  
+  
Mongersen



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

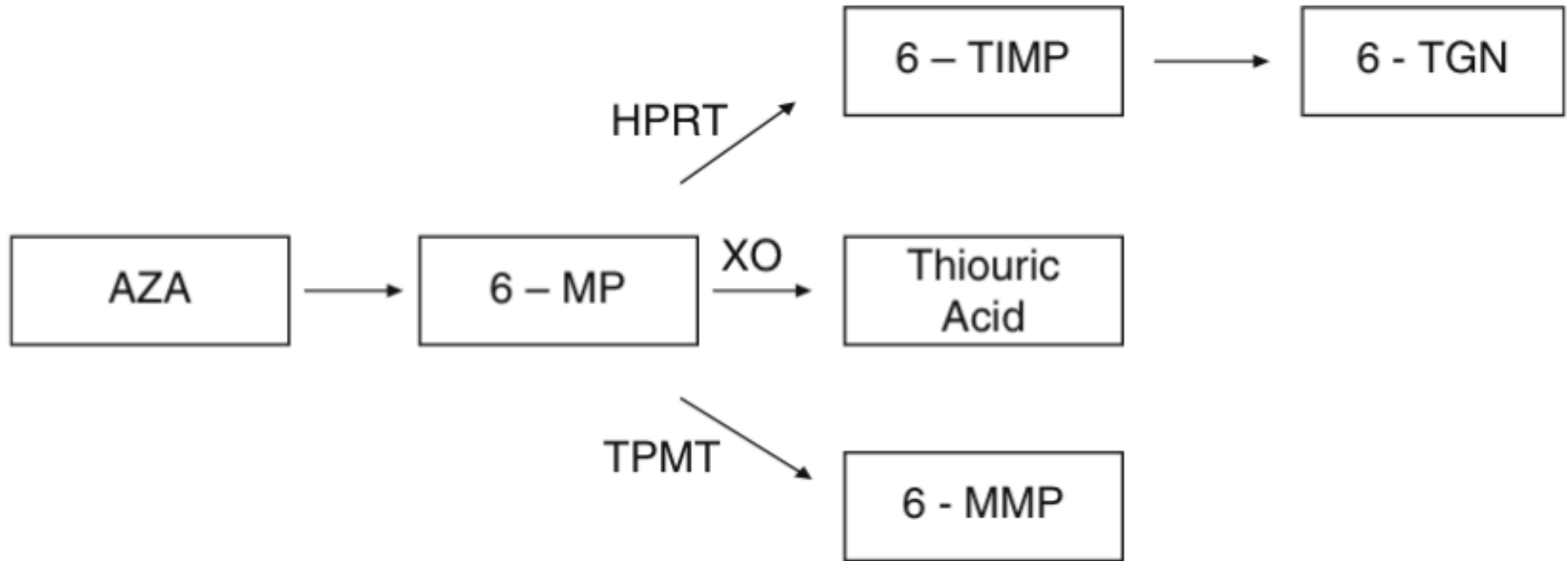
# Mongerson Antisense Therapie bei Morbus Crohn



**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

# Thiopurin Metabolismus



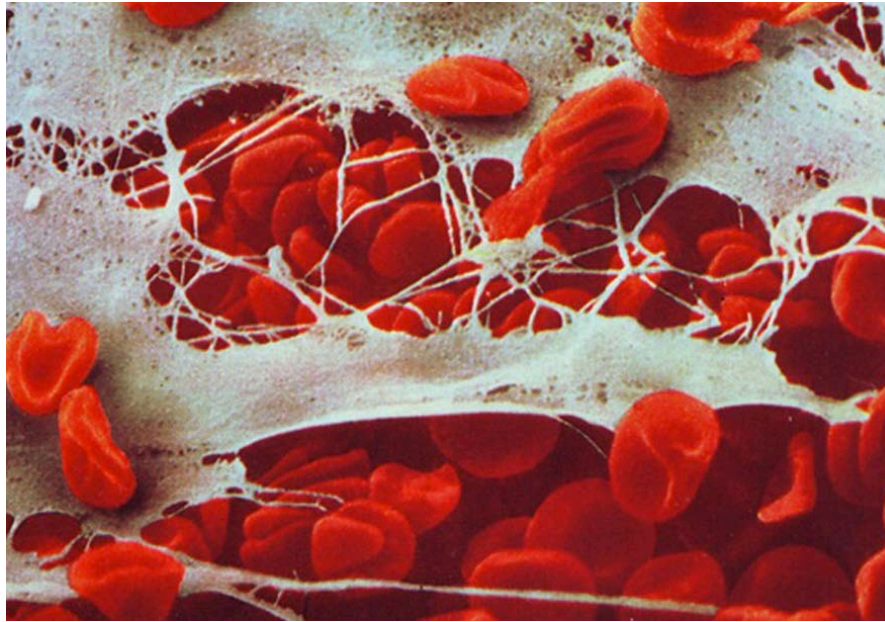
**TPMT Thiopurin Methyltransferase**  
**XO Xanthin Oxidase**  
**HPRT Hypoxanthine phosphorosyl Transferase**  
**6-TIMP 6-Thiosin Monophosphate**  
**6-MMP 6 Methylmercaptapurin**  
**6-TGN 6-Thioguanin Nukleotide**  
**AZA Azathioprin**  
**6-MP 6-Merkaptopurin**

# 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 <sup>†</sup>	OR (95% CI) <sup>†</sup>
<b><i>FcGR2A</i></b>						
Good response (n = 162)	RR: 56 (35); RH: 75 (46); HH: 31 (19)	57.7	<b>0.026</b>	<b>1.43 (1.04–1.98)</b>	<b>0.017</b>	<b>1.53 (1.08–2.17)</b>
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.

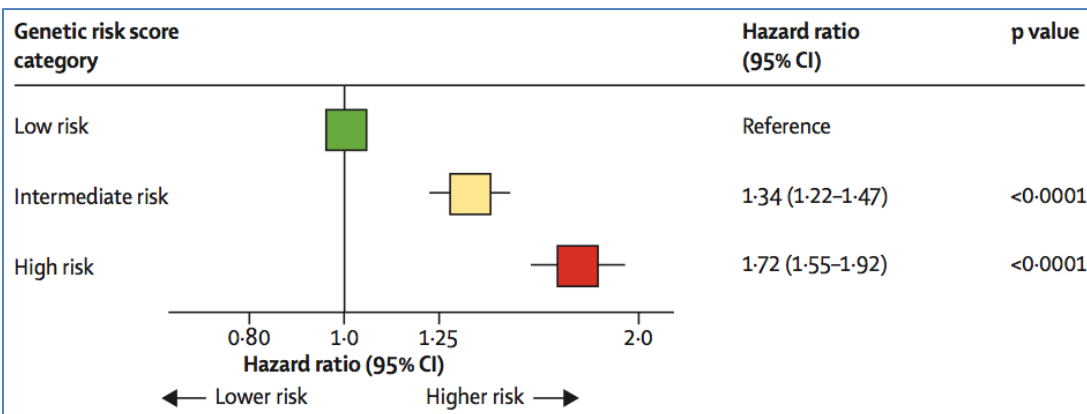


# HERZ- KREISLAUF/GERINNUNG

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

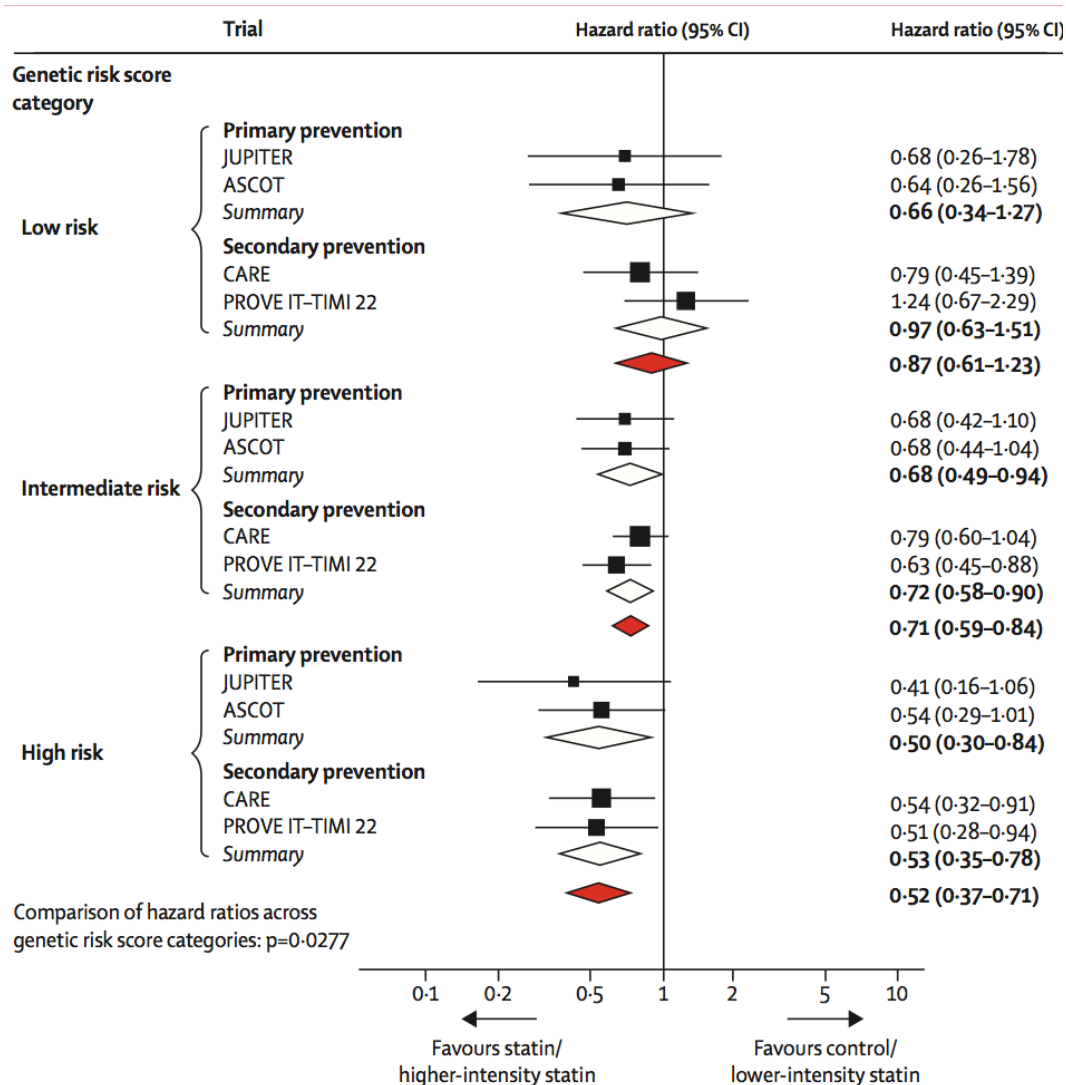
- **Erbliche Faktoren bestimmen 30-60% der Variabilität des koronaren Risikos**
- **Risikoscore mit 27 SNPs (assoziiert mit KHK in früheren GWAS)**

	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





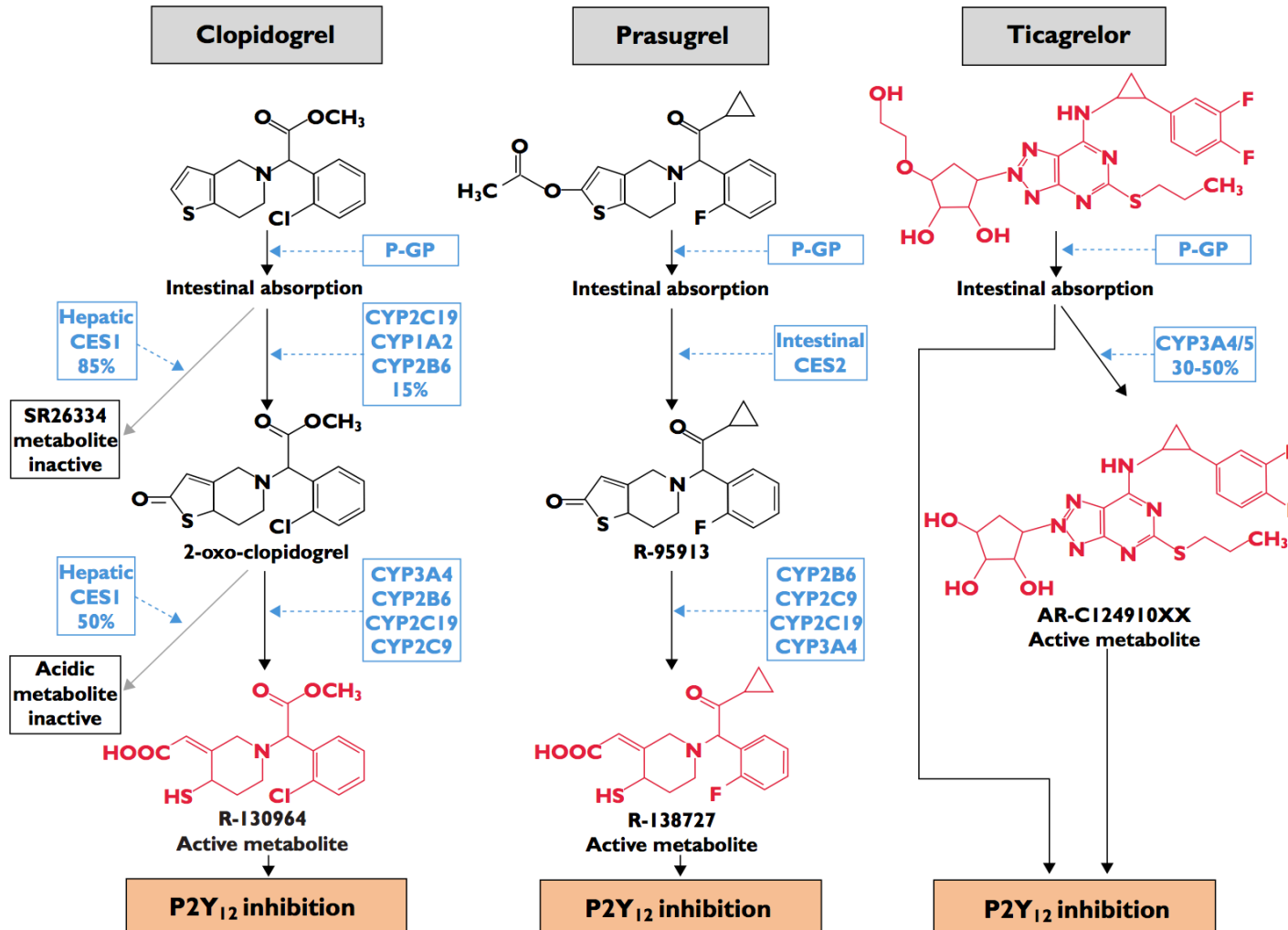
# Hazard ratio der koronaren Herzkrankheit unter Statinen je nach genetischem Risiko Score



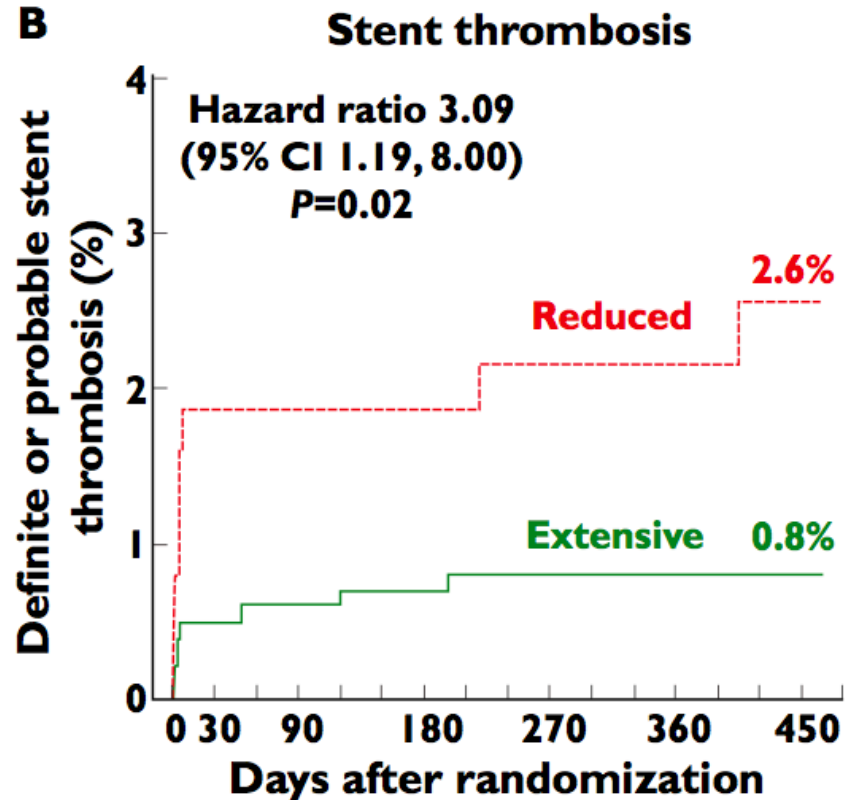
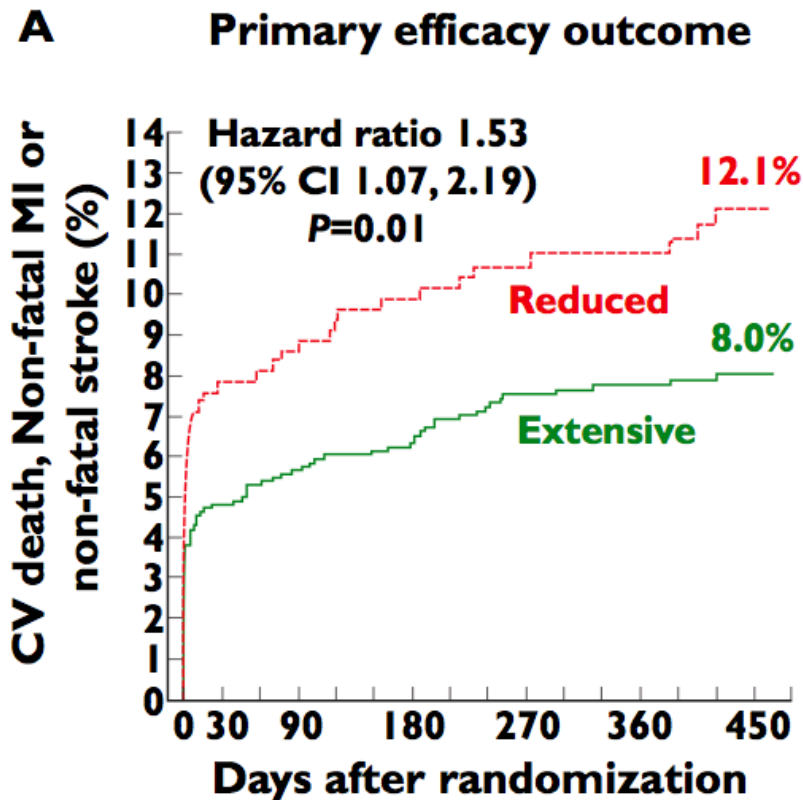
## Relative Risikoreduktion der Statin Therapie

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

# Metabolismus von Clopidogrel, Prasugrel und Ticagrelor

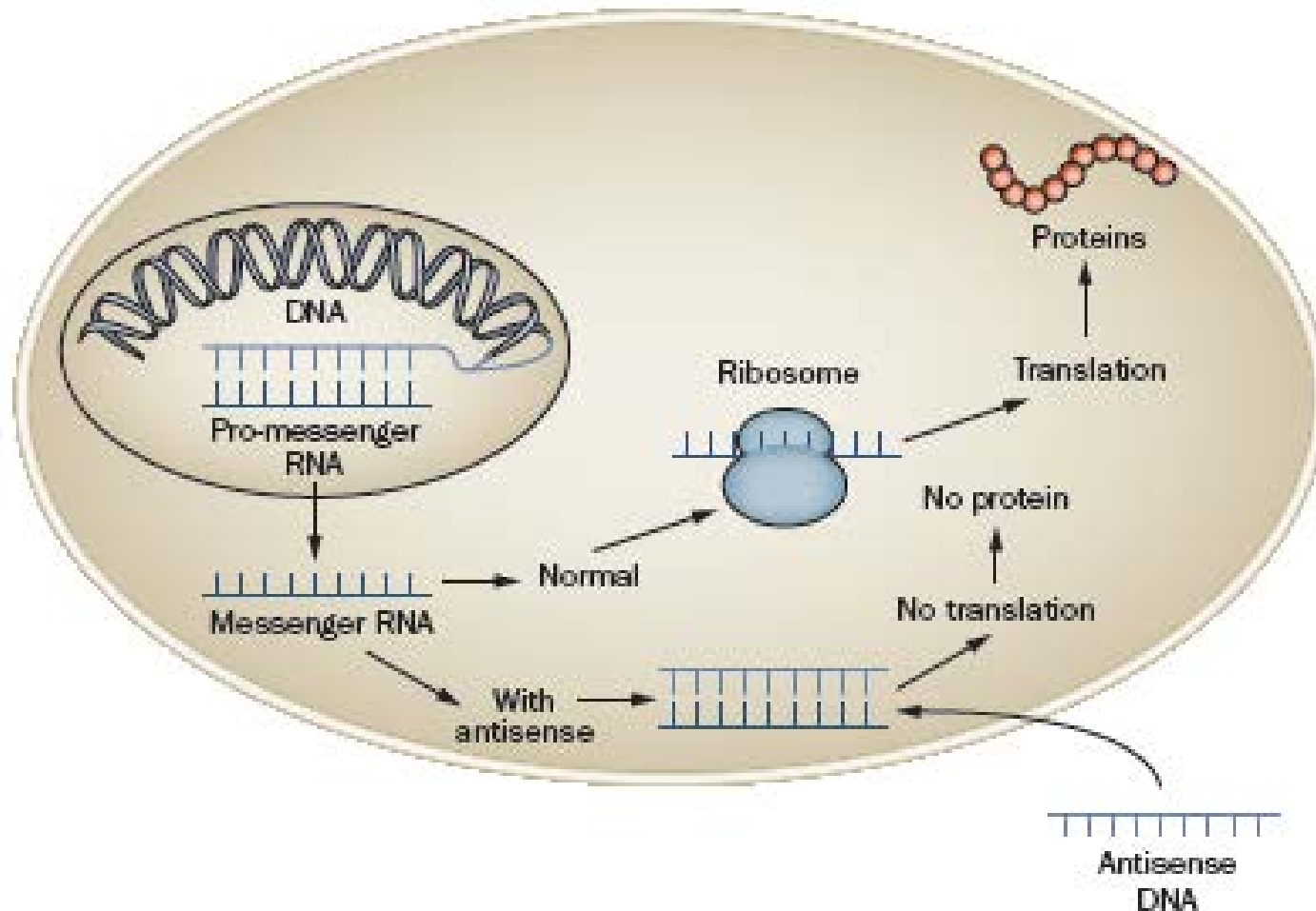


# Clopidogrel Wirkung und CYP2C19 Genotyp

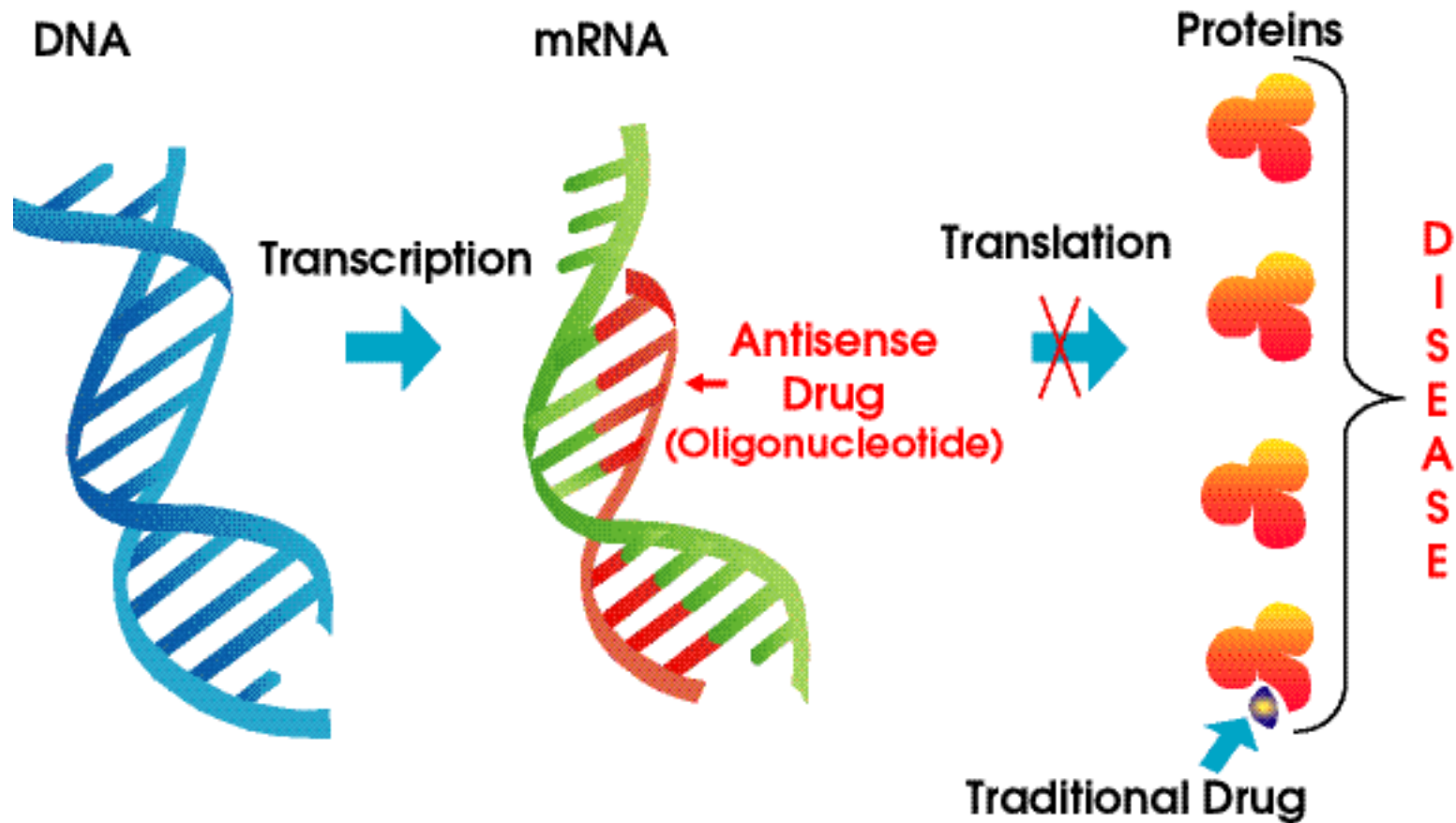


Nicht-Träger(CYP2C19\*1/\*1, \*1/\*17 und \*17/\*17) vs. Träger von CYP2C19 loss-of-function Allelen (Träger von \*2, \*3, \*4,\*5 oder \*8 allele) behandelt in TRITON-TIMI 38 Studie mit Clopidogrel

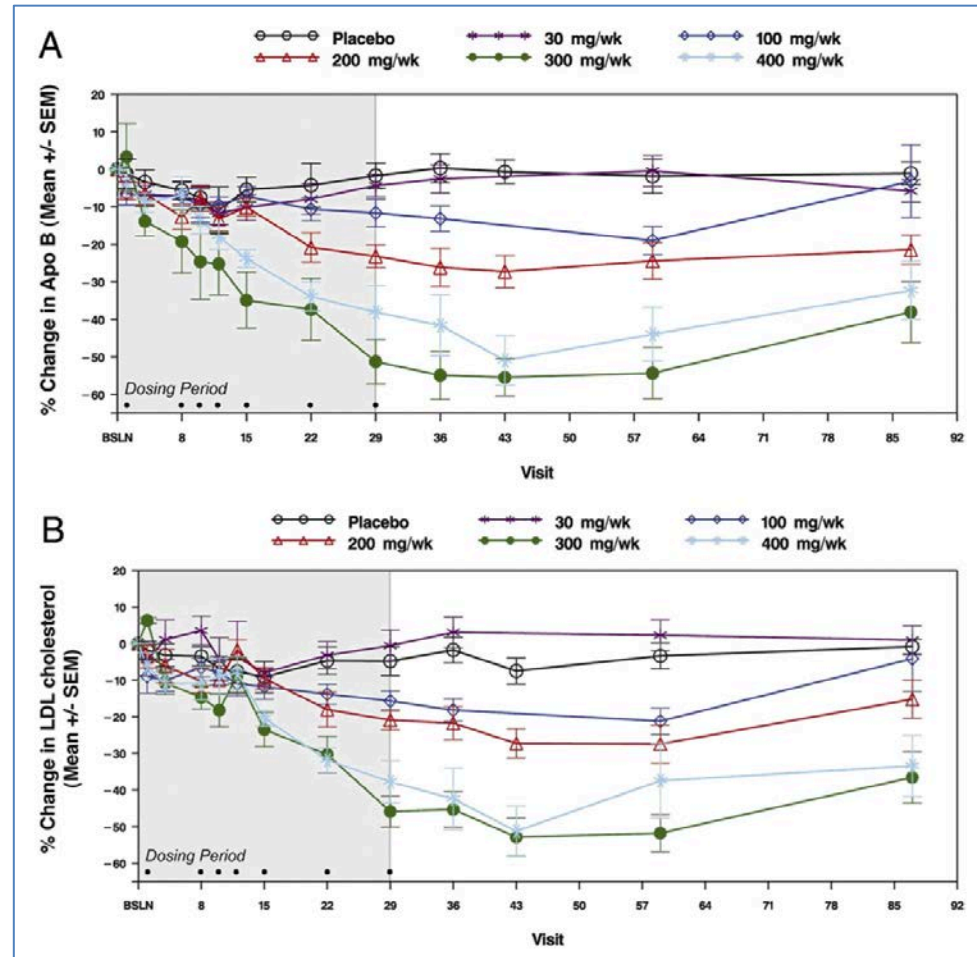
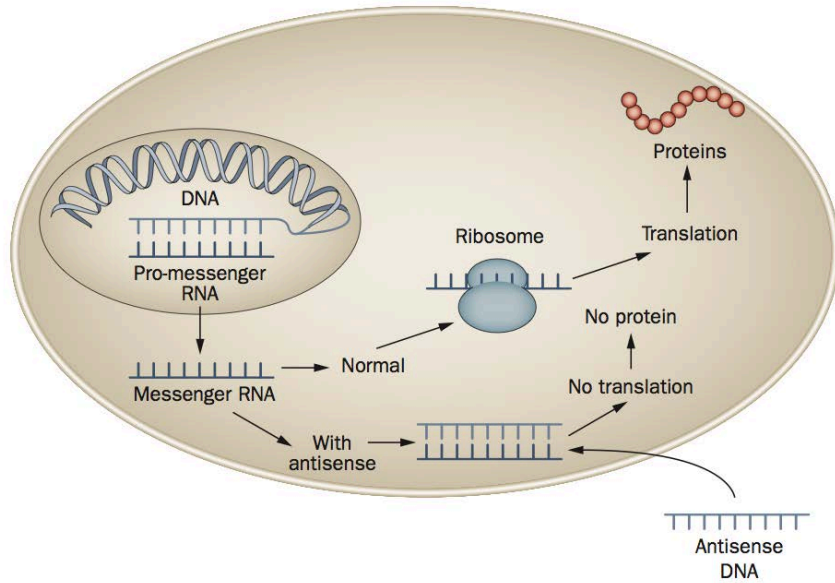
# Wie Antisense funktioniert



# Wie funktioniert Mipomersen?



# Antisense Nukleotide in der Behandlung der familiäre Hypercholesterinämie



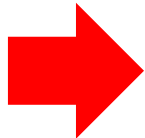
# Veränderungen der Lipide und Apolipoprotein B mit Mipomersen

Lipid parameter	Mipomersen 200mg per week				Mipomersen 300mg per week	
	Total cholesterol <300mg/dl <sup>81</sup> (n=8); trial period 4 weeks	Concomitant statin therapy <sup>63</sup> (n=10); trial period 13 weeks	Heterozygous FH <sup>85</sup> (n=11); trial period 6 weeks	Homozygous FH <sup>85</sup> (n=34); trial period 26 weeks	Concomitant statin therapy <sup>63</sup> (n=8); trial period 5 weeks	Heterozygous FH <sup>85</sup> (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

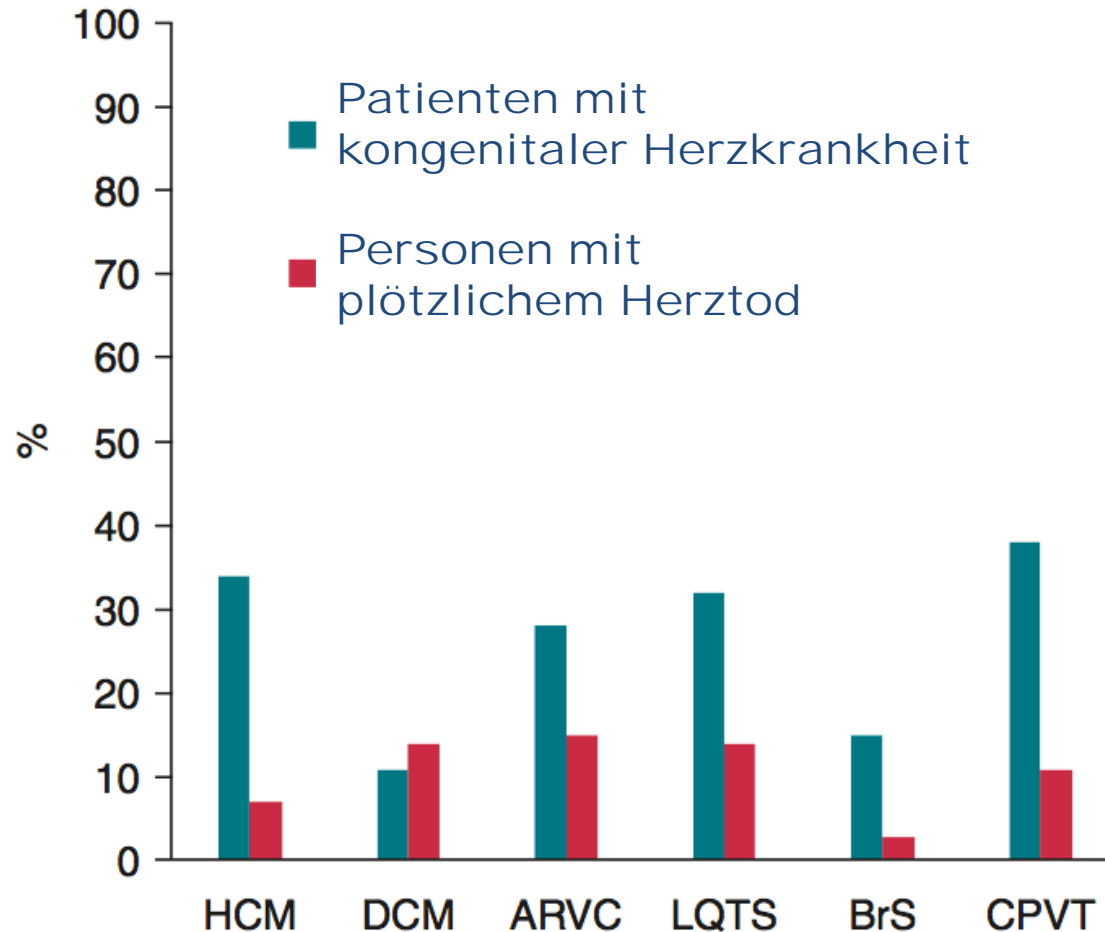


# Plötzlicher Herztod bei jungen Personen (1 - 40 Jahre)

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



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



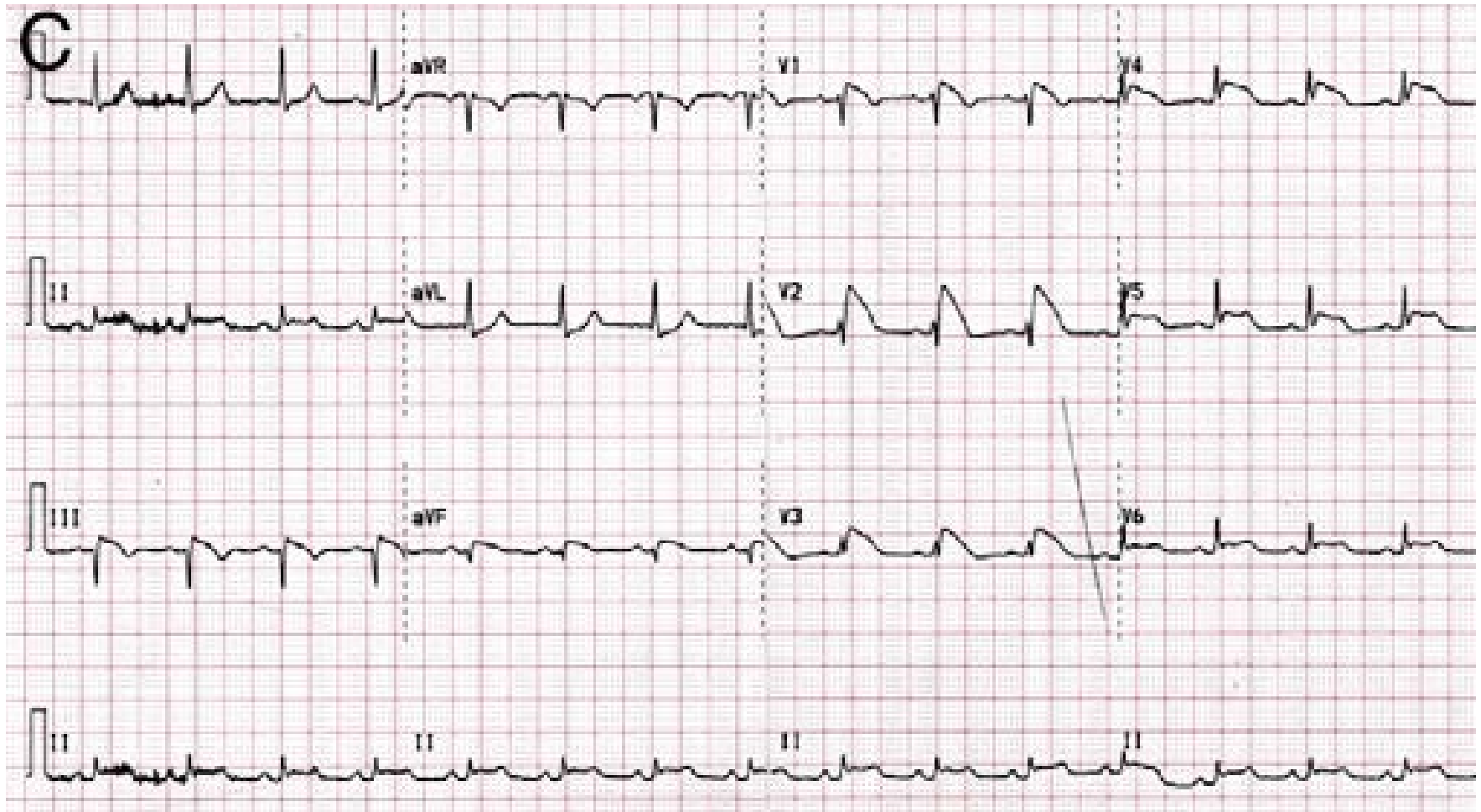
HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; ARVC, arrhythmogenic right ven- tricular cardiomyopathy; LQTS, long QT syndrome; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia.

# Kongenitales Long-QT Syndrom



QTc interval of > 460 ms

# Brugada Syndrome



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

# Genetische Ursachen des Brugada Syndroms

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

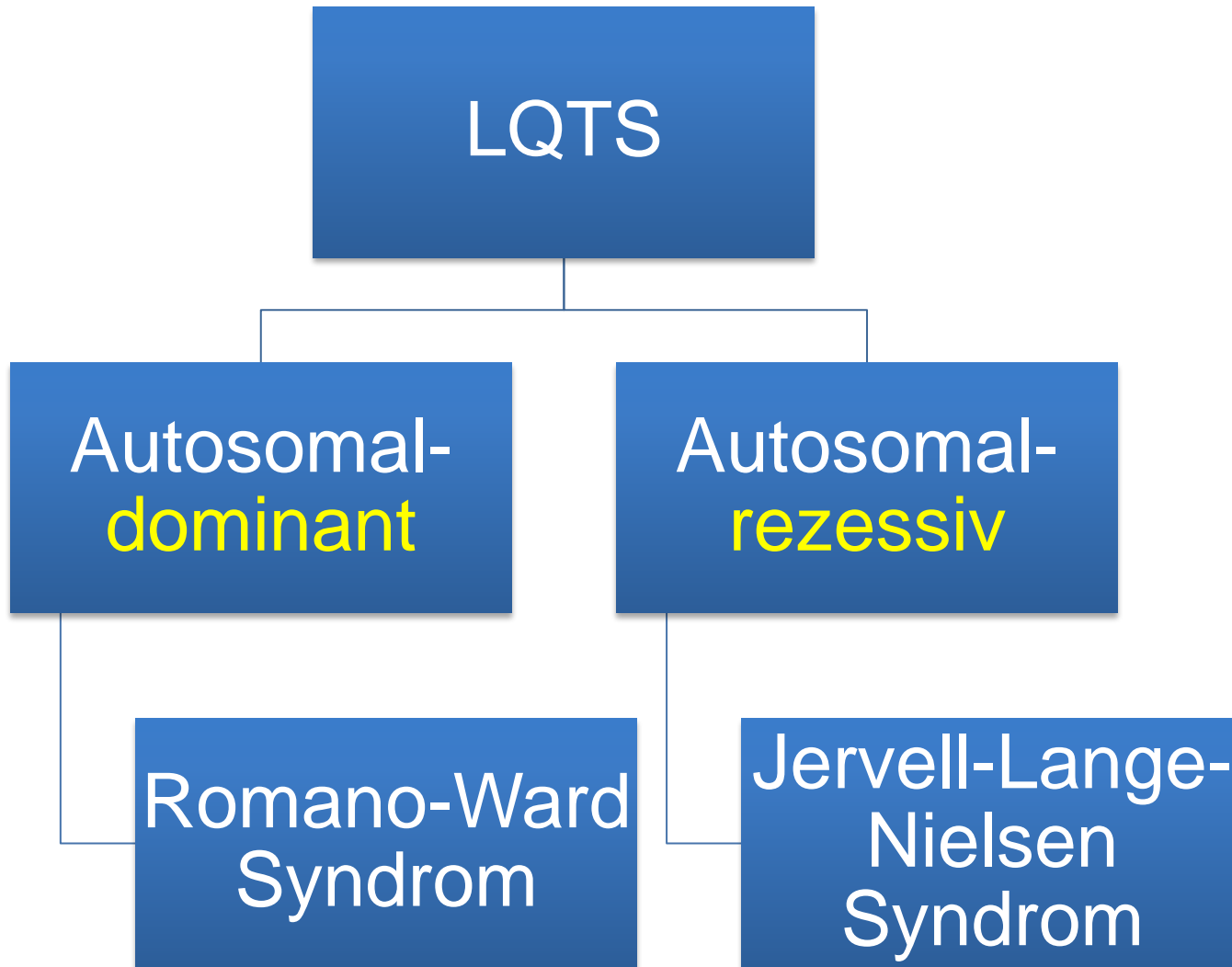
# Genetische Testung des Brugada Syndroms



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

# Long-QT Syndrom (LQTS)

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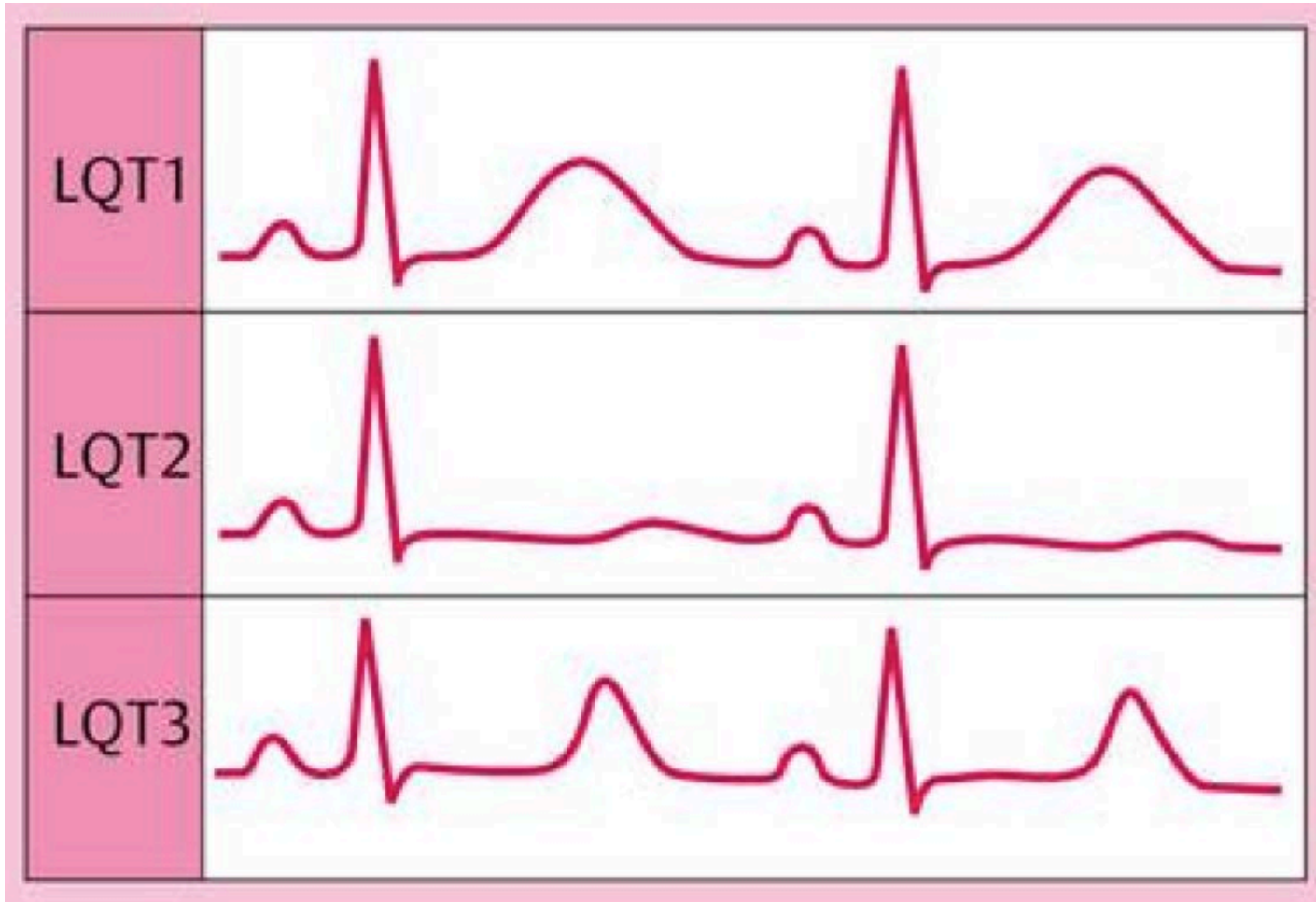
# Genetische Testung des LQTS

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

# LQTS Typen



***KCNQ1***

***KCHN2***

***SCN5A***

# Risikostratifizierung für den plötzlichen Herztod

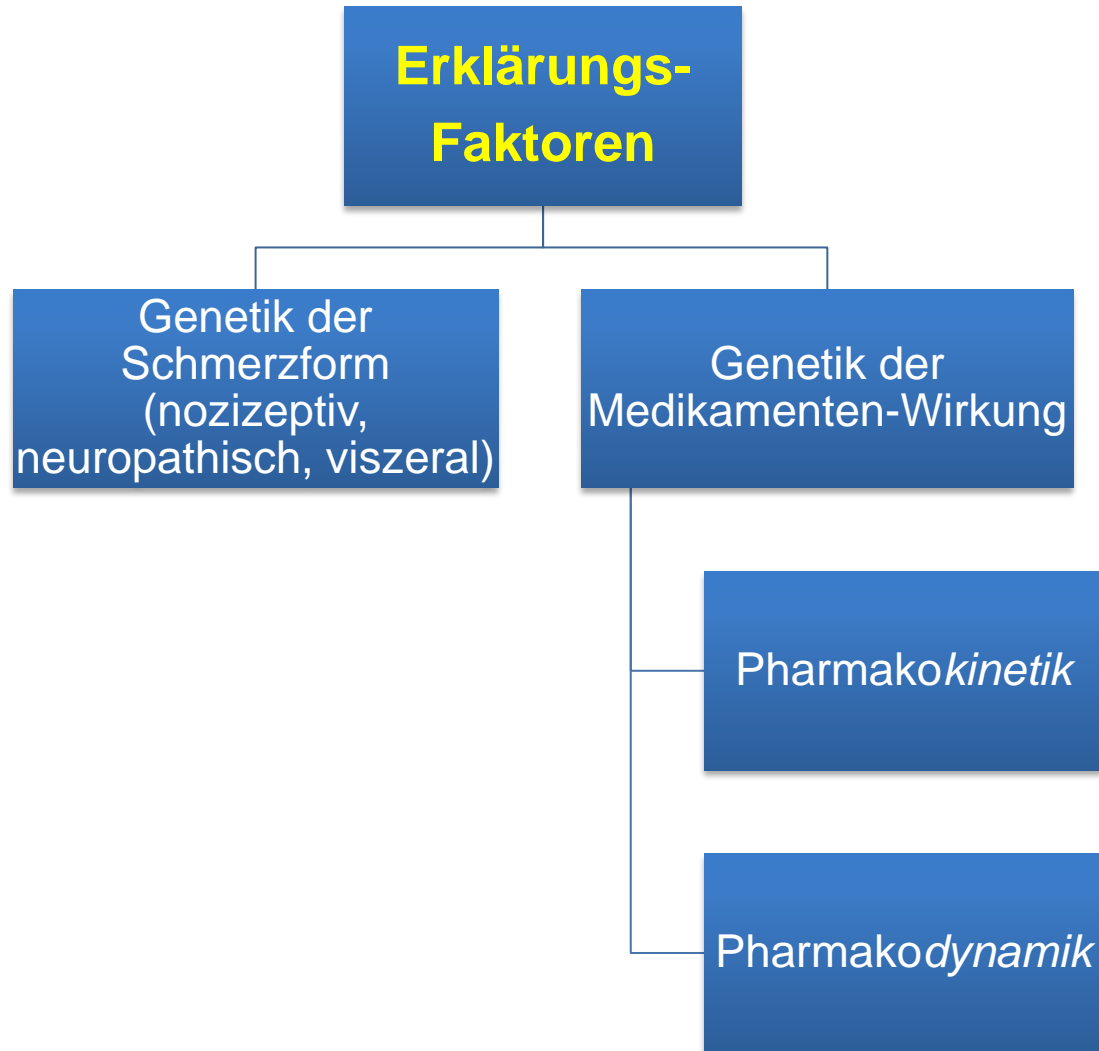
Risiko für Event (Synkope, Herzstillstand, Tod) vor dem 40. Lebensjahr	QTc-Zeit in Abhängigkeit von Genotyp und Geschlecht
> 50%	QTc $\geq$ 500 ms: LQT1 (m/w), LQT2 (m/w), LQT3 (m)
30–50%	QTc $\geq$ 500 ms: LQT3 (w)
	QTc < 500 ms: LQT2 (w), LQT3 (m/w)
< 30%	QTc < 500 ms: LQT1 (m/w), LQT2 (m)

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



# PERIOPERATIVE MEDIZIN/ANÄSTHESIE

# Genetik der Analgesie

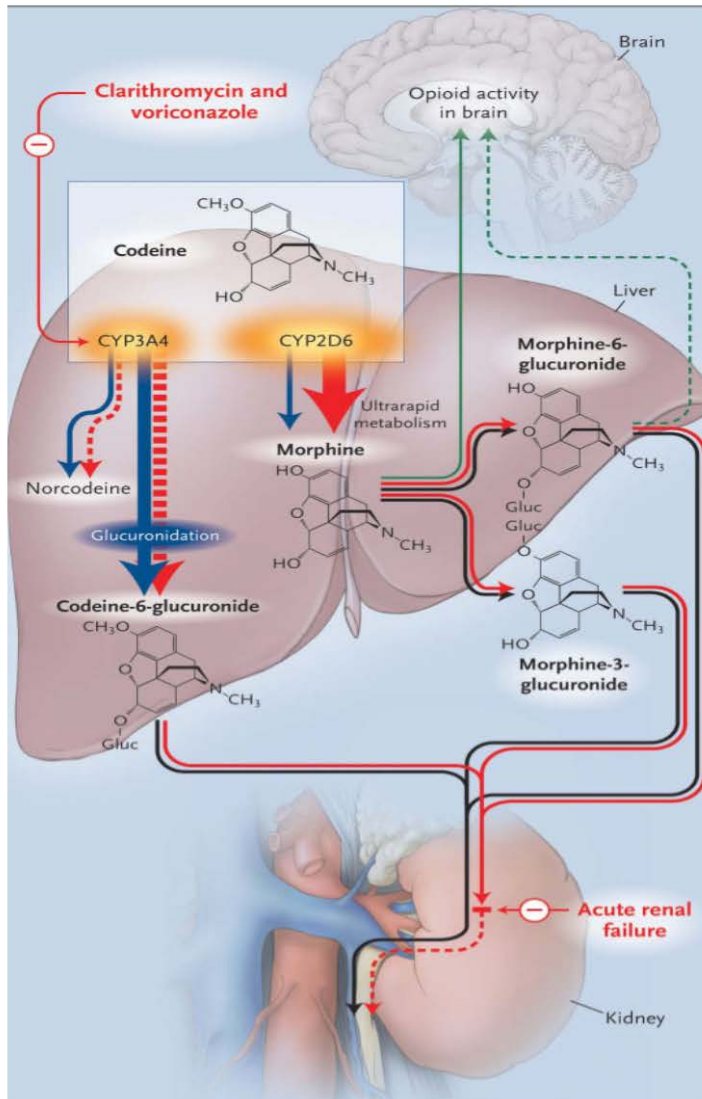


# Melanocortin-1-Rezeptor

**Rot-haarige benötigen  
20% mehr Anästhetika**



# Codeine Toxicität



## 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

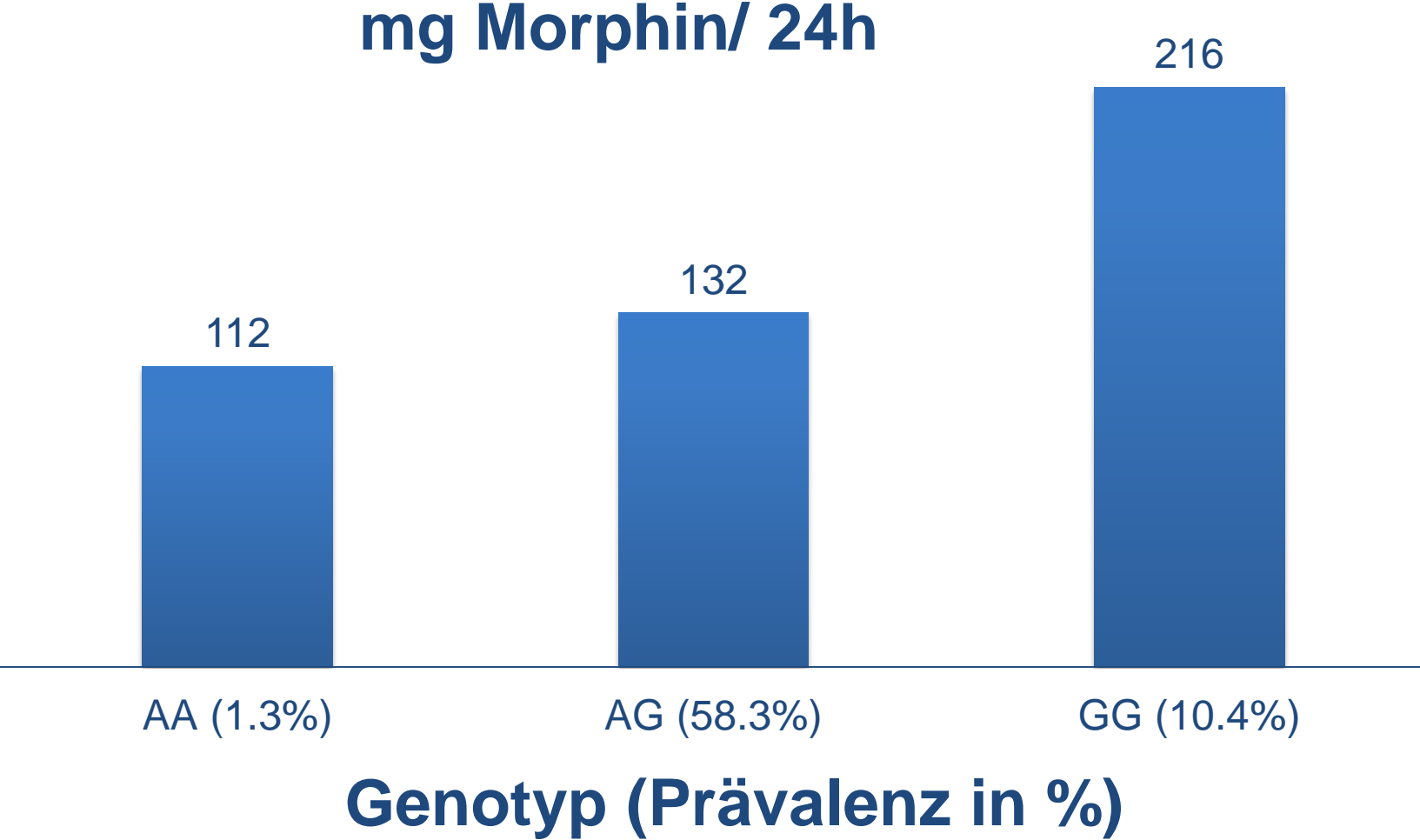
- Hydroxylierung via CYP2B6
- O-Glukuronidierung via UGT1A9
- Bisher einziger SNP: UGT1A1 766G>A → unerwünschte Nebenwirkungen ↑

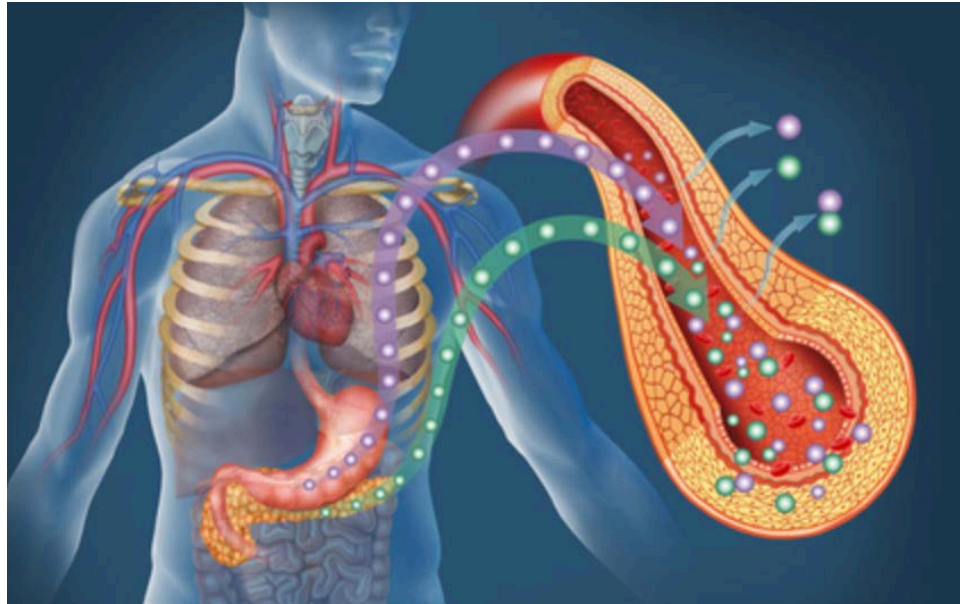


# Hauptsächliche CYP Enzyme und ihre Substrate in der Anästhesie

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

# Morphinverbrauch und OPRM1 Genotyp

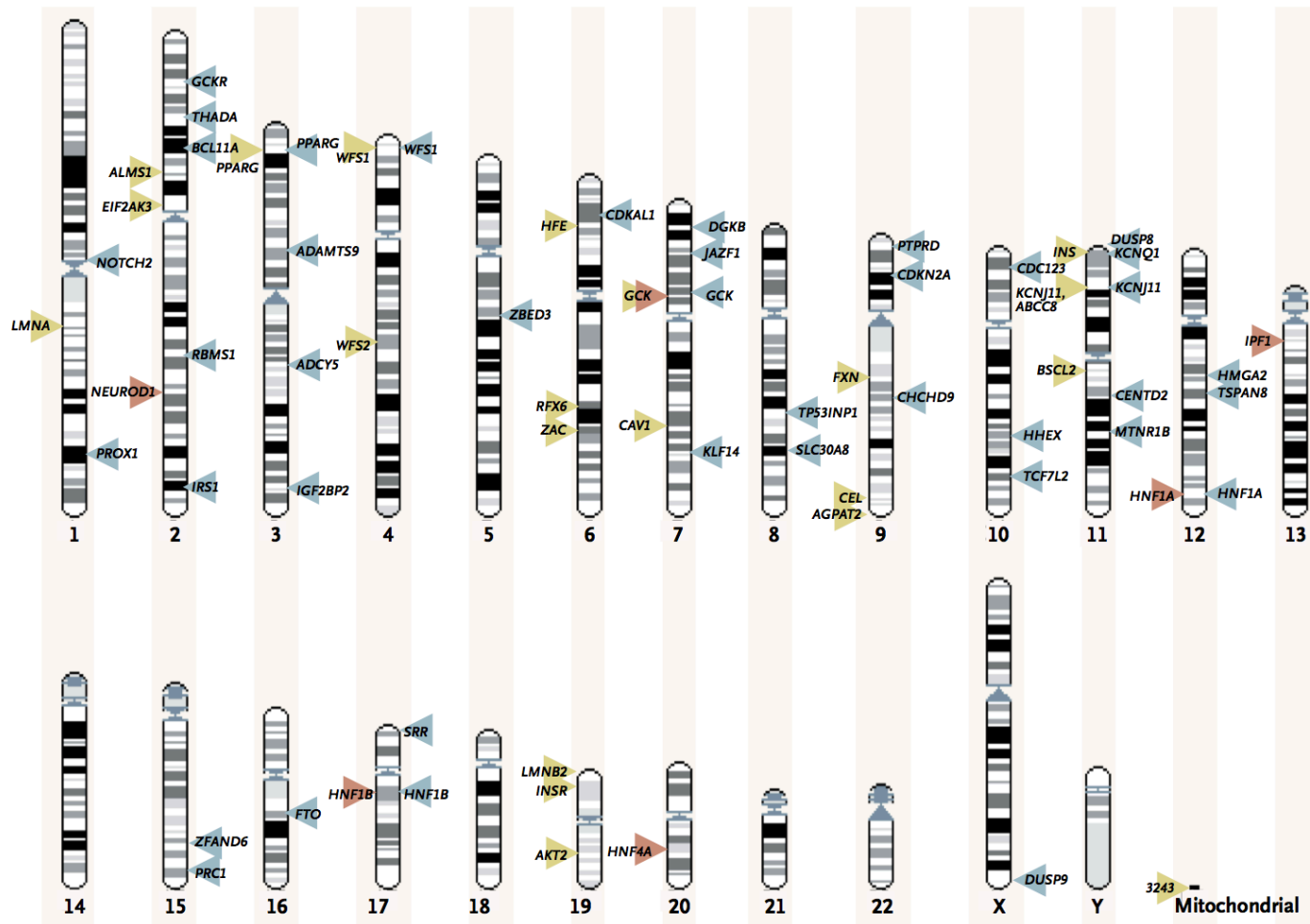




# ENDOKRINOLOGIE/STOFF- WECHSEL

# Genomik, Typ2 Diabetes und Adipositas

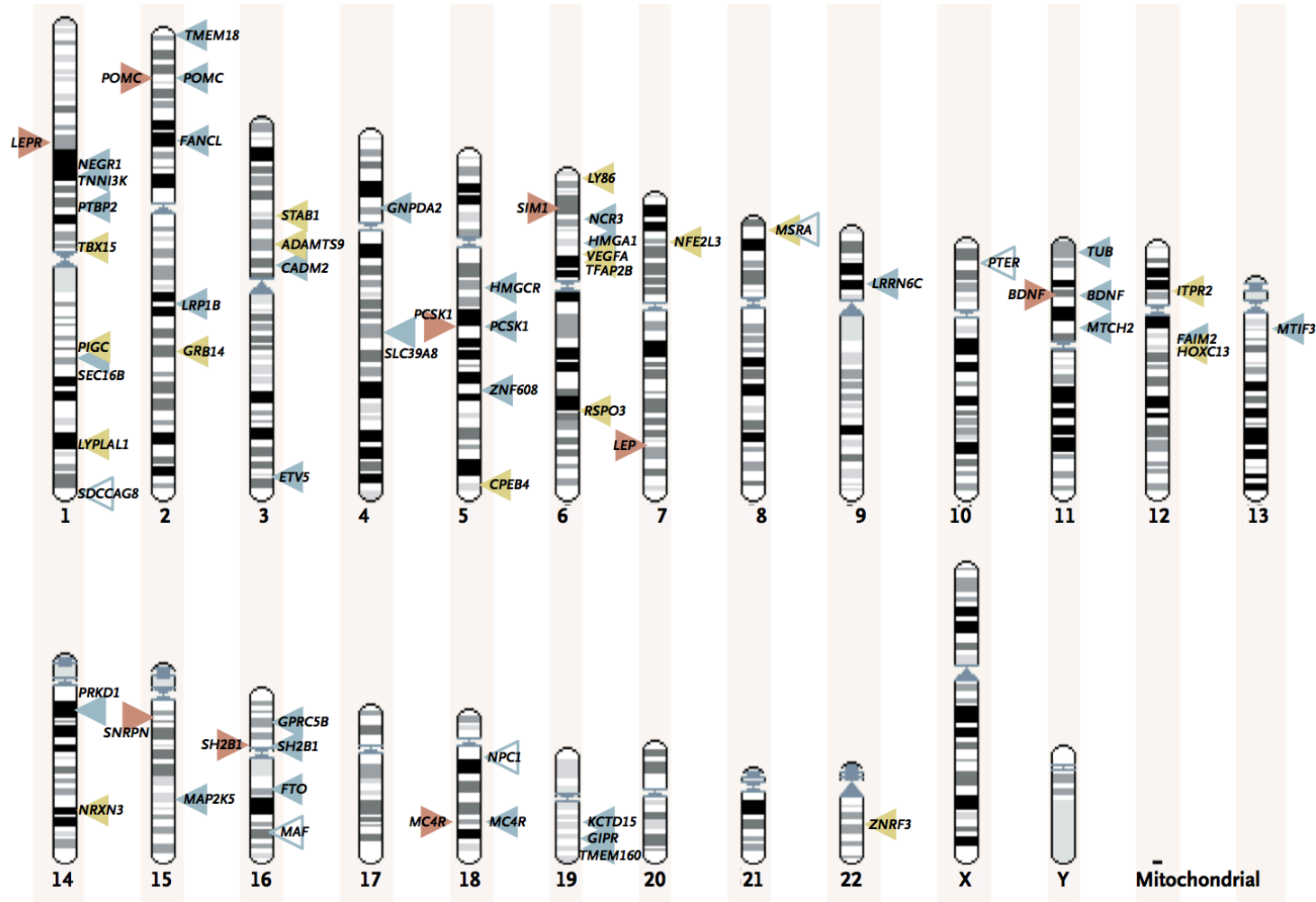
## Genomische Lokalisation von bewiesenen Signalen nicht autoimmuner Formen von Diabetes





# Genomik, Typ2 Diabetes und Adipositas

## Genomische Lokalisation von bewiesenen Signalen des BMI



# 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)	PPAR $\gamma$	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

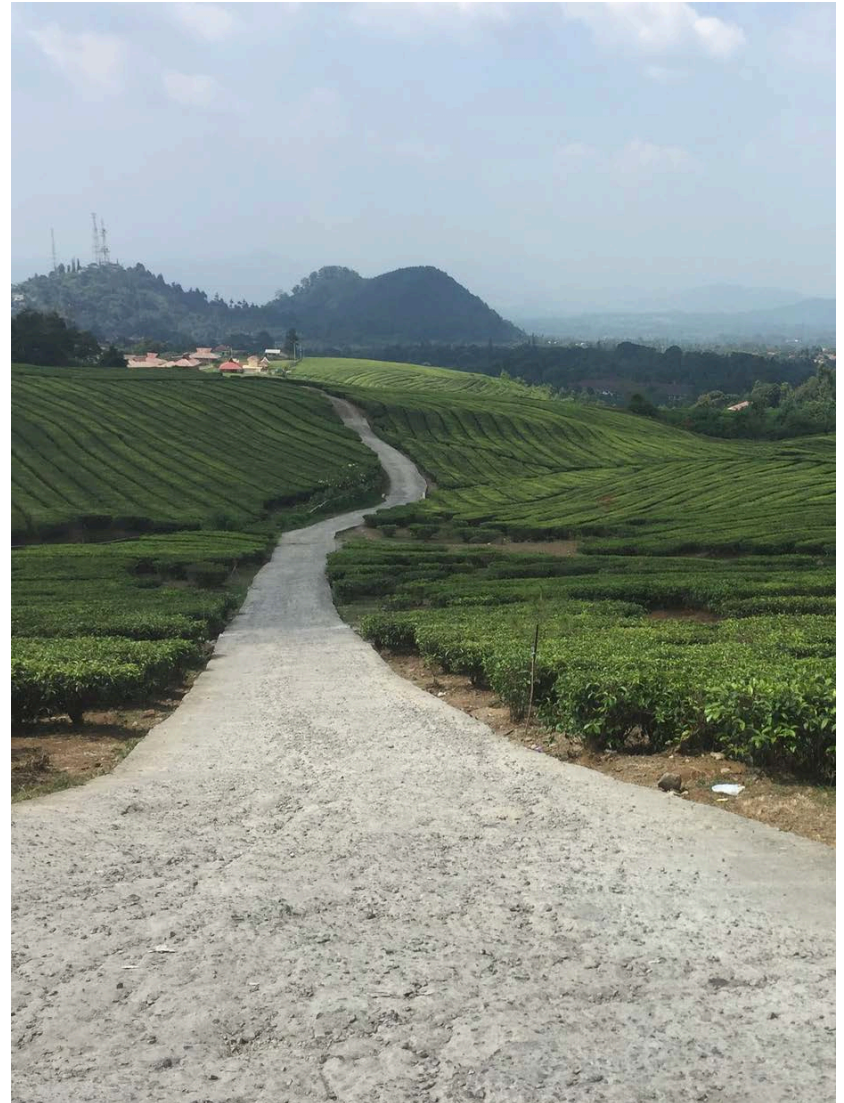
**Kleine Effektgrößen!**

# Fragen?



# Übersicht

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

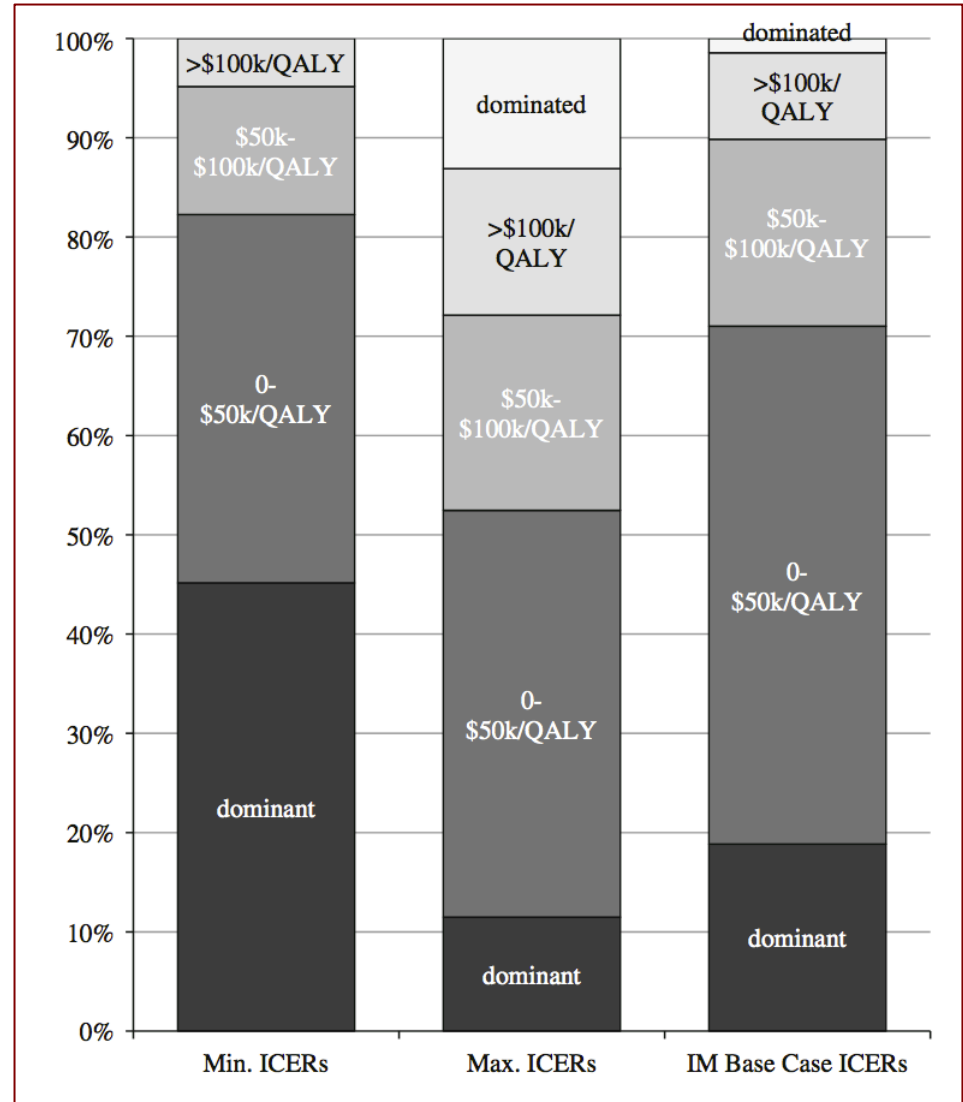


# Cost-effectiveness ratios according to type of tests used in PHC

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

# 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



# 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	<b>Dominant</b>
Furuta (2007)	CYP2C19	PPI	<b>Dominant</b>
Chou (2000)	CYP2D6	Antipsychotics	Undetermined
Marra (2002)	TPMT	AZA	<b>Dominant</b>
Oh (2004)	TPMT	AZA	<b>Dominant</b>
Winter (2004)	TPMT	AZA	GBP487/LYG
Dubinskiy (2005)	TPMT	AZA	<b>Dominant</b>
Priest (2005)	TPMT	AZA	<b>Dominant</b>
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)	$\alpha$ -adductin	Thiazide	<b>Dominant</b>
Maitland van der Zee (2004)	ACE	Statins	<b>Dominant</b>
Costa (2007)	ACE	ACE inhibitors	<b>Dominant</b>
Kim (2006)	MTHFR	MTX	<b>Dominant</b>
Hughes (2004)	HLA	Abacavir	<b>Dominant</b> to EUR 22'811/hypersensitivity reaction avoided
Veenstra (2007)	A1555G	Aminoglycosides	EUR 59759/QALY

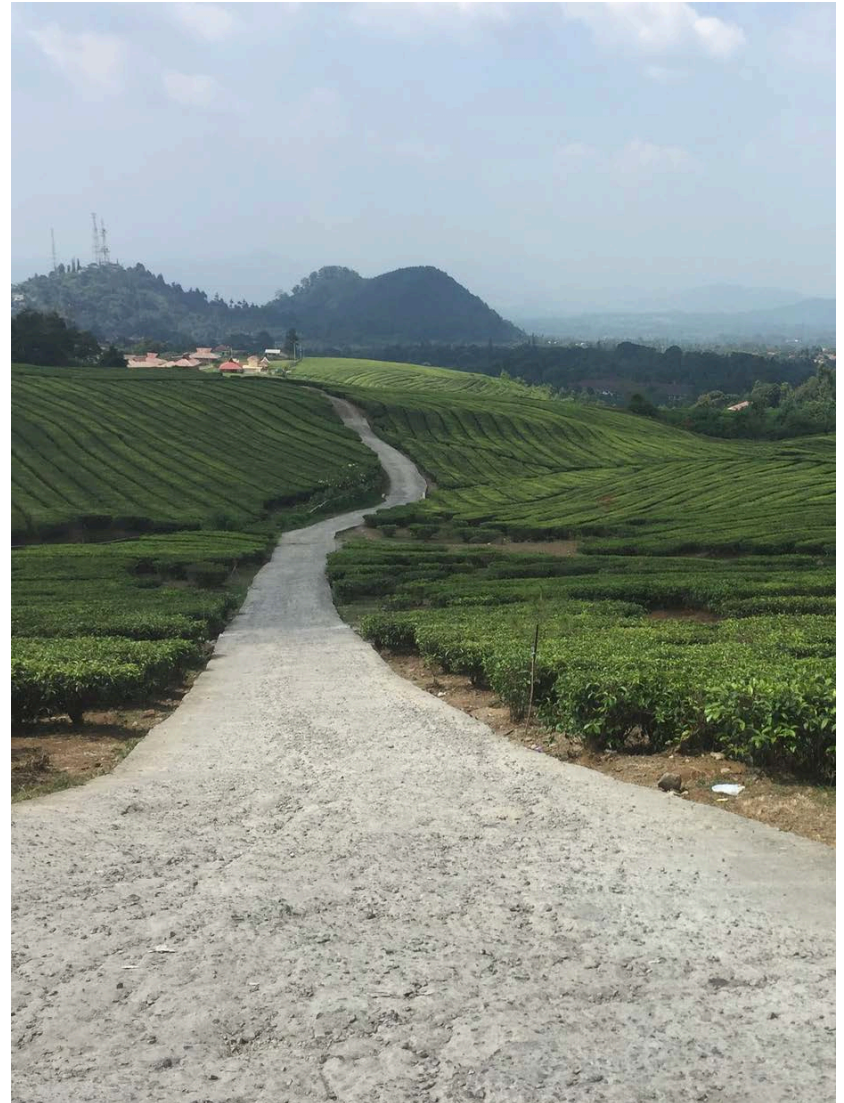


# Cost-effectiveness of high profile drugs and companion diagnostics

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

# Übersicht

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



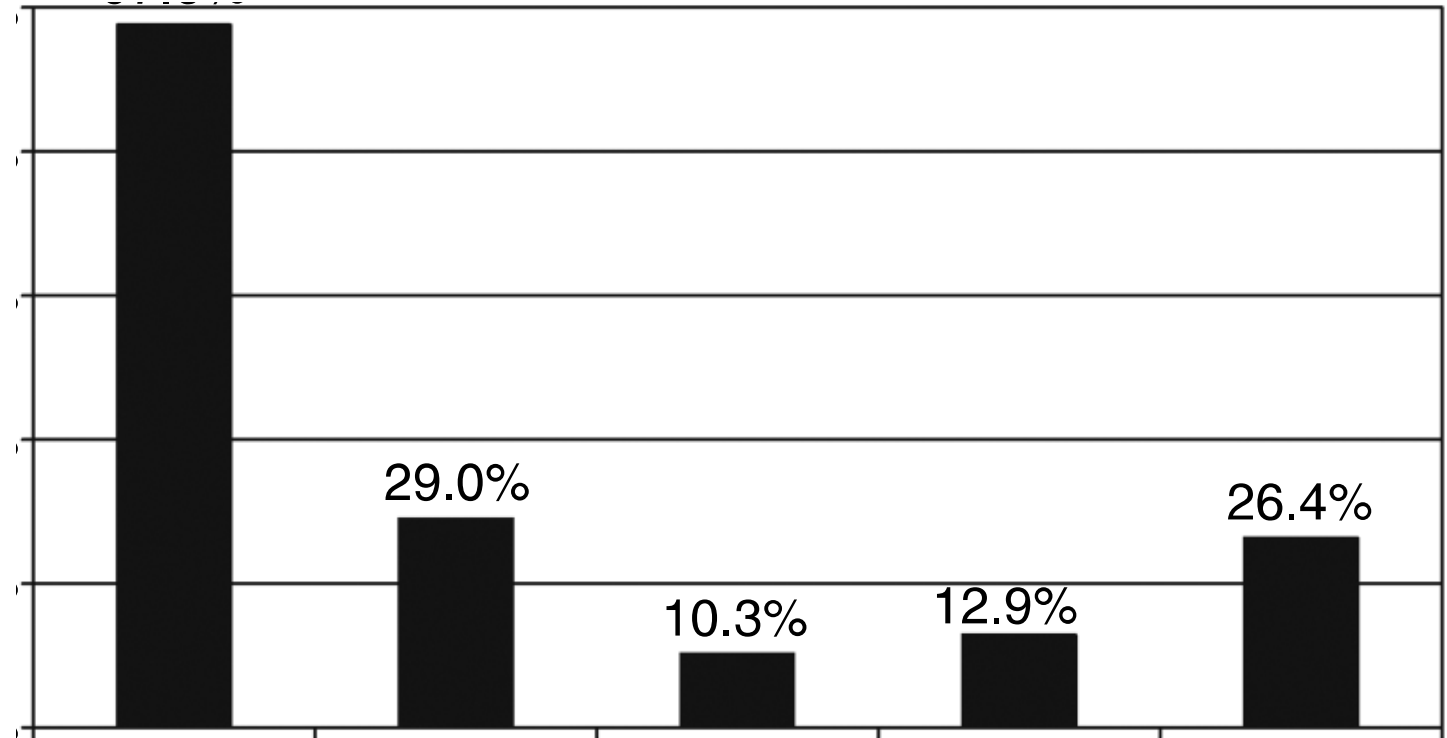
# Education and training

**„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 decisions based on it.“**

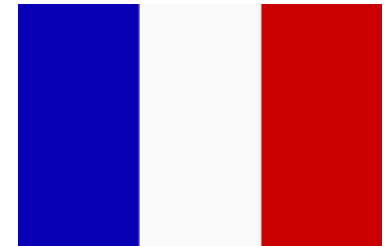
**John Glaser, Chief Information Officer,  
Partners Healthcare**



# Survey on physician knowledge of pharmacogenomics



# Länder mit nationalen Genomstrategien (public health genomics)





# Die Zukunft ist schon heute



This is a screenshot of the Duke Center for Personalized and Precision Medicine website. The header includes the center's name and navigation links for Home, Genetic Testing and Sequencing, Disease Risk and Diagnosis, Pharmacogenomics, Clinical Implementation, Genomic Policy, Genomic Medicine, and About Us. The main content area features a section titled 'This is personalized medicine' with a sub-section for 'Pharmacogenomics' and a quote: 'Imagine knowing about the likelihood of experiencing an adverse event to a drug before it's prescribed.' Below this are sections for 'ANNOUNCEMENTS and EVENTS' and 'NEWS and PUBLICATIONS'. The 'ANNOUNCEMENTS and EVENTS' section lists several upcoming events, including the 'Next Generation Sequencing of Genetic Genealogy for the Clinical Care of Cancer Patients' (9/26/2013), 'The 5th Annual Personalized Medicine Conference: The Emerging Practice of Personalized Medicine' (10/5-10/20/2013), 'C4F Annual Next-Generation Sequencing for Cancer' (10/23/2013), '9th Annual Harvard Partners Personalized Medicine Conference' (11/6-11/7/2013), 'Precision Medicine: Personal Genomes & Pharmacogenomics' (11/14-11/16/2013), and 'Molecular Med TricEx' (2/9-2/14/2014). The 'NEWS and PUBLICATIONS' section includes articles such as 'S2M NCI project will set up genetic variant database for clinical use' (9/25/2013), 'Uniquer Genomics Researchers Take Leading Role in Clinical Genome Project' (9/25/2013), 'Activable, Pathogenic Incidental Findings in 1,000 Participants' (9/26/2013), 'Opportunities for genomic clinical decision support interventions' (9/19/2013), 'Genomic medicine: educational challenges' (9/20/2013), 'Rare-disease genetics in the era of next-generation sequencing: discovery to translation' (9/20/2013), and 'Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting' (October 2013).

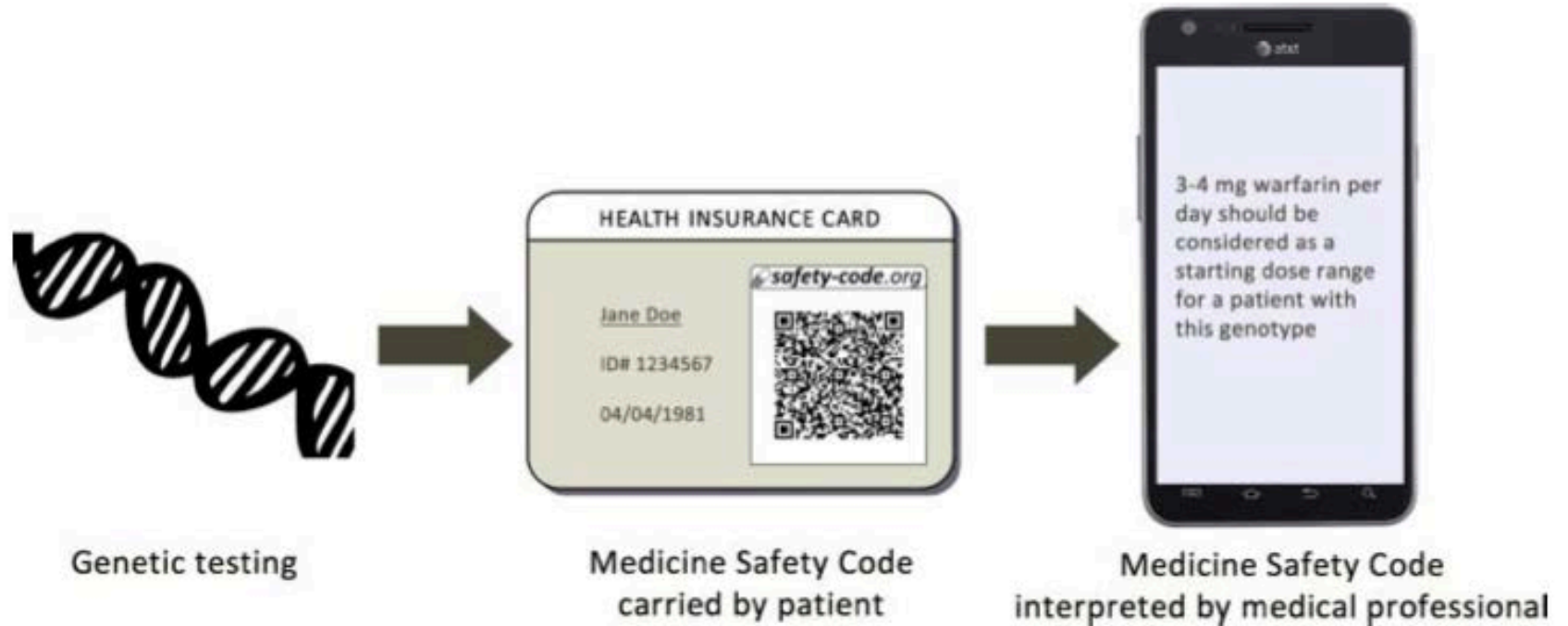
This is a screenshot of the Mayo Clinic Center for Individualized Medicine website. The header includes the center's name and navigation links for Home, Contact Us, and Search. The main content area features a large banner with the text 'LIVING BETTER, LIVING LONGER' and a 'WATCH' button. Below the banner are sections for 'ABOUT' (The team and vision advancing the practice of individualized medicine), 'CONNECT' (Careers, collaboration opportunities and laboratory services), 'GENOMICS IN PATIENT CARE' (Patient care services, clinical trials and in-depth information), and 'PROGRAMS' (Focused efforts to bring genomic discoveries to patient care). At the bottom, the text reads 'FROM PROMISE TO PRACTICE'.

This is a screenshot of the Stanford Center for Genomics and Personalized Medicine website. The header includes the center's name and navigation links for Home, Education, Research, Technology, Contact, and Community. The main content area features a section titled 'GENOMICS PROMISED TO ADVANCE CARE' and a 'MESSAGE FROM THE DIRECTOR' by Mike Bayne, PhD. Below this are sections for 'SCGPM FACILITATES TRANSLATION OF GENOMICS INTO PATIENT CENTERED MEDICINE', 'ANNOUNCEMENTS' (including 'SCGPM 2013 Symposium' and '4th Annual Symposium on Genomics and Personalized Medicine'), 'SCGPM MEMBER RESEARCH AND NEWS', 'STANFORD PRIORITIZED TO ADVANCE SCGPM GOALS', 'SCGPM SEEKS VISITING INDIVIDUALS', and 'MORE ABOUT THE SCGPM'.

This is a screenshot of the Partners Biomedical Center for Personalized Genetic Medicine website. The header includes the center's name and navigation links for Home, Contact Us, and Search. The main content area features a large banner with the text 'Improved Clinical Data for Patient Care' and a 'Learn More' button. Below the banner are sections for 'Laboratory for Molecular Medicine', 'Personalized Medicine Conference', and 'Personalized Medicine Projects RFP'. At the bottom, there is a section for '2013 William K. Bowes, Jr. Award in Medical Genetics Winner' (Christiaan P. Schaaf, M.D., Ph.D., FACMG) and a 'Highlights' section for 'The Partners Biorepository for Medical Discovery'.



# A Medicine Safety Code



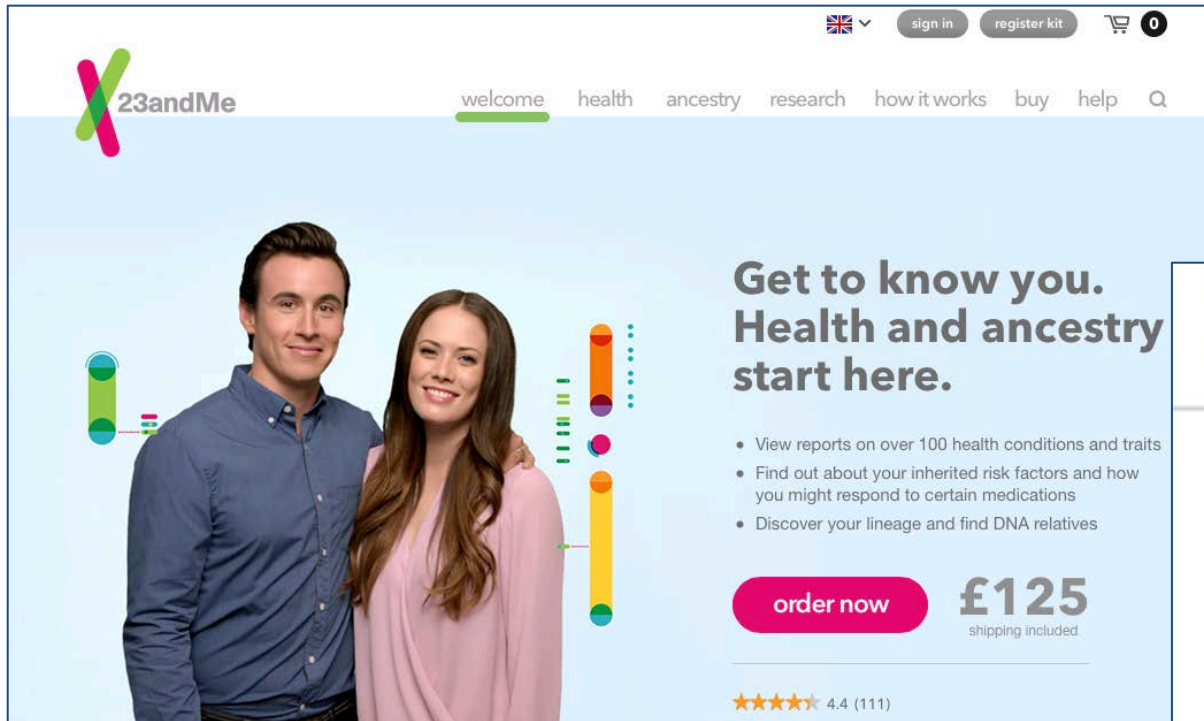


# Training for the London Marathon? It's now as simple as DNA



- · 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)



The image shows the 23andMe website homepage. At the top, there is a navigation bar with the 23andMe logo on the left, a language selector (UK flag), and buttons for 'sign in', 'register kit', and a shopping cart icon. Below the navigation bar, there is a main navigation menu with links for 'welcome', 'health', 'ancestry', 'research', 'how it works', 'buy', and 'help'. The main content area features a large image of a man and a woman standing together, with colorful vertical bars representing genetic data. To the right of the image, the headline reads 'Get to know you. Health and ancestry start here.' Below the headline, there are three bullet points: 'View reports on over 100 health conditions and traits', 'Find out about your inherited risk factors and how you might respond to certain medications', and 'Discover your lineage and find DNA relatives'. At the bottom of the main content area, there is a pink 'order now' button and a price tag of '£125 shipping included'. Below the price tag, there is a star rating of 4.4 (111).

23andMe

welcome health ancestry research how it works buy help

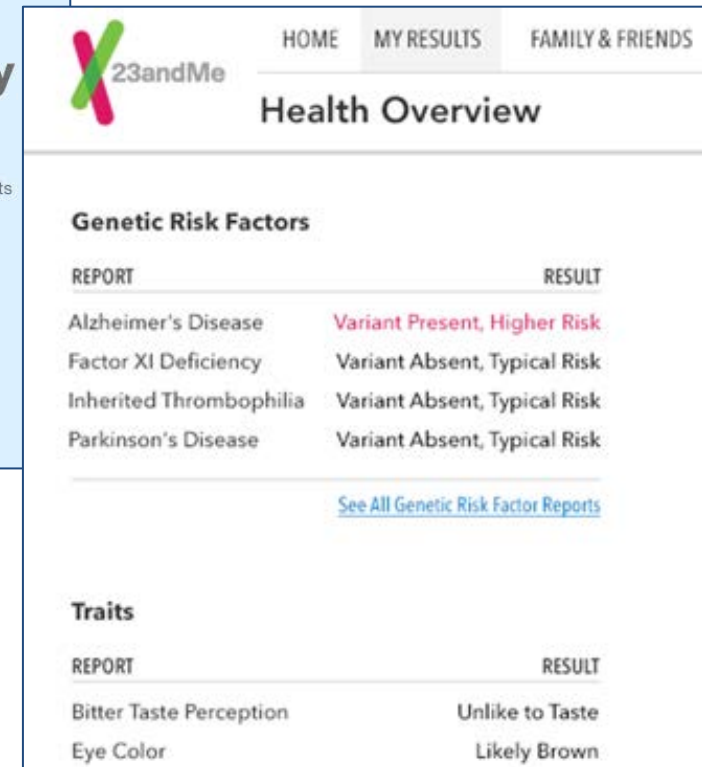
Get to know you.  
Health and ancestry  
start here.

- View reports on over 100 health conditions and traits
- Find out about your inherited risk factors and how you might respond to certain medications
- Discover your lineage and find DNA relatives

order now

£125  
shipping included

★★★★★ 4.4 (111)



The image shows a screenshot of the 23andMe 'Health Overview' page. At the top, there is a navigation bar with the 23andMe logo, and links for 'HOME', 'MY RESULTS', and 'FAMILY & FRIENDS'. The main heading is 'Health Overview'. Below the heading, there is a section titled 'Genetic Risk Factors'. This section contains a table with two columns: 'REPORT' and 'RESULT'. The table lists four genetic risk factors: Alzheimer's Disease, Factor XI Deficiency, Inherited Thrombophilia, and Parkinson's Disease. The results for each are: Variant Present, Higher Risk; Variant Absent, Typical Risk; Variant Absent, Typical Risk; and Variant Absent, Typical Risk. Below the table, there is a link to 'See All Genetic Risk Factor Reports'. At the bottom of the page, there is a section titled 'Traits'. This section contains a table with two columns: 'REPORT' and 'RESULT'. The table lists two traits: Bitter Taste Perception and Eye Color. The results for each are: Unlike to Taste and Likely Brown.

23andMe

HOME MY RESULTS FAMILY & FRIENDS

## Health Overview

### Genetic Risk Factors

REPORT	RESULT
Alzheimer's Disease	Variant Present, Higher Risk
Factor XI Deficiency	Variant Absent, Typical Risk
Inherited Thrombophilia	Variant Absent, Typical Risk
Parkinson's Disease	Variant Absent, Typical Risk

[See All Genetic Risk Factor Reports](#)

### Traits

REPORT	RESULT
Bitter Taste Perception	Unlike to Taste
Eye Color	Likely Brown

# Zukünftiger Ausblick der personalisierten Medizin

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- 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





**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](mailto:thomas.szucs@unibas.ch)**

