Universitätsspital Basel
Institut für Medizinische Genetik und Pathologie
UNI BASEL

Polygene Risiko-Scores in der Onkologie:
„Ready for prime time?"

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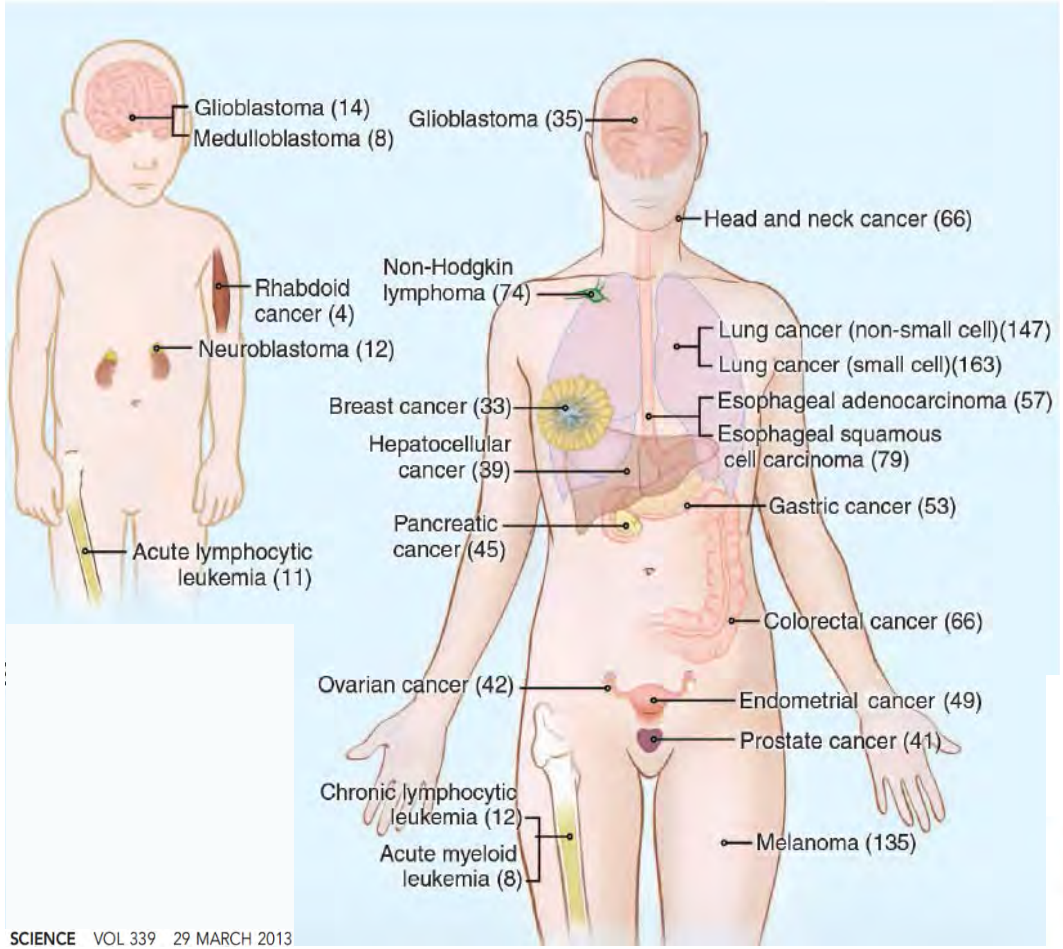
Fortbildung Tumorzentrum Luzerner Kantonsspital
30.05.2022

Krebs ist eine genetische Erkrankung !

Anzahl somatischer Mutationen pro Tumor



SCIENCE VOL 339 29 MARCH 2013

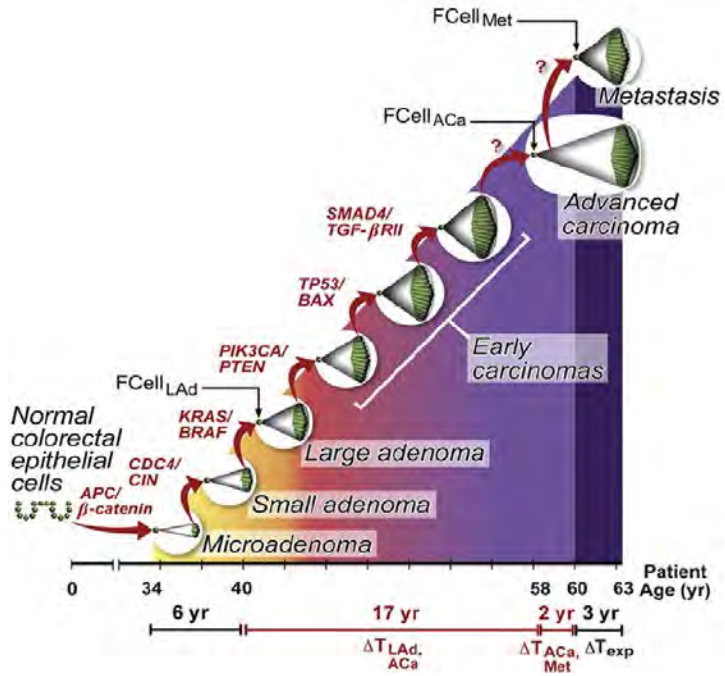
The Cancer Genome Atlas — *Understanding genomics to improve cancer care*

Article Nature | Vol 578 | 6 February 2020

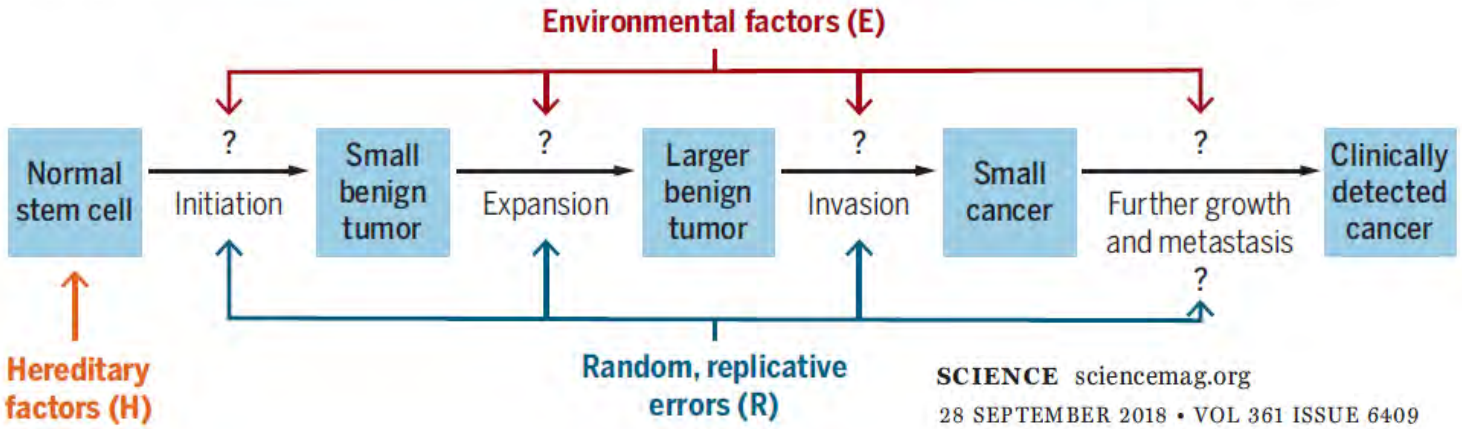
Pan-cancer analysis of whole genomes

The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium

Sequentielle, mehrstufige Akkumulation von Mutationen in Tumorsuppressor- und Onkogenen



Emery and Rimoin's Principles and Practice of Medical Genetics, Elsevier 2013



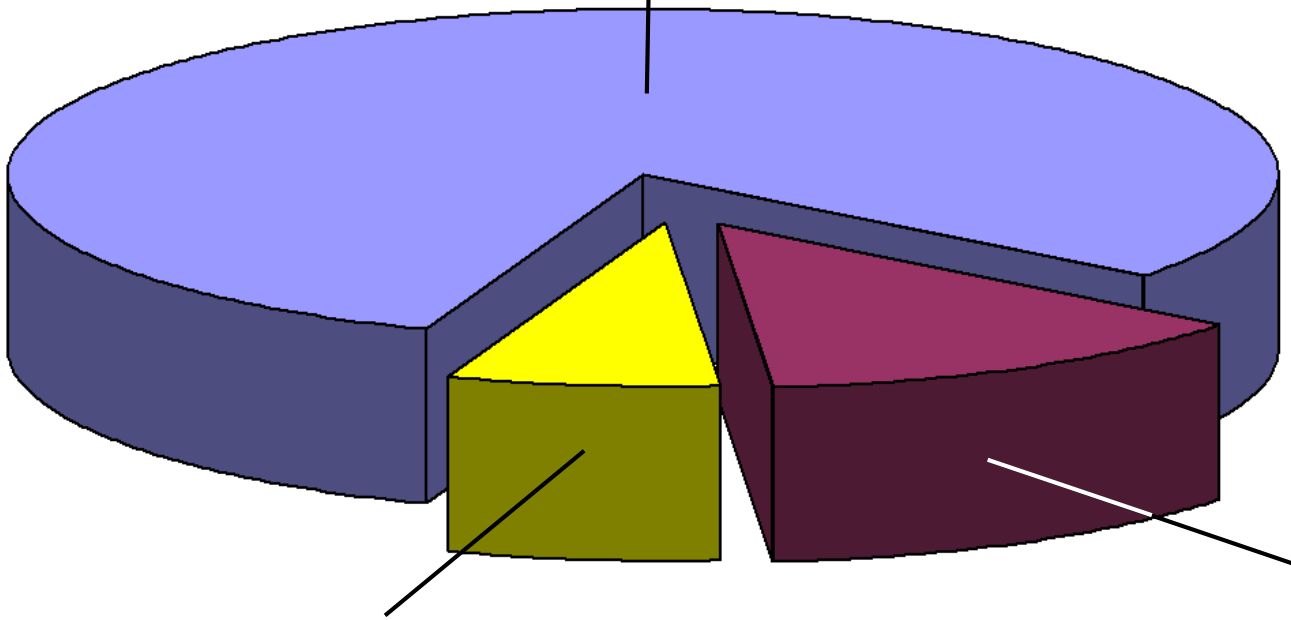
SCIENCE sciencemag.org

28 SEPTEMBER 2018 • VOL 361 ISSUE 6409

Ätiologie von Tumorerkrankungen

sporadisch – familiär – hereditär

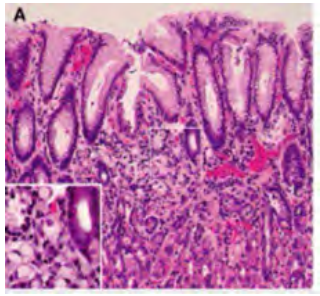
ca. 70-80% sporadisch (zufällig)
Somatische Varianten
Polygen

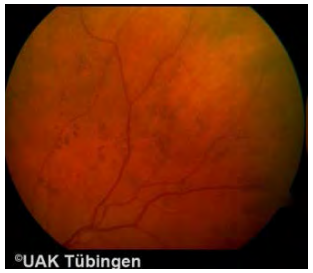


ca. 5-10% hereditär
Keimbahn- und
somatische Varianten
Monogen

ca. 15-20% „familiär gehäuft"
Mono- und polygen

Hinweise auf eine Tumorveranlagung





- Krebs **vor dem 50.** Lebensjahr

oder / und

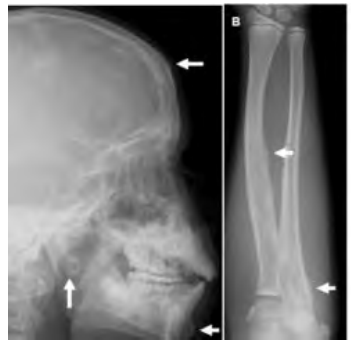
- **Mehrfach-** / **Doppel**karzinome

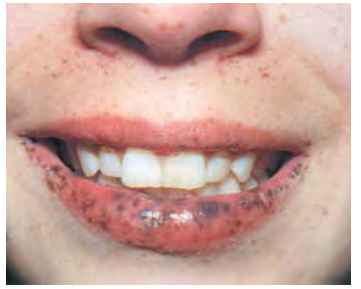
oder / und

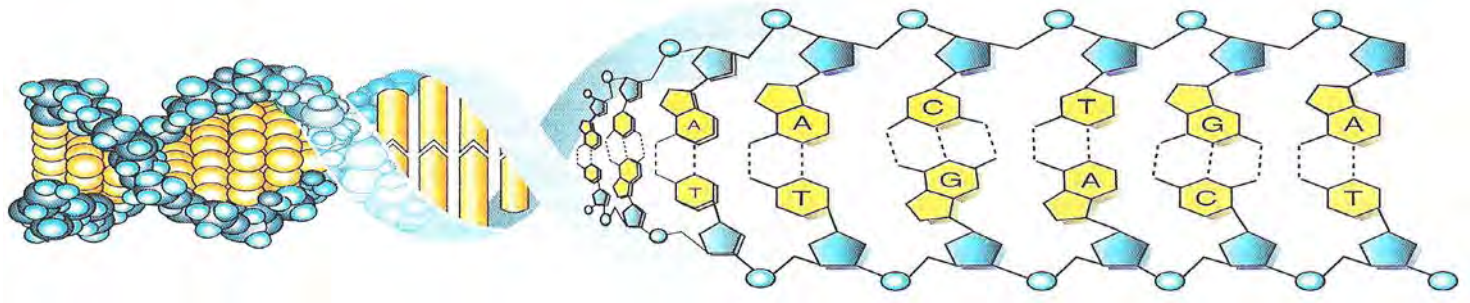
- Auffällige **Familienanamnese**

oder / und

- Ungewöhnlicher / seltener **Tumortyp**



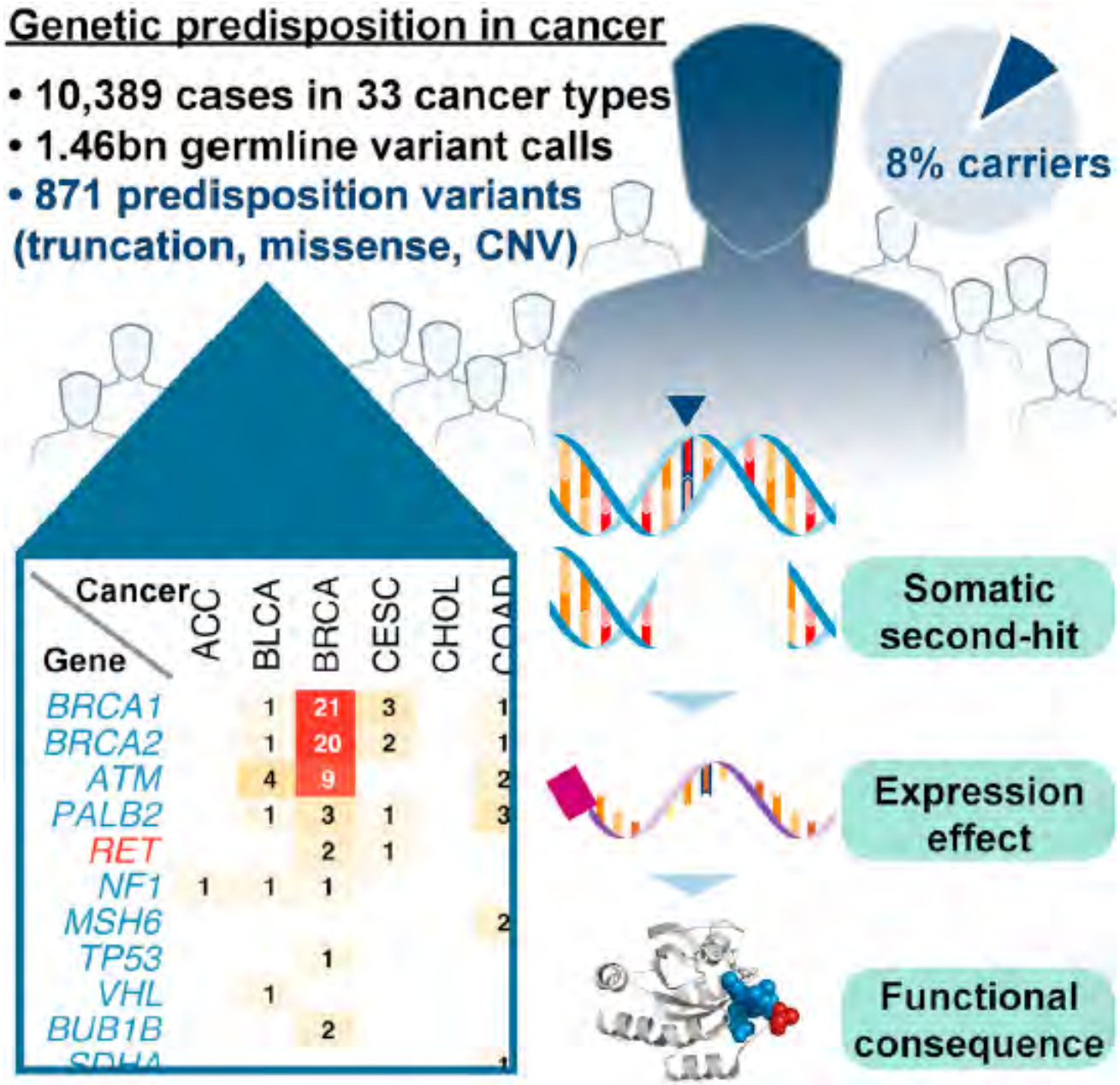




Genetische Prädisposition zu Krebs bei 8% aller Krebserkrankungen

- Family history curation is essential («phenotyping» !)
- Integration of *somatic* molecular data in variant classification guidelines

Cell *173*, 355–370, April 5, 2018



Gene \ Cancer	ACC	BLCA	BRCA	CESC	CHOL	COAD
BRCA1		1	21	3		1
BRCA2		1	20	2		1
ATM		4	9			2
PALB2		1	3	1		3
RET			2	1		
NF1	1	1	1			
MSH6						2
TP53			1			
VHL		1				
BUB1B			2			
SDHA						1

Ätiologie des erblichen Brustkrebses

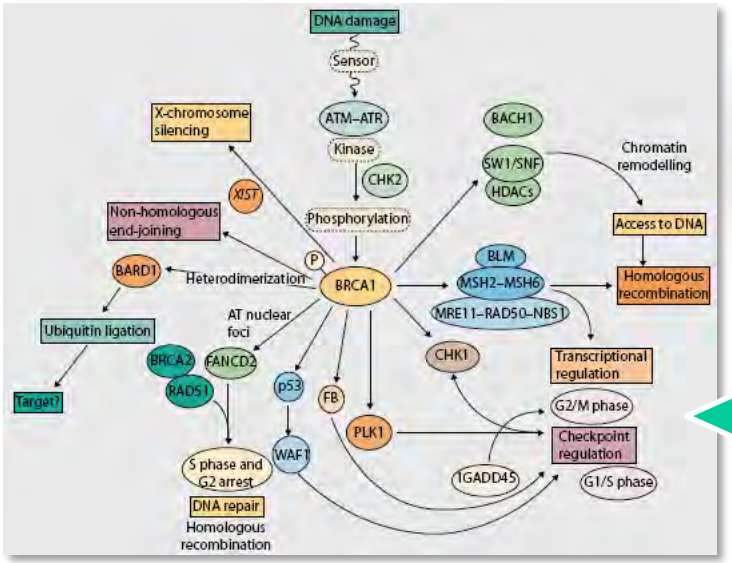
…nur teilweise geklärt…

Moderates Risiko (RR 1.5 to 5)

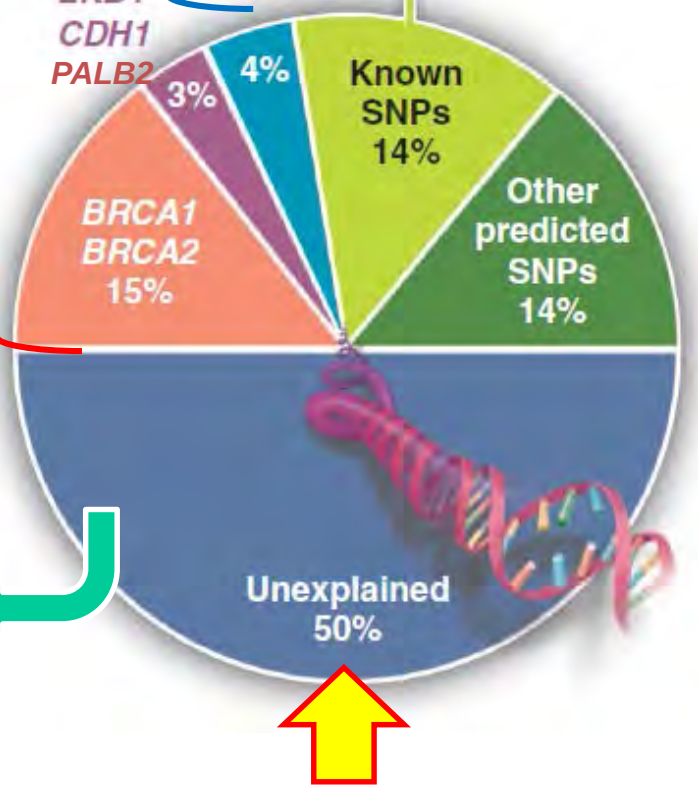
CHEK2
ATM
BRIP1
RAD51C
RAD51D
BARD1

Hohes Risiko (RR >5 to 20)

TP53
PTEN
LKB1
CDH1
PALB2



medgen 2013 · 25:259–277



Locus
6q14.1
*BRCA2
CCND1
ESR1
FGFR2
CCND1
FGFR2
*MERIT40
TERT
DNAJC1
CCDN1
MKL1
MDM4
ESR1
HNF4G
5p12
12p13.1
MAP3K1
TCF7L2
22q12.2
2p24.1
2q31.1
SLC4A7
EBF1
FTO
1p11.2

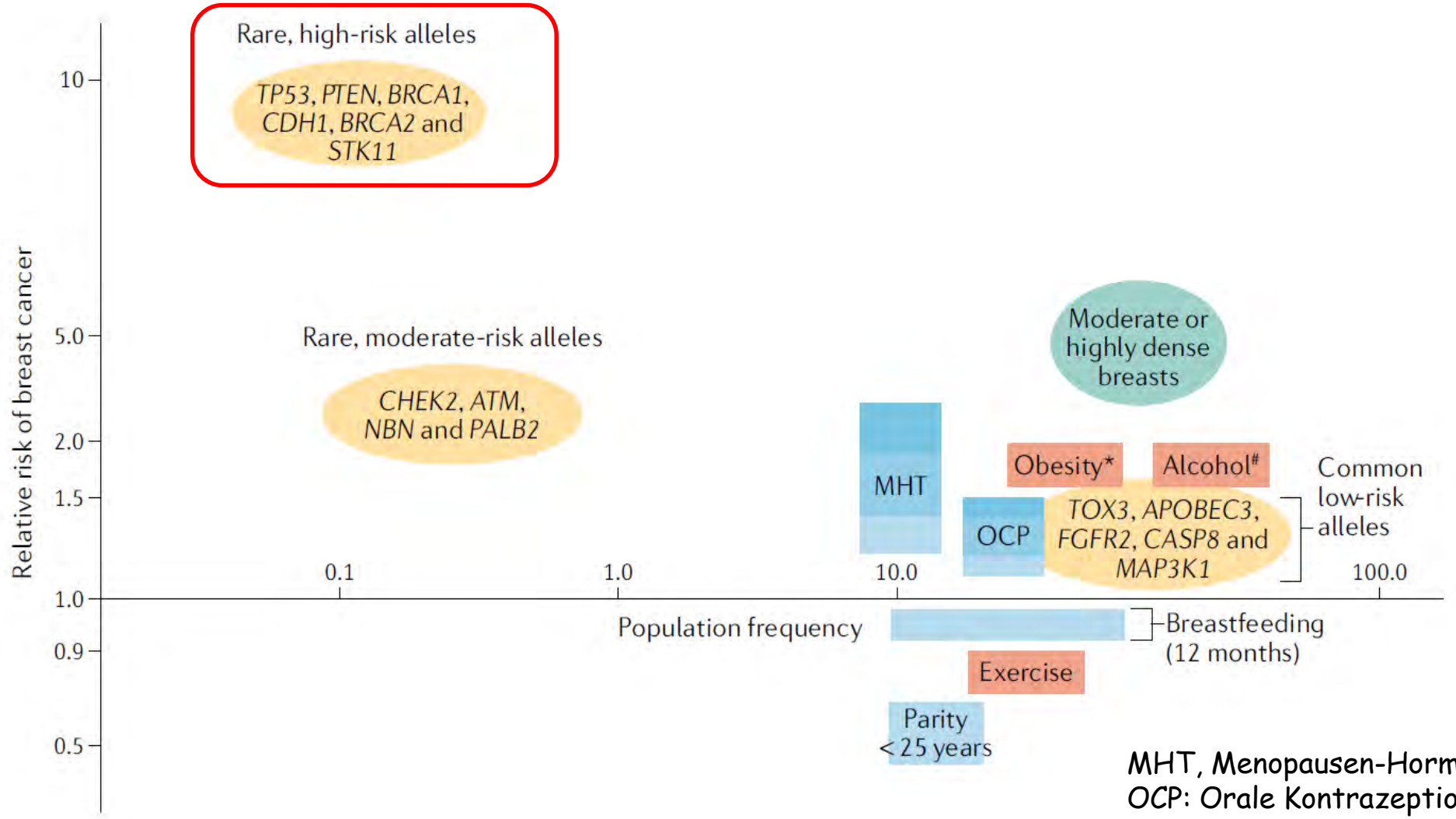
low risk (RR <1.5)

RR: Relatives Risiko (Verhältnis der Ereignisraten zwischen 2 Vergleichsgruppen

28 MARCH 2014 VOL 343 SCIENCE

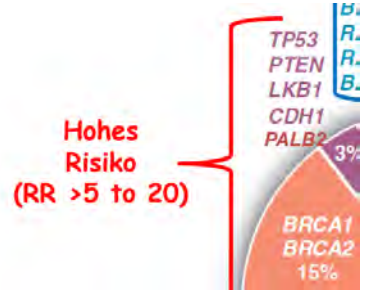
Brustkrebs-Risiko bei der Frau

Einfluss von genetischen und nicht-genetischen Faktoren



MHT, Menopausen-Hormontherapie
OCP: Orale Kontrazeption («Pille»)

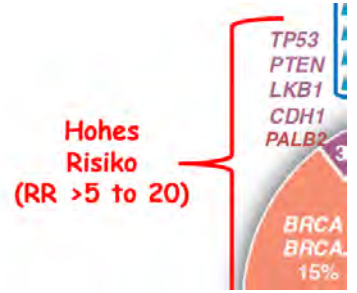
BRCA1- und *BRCA2*-Anlageträgerinnen
Erkrankungswahrscheinlichkeiten



Organ	Allgemein-Bevölkerung	BRCA1-Anlageträgerin	BRCA2-Anlageträgerin
Brustkrebs	ca. 12%	ca. 55-72% (70.Lj.)	ca. 45-69%
- Kontralateraler Brustkrebs	ca. 2% (inn. 5 J.)	ca. 20-30% (inn. 10 J.) ca. 40-50% (inn. 20 J.)	
Eierstock-Krebs	ca. 1-2%	ca. 39-44%	ca. 11-17%
Bauchspeicheldrüsen-Krebs	ca. 0.5%	ca. 1-3%	ca. 3-5% (70. Lj.)
Melanom (Haut & Auge)	ca. 1.6%		erhöht

GeneReviews 02/2022:
https://www.ncbi.nlm.nih.gov/books/NBK1247/

BRCA1/2-Anlageträgerinnen
Empfohlene Krebs-Vorsorgeuntersuchungen



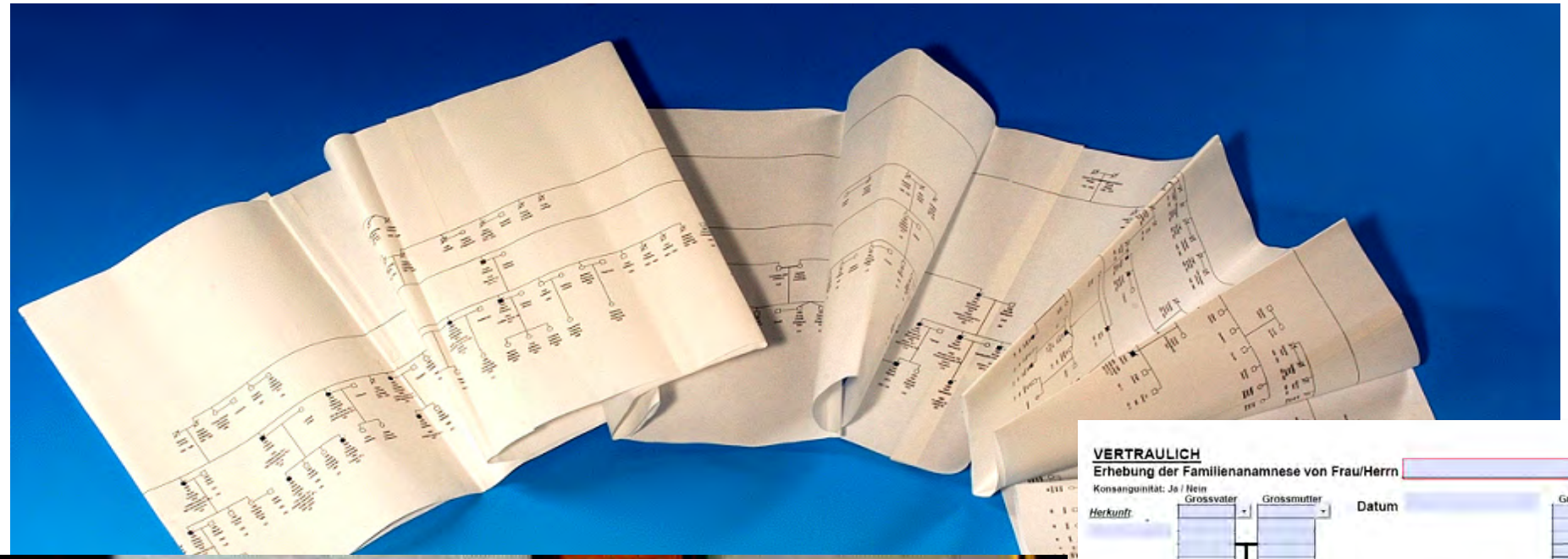
Empfehlungen/Optionen	Beginn	Intervall
Selbstuntersuchung der Brust	18	Monatlich
Ärztliche Untersuchung der Brust	25	½-bis jährlich
MRT/MRI der Brust	25.-29.	Jährlich
(3D-)Mammographie der Brust	30.-75.	Jährlich
ggfs. Ultraschall der Brust		
Transvaginaler Ultraschall	30.-35.	Jährlich ?
Tumormarker CA-125 im Blut	30.-35.	Jährlich ?
BRCA2: Haut- & Augenkontrolle	Individuell	Jährlich ?
Bauchspeicheldrüse	Je nach Familiengeschichte	Individuell

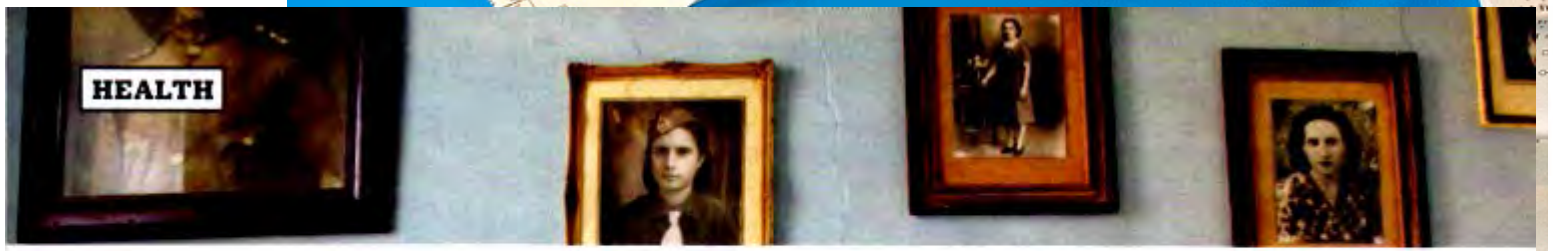
Risiko-mindernde chirurgische Optionen	
Beidseitige Brustdrüsen-Entfernung (mit Rekonstruktion)	Individuell
Beidseitige Eileiter-/Eierstock-Entfernung	BRCA1: 35-40, BRCA2: 40-45 bzw. abhängig von Familiengeschichte

NCCN Guidelines
v 1.2022

„There is still life in the old dog!“

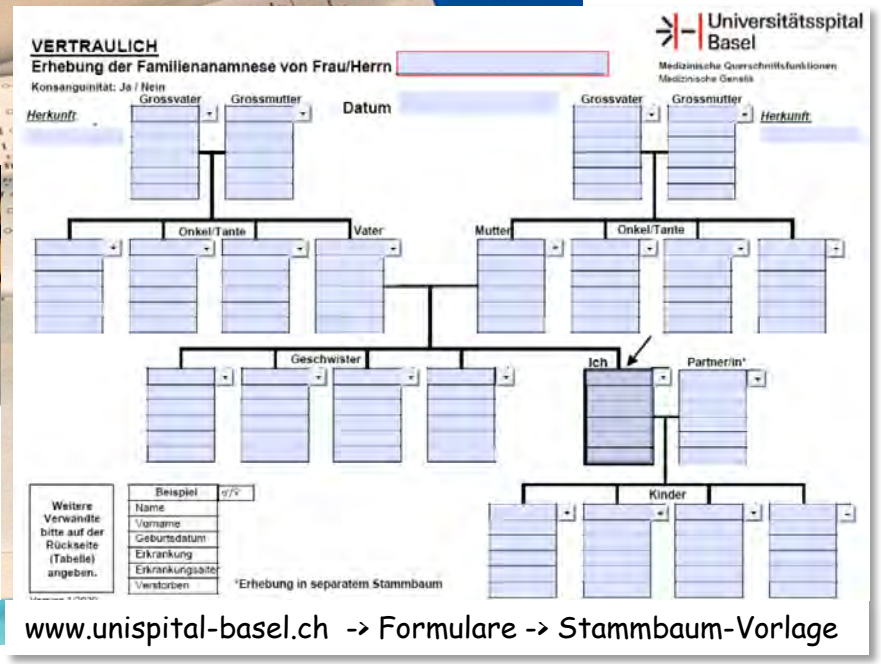
Die Familienanamnese





Back to the Genetic Future

Why family medical history is key.



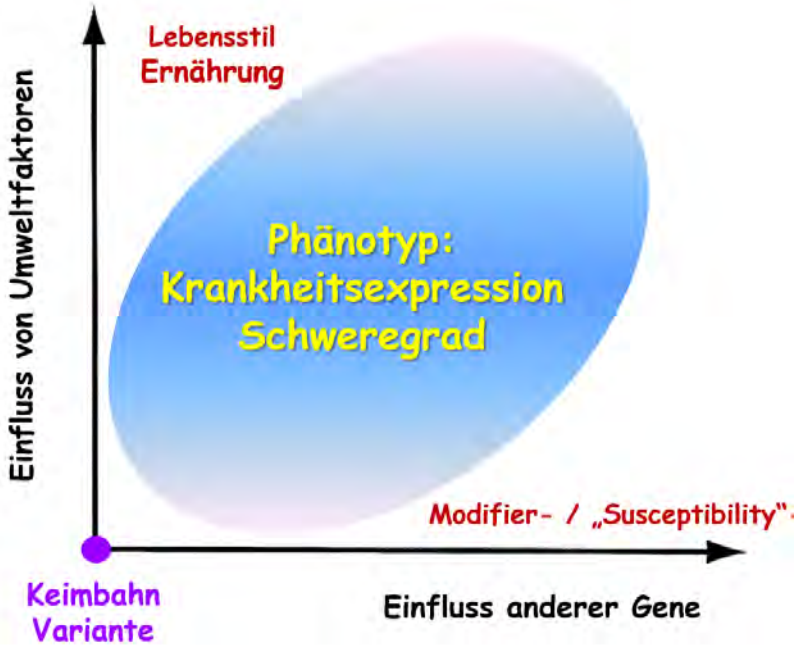
www.unispital-basel.ch -> Formulare -> Stammbaum-Vorlage

Brustkrebs-Risiko beim Mann

Einfluss von genetischen und nicht-genetischen Faktoren

1) **General risk factors** [4-7]

- Age
- Family history of breast cancer
- Elevated estrogen levels
- Orchitis/epididymitis
- Gynecomastia
- Klinefelter syndrome
- Radiation exposure
- Obesity
- External use of estradiol and testosterone



2) **Genetic risk factors for MBC**

Well known mutations

- BRCA2 [16-18]
- BRCA1 [20-22]

Possible mutations

- PALB2 [27]
- CHEK2 [24]
- BRIP1 [25]

ATM [27]

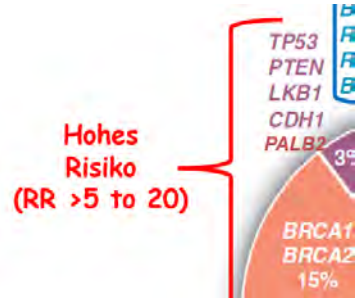
Medical Oncology (2021) 38:39

BRCA1 -/BRCA2-Anlageträger
Erkrankungswahrscheinlichkeiten

Organ	Allgemeinbevölkerung	BRCA1-Anlageträger	BRCA2-Anlageträger
Brustkrebs	ca. 0.1%	ca. 1-2%	6-8%
Prostatakrebs	ca. 6% (69. Lj.)	ca. 29% (85. Lj.)	60% (85. Lj.)
Bauchspeicheldrüsen-Krebs	ca. 0.5%	ca. 1-3%	3-5% (70.Lj.)
Melanom (Haut & Auge)	ca. 1.6%		erhöht

GeneReviews 02/2022:
https://www.ncbi.nlm.nih.gov/books/NBK1247/

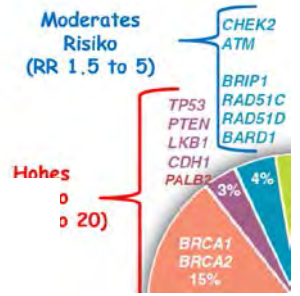
BRCA1/2-Anlageträger
Empfohlene Krebs-Vorsorgeuntersuchungen



Massnahmen	Beginn	Intervall
Selbstuntersuchung der Brust	35	Monatlich
Ärztliche Untersuchung der Brust	35	Jährlich
Mammographie der Brust bei Männern mit Gynäkomastie	50 (od. 10 Jahre vor frühestem männlichen Brustkrebs in Familie)	Jährlich ?
Prostata-Screening (Tastbefund & PSA)	40	Jährlich
BRCA2: Haut- und Augenkontrolle	Individuell	Jährlich ?
Bauchspeicheldrüse	Je nach Familiengeschichte	Individuell

NCCN Guidelines
v 1/2022

BAG-Empfehlungen zur bildgebenden Überwachung bei Brustkrebs abhängig vom LZR



Bundesamt für Gesundheit BAG
Direktionsbereich Kranken- und Unfallversicherung

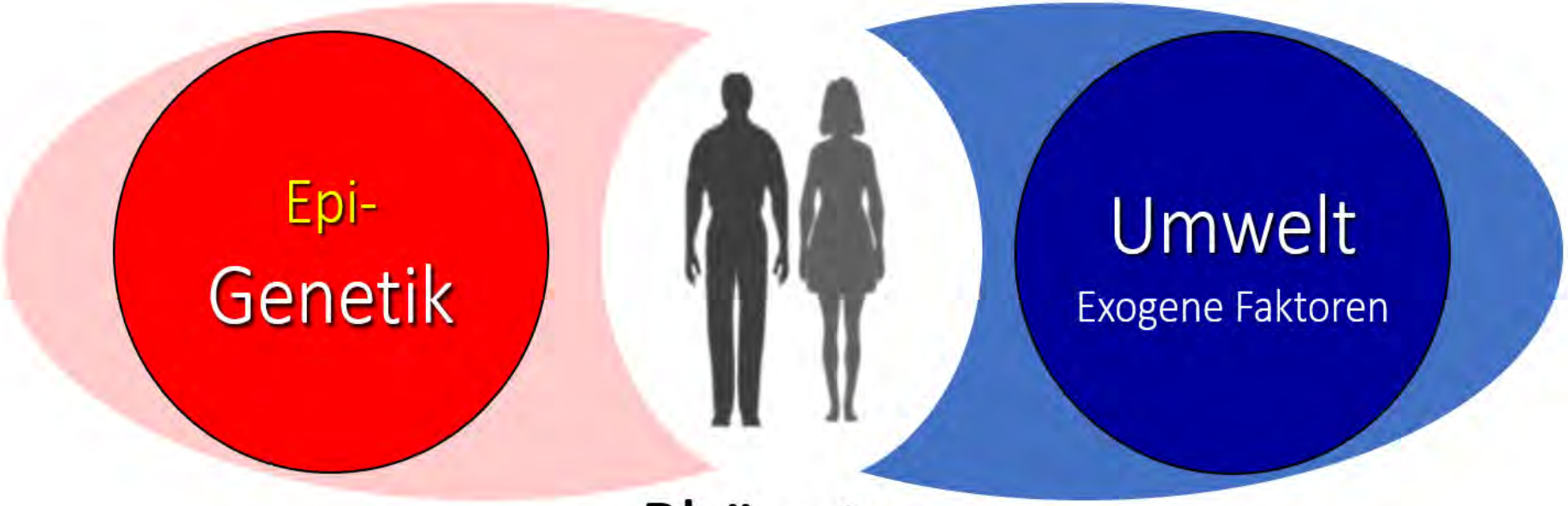
Referenzdokument «Überwachungsprotokoll»
zu Artikel 12*d* Absatz 1 Buchstabe d der Krankenpflege-Leistungsverordnung (KLV) - Stand 01/2021

Grund für die Überwachung	Alter / Bildgebungsmodalität (MRI = Kernspintomografie, MG = Mammografie)											
	20 - 29		30 - 39		40 - 49		50 - 59		60 – 69		70 - 75	
	MRI	MG	MRI	MG	MRI	MG	MRI	MG	MRI	MG	MRI	MG
Lebenszeitrisiko mässig erhöht (17 – 29%)	kein Screening		kein Screening		-	jährlich	-	jährlich	-	alle 2 Jahre	-	alle 2 Jahre
Lebenszeitrisiko stark erhöht (≥30 %)	kein Screening		jährlich[1)]	jährlich[2), 3)]	jährlich[1)]	jährlich	jährlich[1)]	jährlich	alle 2 Jahre[1), 4)]	alle 2 Jahre[4)]	-	alle 2 Jahre
BRCA1/2-Mutation	jährlich ab 25 J[5)]	-	jährlich	jährlich	jährlich	jährlich	jährlich	jährlich	jährlich	jährlich	-	alle 2 Jahre
STK11-Mutation	jährlich ab 25J[5)]	-	jährlich	jährlich[3)]	jährlich	jährlich	jährlich	jährlich	jährlich	jährlich	-	alle 2 Jahre
TP53-Mutation	jährlich	-	jährlich	-	jährlich	-	jährlich	-	jährlich	-	kein Screening	

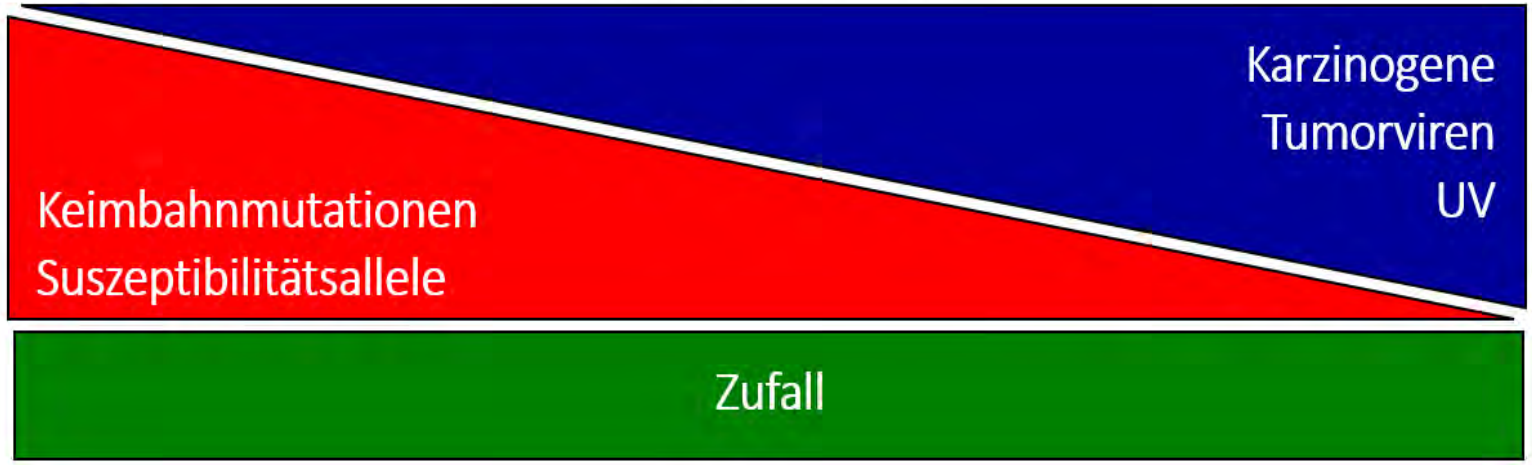
LZR: Lebenszeitrisiko

Einfluss von Genen *und* Umwelt

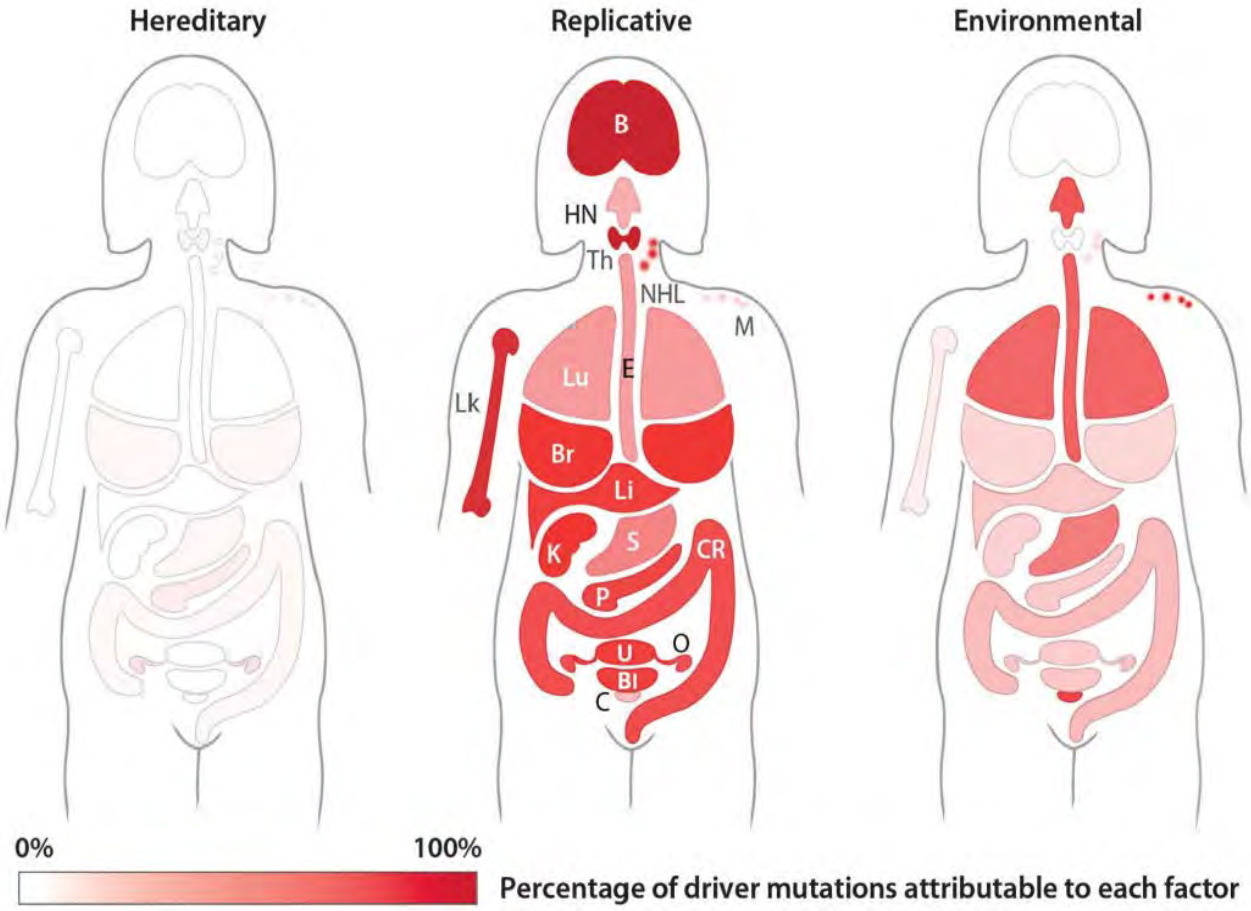
«monogen» ist relativ ...



Phänotyp



Gene & Umwelt - und der unvermeidliche R-Faktor



Science. 2017 March 24; 355(6331): 1330–1334.

Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention

Cristian Tomasetti[1,2,*], Lu Li[2], and Bert Vogelstein[3,*]

Cancer and the unavoidable R factor

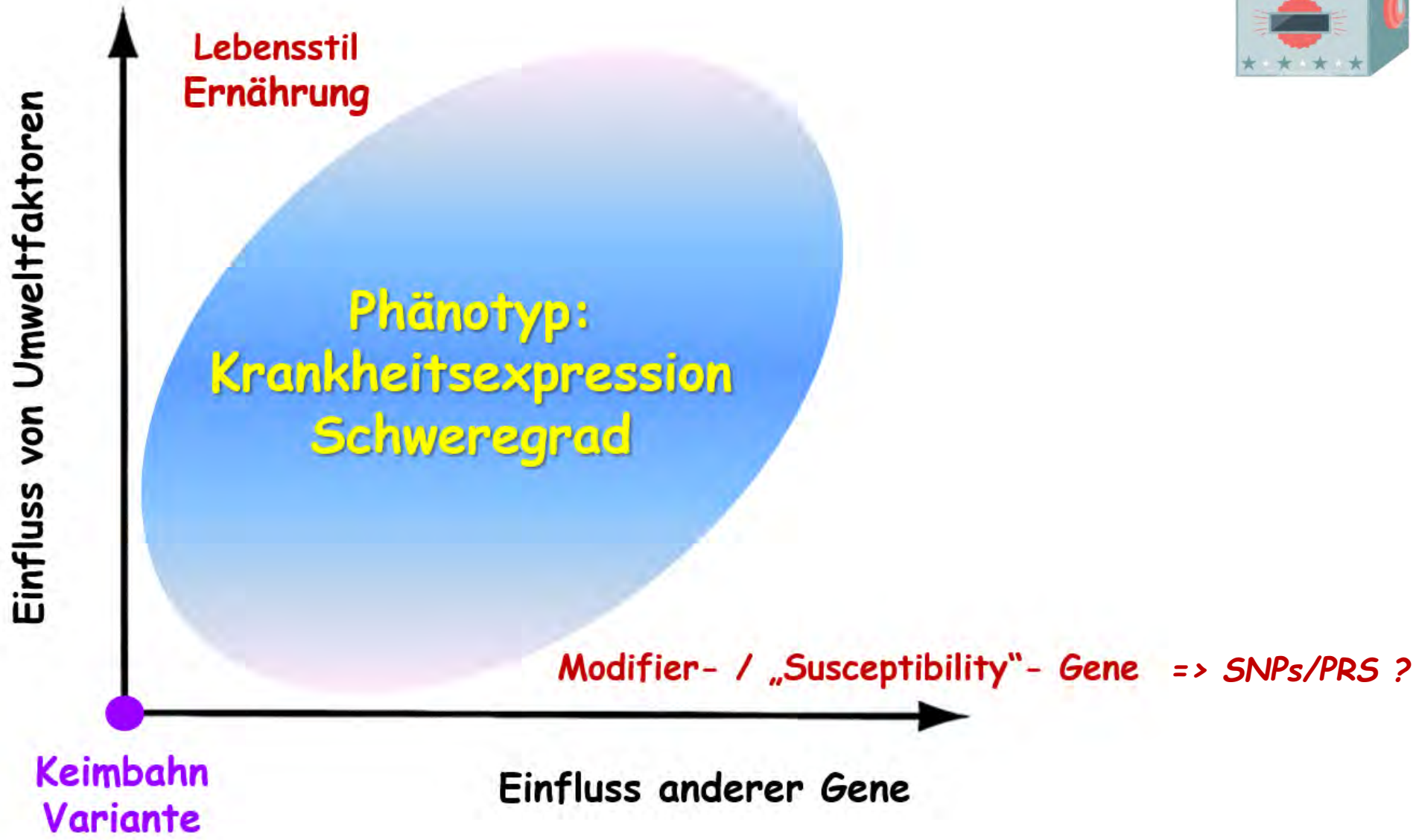
Most textbooks attribute cancer-causing mutations to two major sources: inherited and environmental factors. A recent study highlighted the prominent role in cancer of replicative (R) mutations that arise from a third source: unavoidable errors associated with DNA replication. Tomasetti *et al.* developed a method for deter-

"**Primary prevention** is the best way to reduce cancer deaths. Recognition of a third contributor to cancer—R mutations—does not diminish the importance of primary prevention but emphasizes that not all cancers can be prevented by avoiding environmental risk factors. ....

Secondary prevention, i.e., early detection and intervention, can also be lifesaving. For cancers in which all mutations are the result of R, secondary prevention is the only option."

Einfluss von Genen und Umwelt

«monogen» ist relativ ...

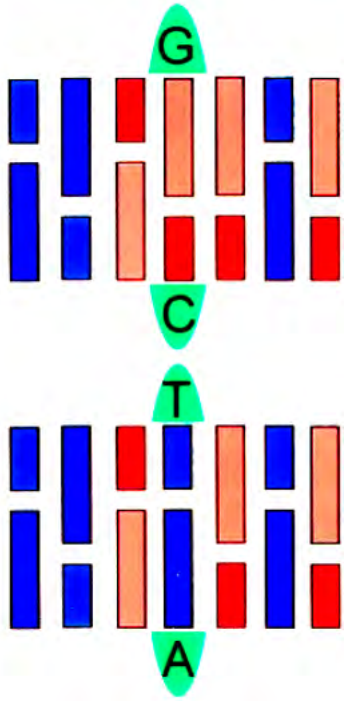


Single Nucleotide Polymorphisms (SNPs)

Einzelnukleotid-Polymorphismen

Mütterliches Allel (G)

Väterliches Allel (T)

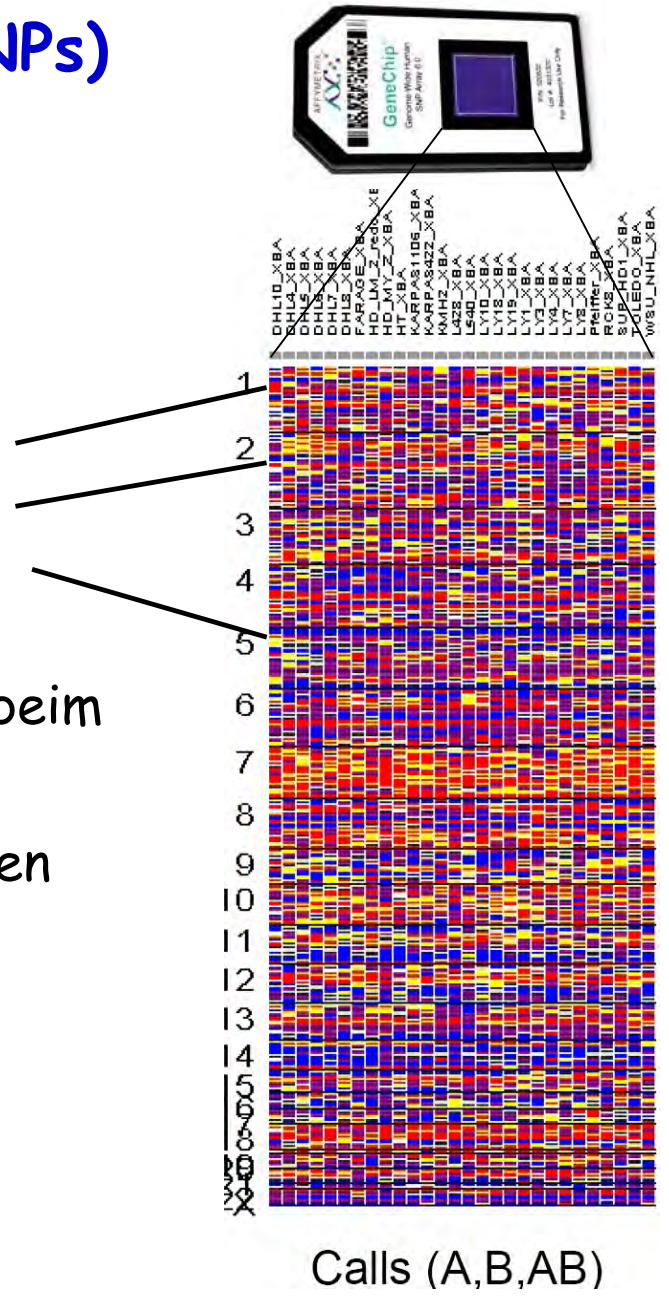


- Einzelne Basen sind polymorph

SNP-Auswertung:

AA = homozygot «A»
BB = homozygot «B»
AB = heterozygot

- ca. 90% der genetischen Variation beim Menschen stabil vererbt
- Sehr häufig ca. bis zu 10 (?) Millionen SNPs ⇒ 1 SNP auf ca. 300 bp
- Hoher Analysedurchsatz möglich (SNP-Arrays, Microarrays, NGS)



Calls (A,B,AB)

SNP rs6983267 und Kolonkarzinom-Risiko

GWAS Catalog
The NHGRI-EBI Catalog of published genome-

Studies

Author	Date	Journal	Title	Reported trait
Schumacher FR (PMID: 26151821)	2015-07-07	Nat Commun	Genome-wide association study of colorectal cancer identifies six new susceptibility loci.	Colorectal cancer
Hoffmann TJ (PMID: 26034056)	2015-06-01	Cancer Discov	A large multi-ethnic genome-wide association study of prostate cancer identifies novel risk variants and substantial ethnic differences.	Prostate cancer
Berndt SI (PMID: 25939597)	2015-05-05	Nat Commun	Two susceptibility loci identified for prostate cancer aggressiveness.	Prostate cancer
Zhang B (PMID: 24836286)	2014-05-18	Nat Genet	Large-scale genetic study in East Asians identifies six new loci associated with colorectal cancer risk.	Colorectal cancer
Knipe DW (PMID: 24753544)	2014-04-21	Cancer Epidemiol Biomarkers Prev	Genetic variation in prostate-specific antigen-detected prostate cancer and the effect of control selection on genetic association studies.	Prostate cancer

SNP rs6983267 und Kolonkarzinom-Risiko

GWAS Catalog
The NHGRI-EBI Catalog of published genome-

Associations

SNP	RAF	p-value	OR	Beta	CI	Region	Location	Functional class	Reported gene(s)	Mapped gene(s)
rs6983267-G	0.51	3 x10^{-27}	1.25		[1.20-1.30]	8q24.21	chr8:127401060	non_coding_transcript_exon_variant	NR	CASC8, CCAT2

Odds Ratio

Quoten/Chancen-Verhältnis für das **Eintreten zum Nicht-Eintreten** eines Ereignisses

Risikofaktor	Krankheit		TOTAL
	Ja	Nein	
Ja	a	b	a+b
Nein	c	d	c+d
TOTAL	a+c	b+d	a+b+c+d

$$\text{Odds}(p_1) = \frac{a/(a+b)}{1-a/(a+b)}$$

$$\text{Odds}(p_0) = \frac{c/(c+d)}{1-c/(c+d)}$$

$$\text{OR} = \frac{Odds\,(p_1)}{Odds\,(p_0)}$$

OR=1: Risiko gleich gross
OR=2: Risiko für Exponierte doppelt so hoch

kann auch bei nicht-repräsentativen Stichproben (Fall-Kontroll-Studien) berechnet werden

u.U. sehr gross, wenn häufige Krankheit

Gentests als Geschäft
«Direct to Consumer»

20 minuten

Drogerien verkaufen Lifestyle-Gentests

ZÜRICH. DNA-Analysen sind der neuste Verkaufsrenner in Drogerien, Apotheken und bei Ärzten. Sie sollen zeigen, wie man am besten abnimmt oder welcher Sporttyp man ist. Die Tests kosten zwischen 300 und 1200 Franken. Kritiker sprechen von Abzocke und befürchten, dass der Datenschutz in Gefahr ist. Der Vertreiber dagegen findet, dass die Krankenkasse die Kosten für die Analysen übernehmen sollte, da die Gesundheitskosten gesenkt werden könnten. **SEITE 2**

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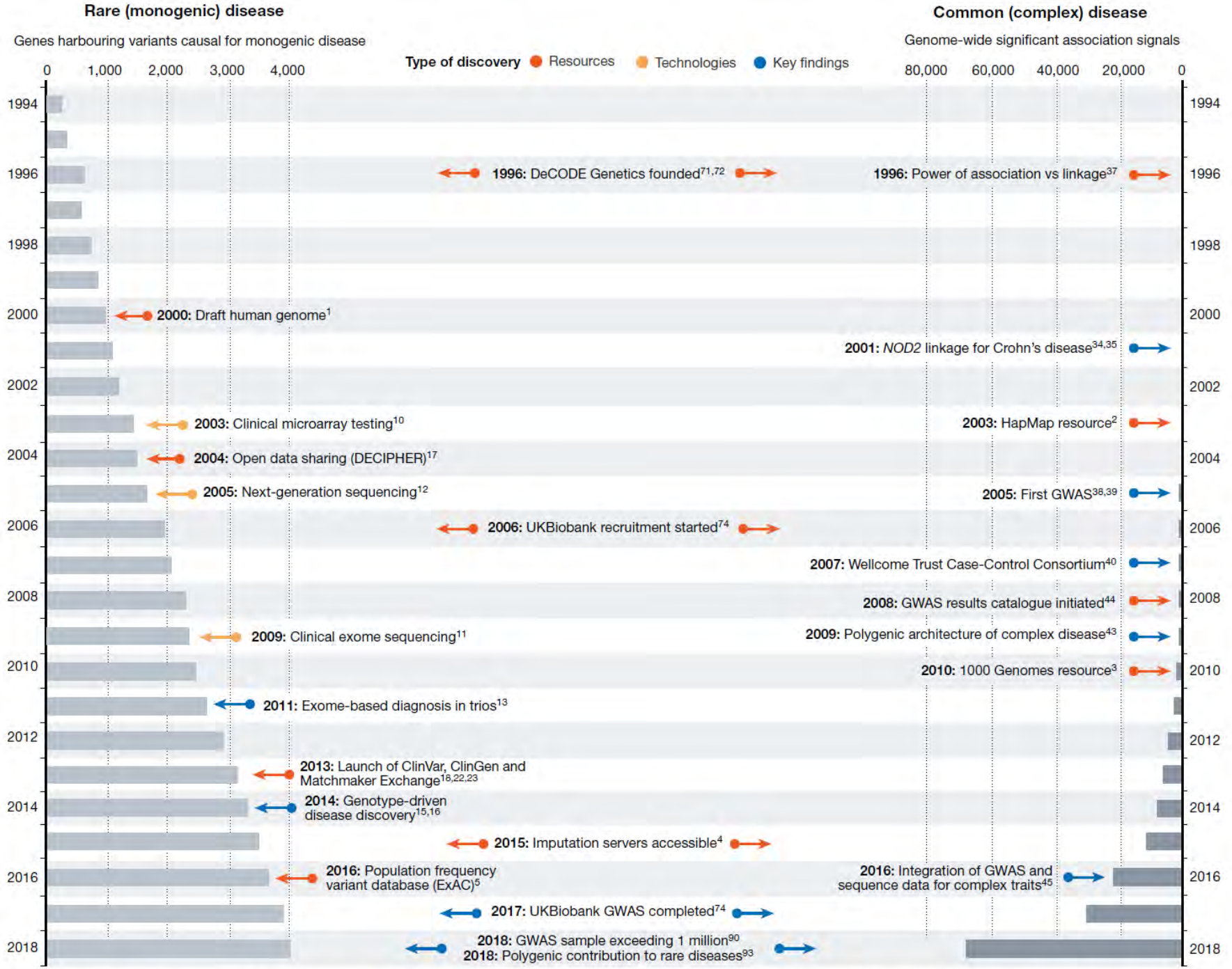
- Discover DNA relatives from around the world
- Share reports with family and friends
- Learn how your DNA influences your facial features, taste, smell and other traits

order now ~~USD$99~~ USD$79

PLUS

Ancestry 5 reports
Genetic Health Risks* 5+ reports
Wellness 5+ reports
Carrier Status* 40+ reports
Traits 15+ reports

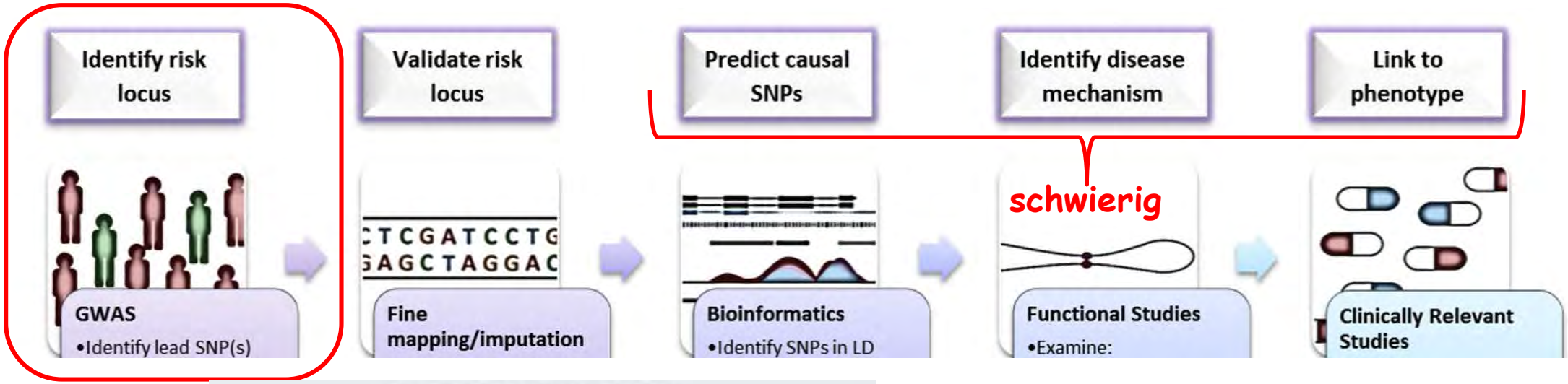
Entdeckung krankheitsbedingter genetischer Variation: 1994-2018

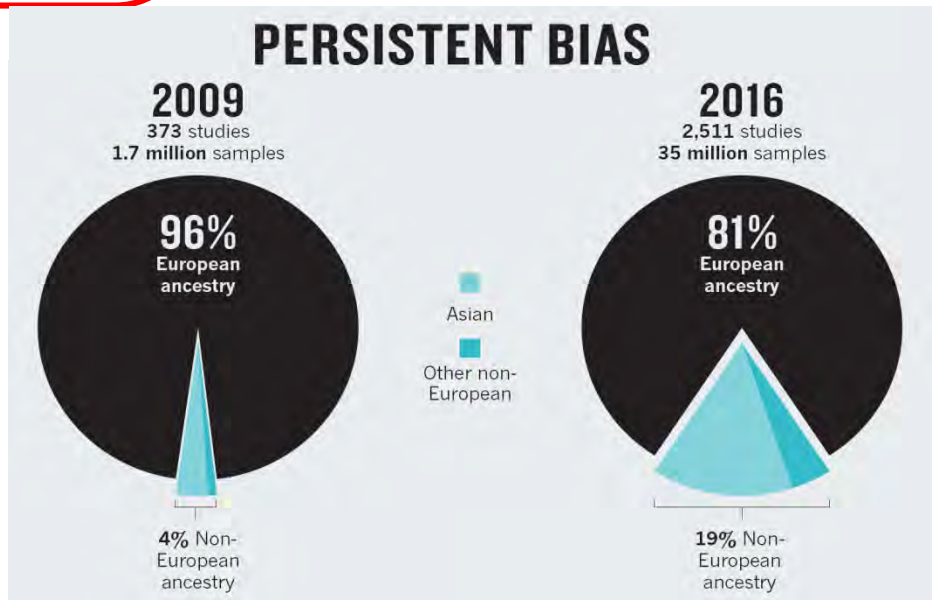


Nature | Vol 577 | 9 January 2020

Genom-weite Assoziationsstudien

Risiko-Locus/-SNP entdeckt: Wie weiter...?





NATURE | VOL 538 | 13 OCTOBER 2016

Probleme von Assoziationsstudien:

- Studien-/Kontroll-Population
- Ethnische Unterschiede
- Widersprüchliche Resultate
- «Publication bias»
- «Indirekt»: *keine* biologische Erklärung

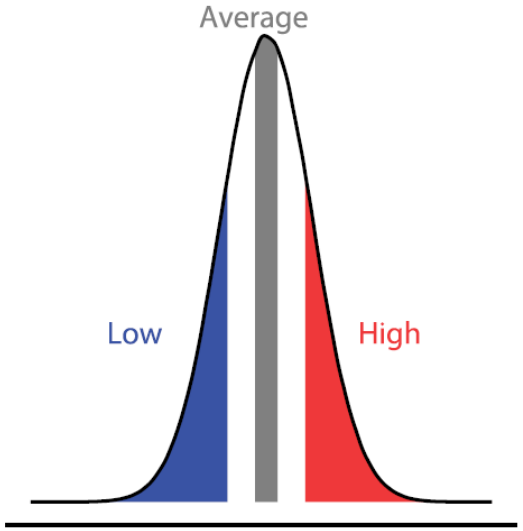
Polygene Risiko-Scores (PRS)
Definitionen und Konzept

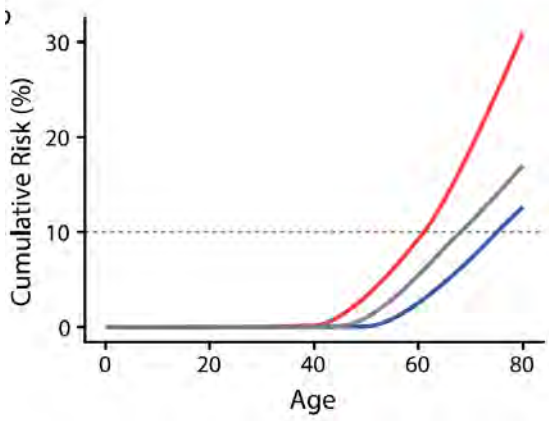
- **Quantifizierung** der **Gesamtheit der genetischen Faktoren**, die zur Entstehung häufiger Krankheiten bzw. Mermale beitragen

- Berechnung i.d.R. als **gewichtete Summe der Risiko-Allele von Einzelnukleotid-Polymorphismen (single nucleotide polymorphisms, SNPs)**

$$score = \beta_1 * snp_1 + \beta_2 * snp_2 + \cdots \beta_n * snp_n$$

- Analyse des **Potenzials von PRS**, die **Vorhersage** häufiger Krankheiten in der Klinik **zu verbessern** => **Anleitung zu präventiven und therapeutischer Massnahmen**





Human Molecular Genetics, 2019, Vol. 28, No. R2

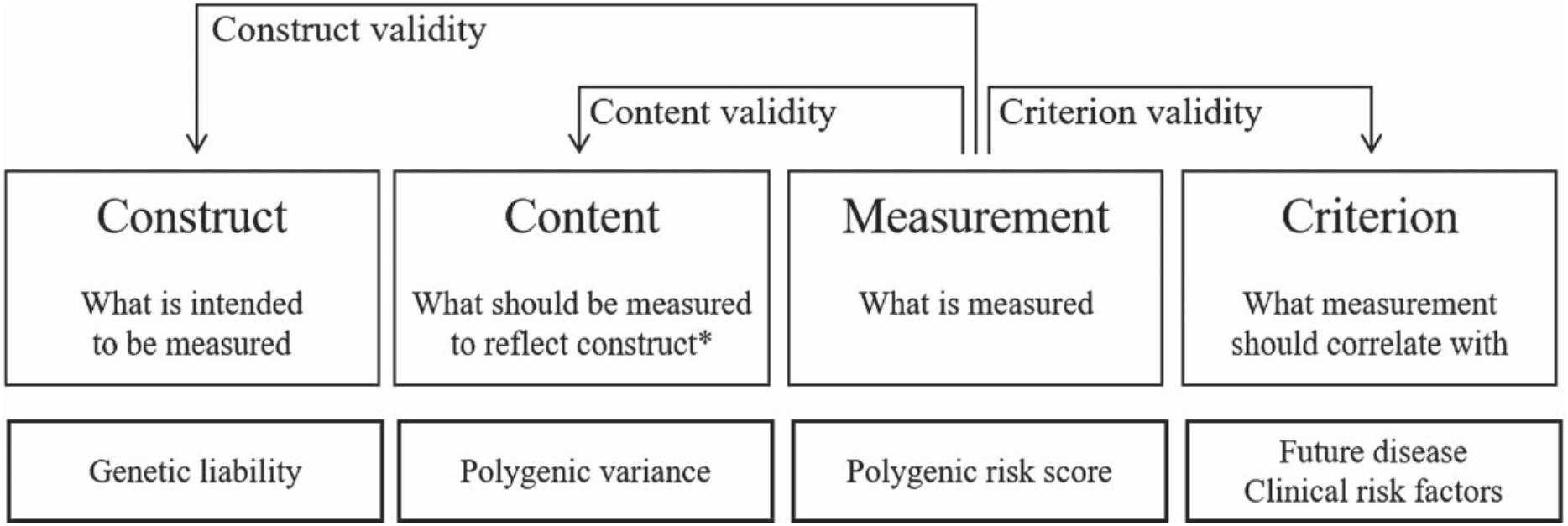
Validity of polygenic risk scores: are we measuring what we think we are?

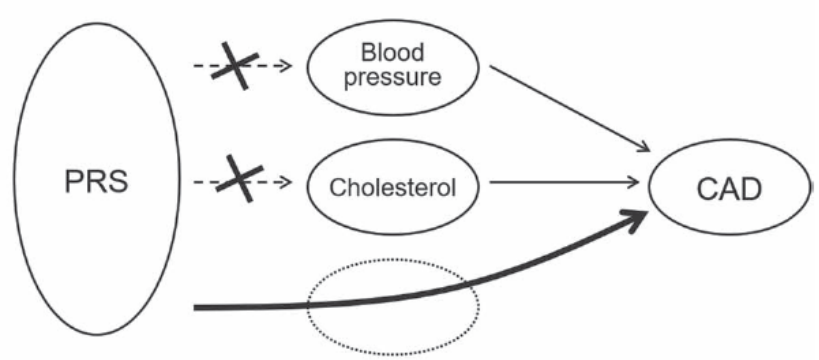
A. Cecile J.W. Janssens*

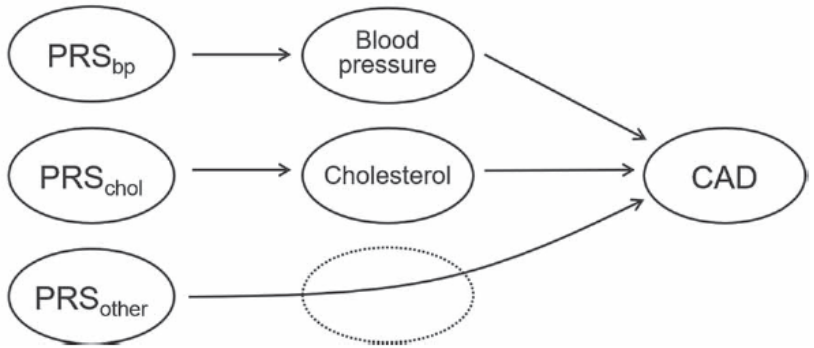
Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Road NE, Atlanta, GA, USA

Polygene Risiko-Scores (PRS)

Mehrere Ebenen der Validität



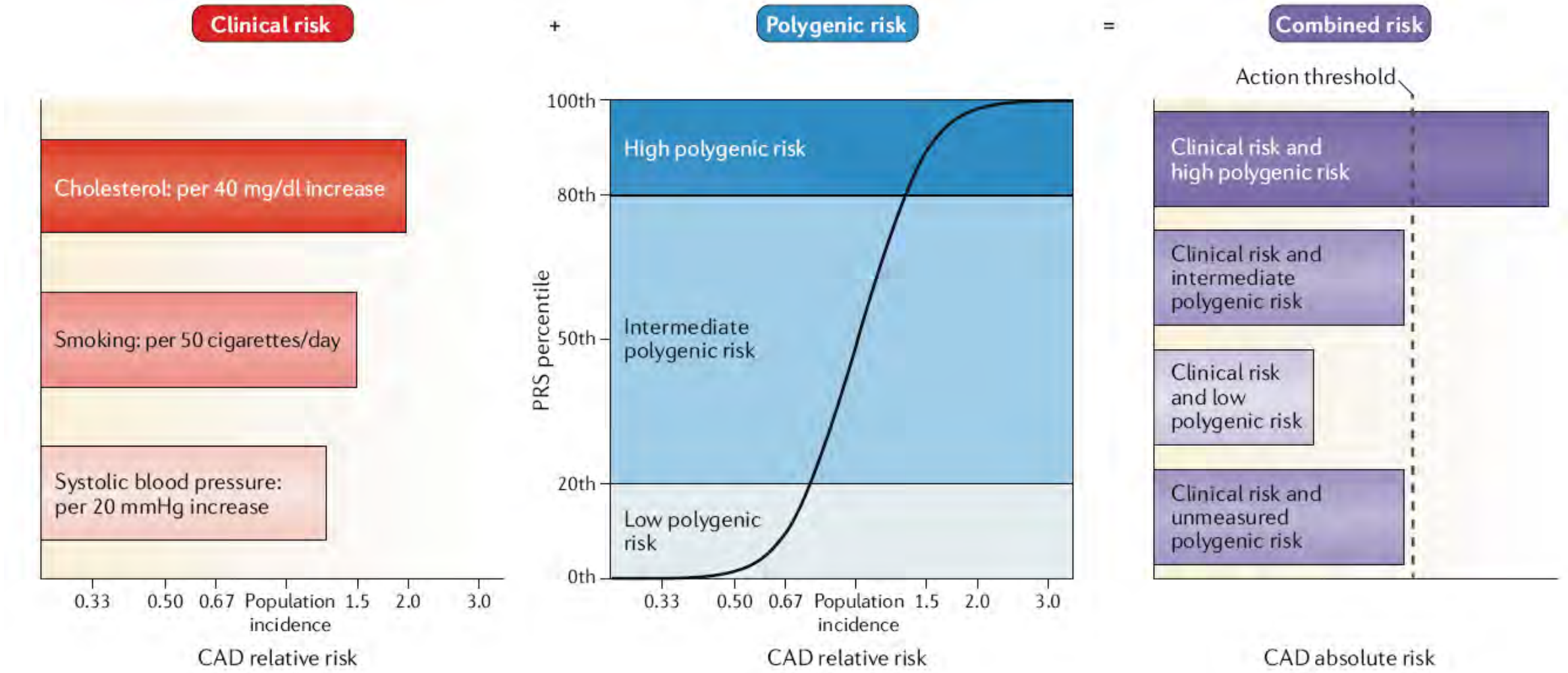




CAD: Coronary Artery Disease

Human Molecular Genetics, 2019, Vol. 28, No. R2

Klinische Risikofaktoren und PRS



CAD: Coronary Artery Disease

Bedeutung eines Testverfahrens ?

Beispiel Genpanels: Validität oft Gen-spezifisch

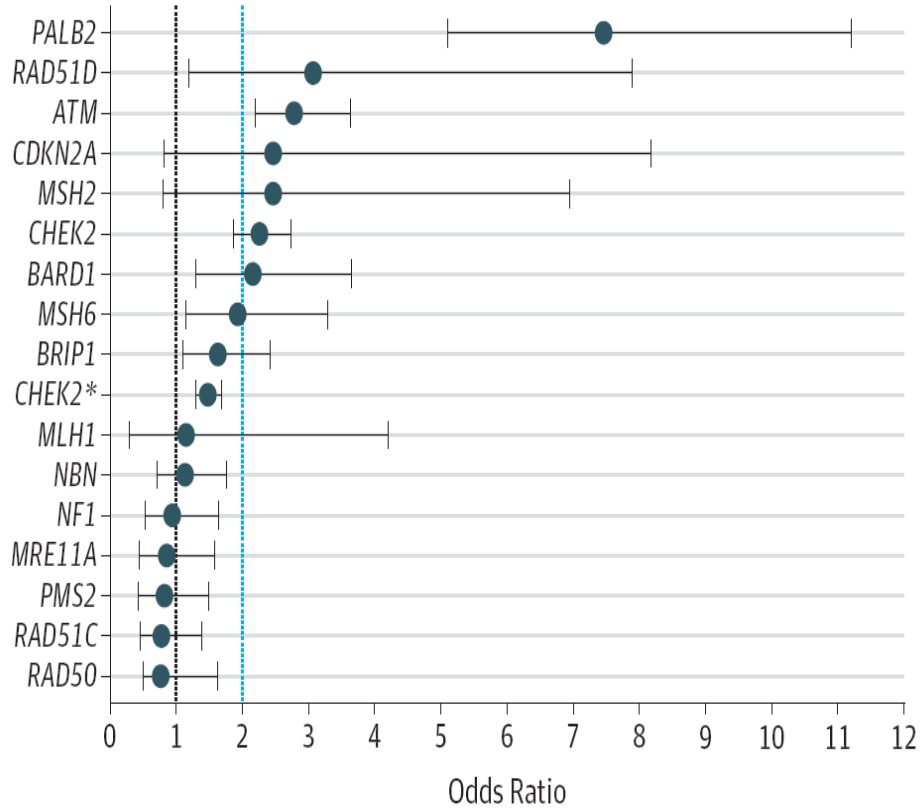
Test characteristics	Current knowledge
Analytic validity	EMQN pilot trials / CLIA
Clinical validity (future disease outcomes, risk prediction)	Association, magnitude and precision of risk estimate: Specific for each gene – and for many marginal/not known!
Clinical utility (improvement of health outcome)	Only for a few genes known
Ethical, legal, social impact	…only slowly emerging…

SPECIAL REPORT N ENGL J MED 372;23 NEJM.ORG JUNE 4, 2015

Gene-Panel Sequencing and the Prediction of Breast-Cancer Risk

Douglas F. Easton, Ph.D., Paul D.P. Pharoah, Ph.D., Antonis C. Antoniou, Ph.D., Marc Tischkowitz, M.D., Ph.D., Sean V.

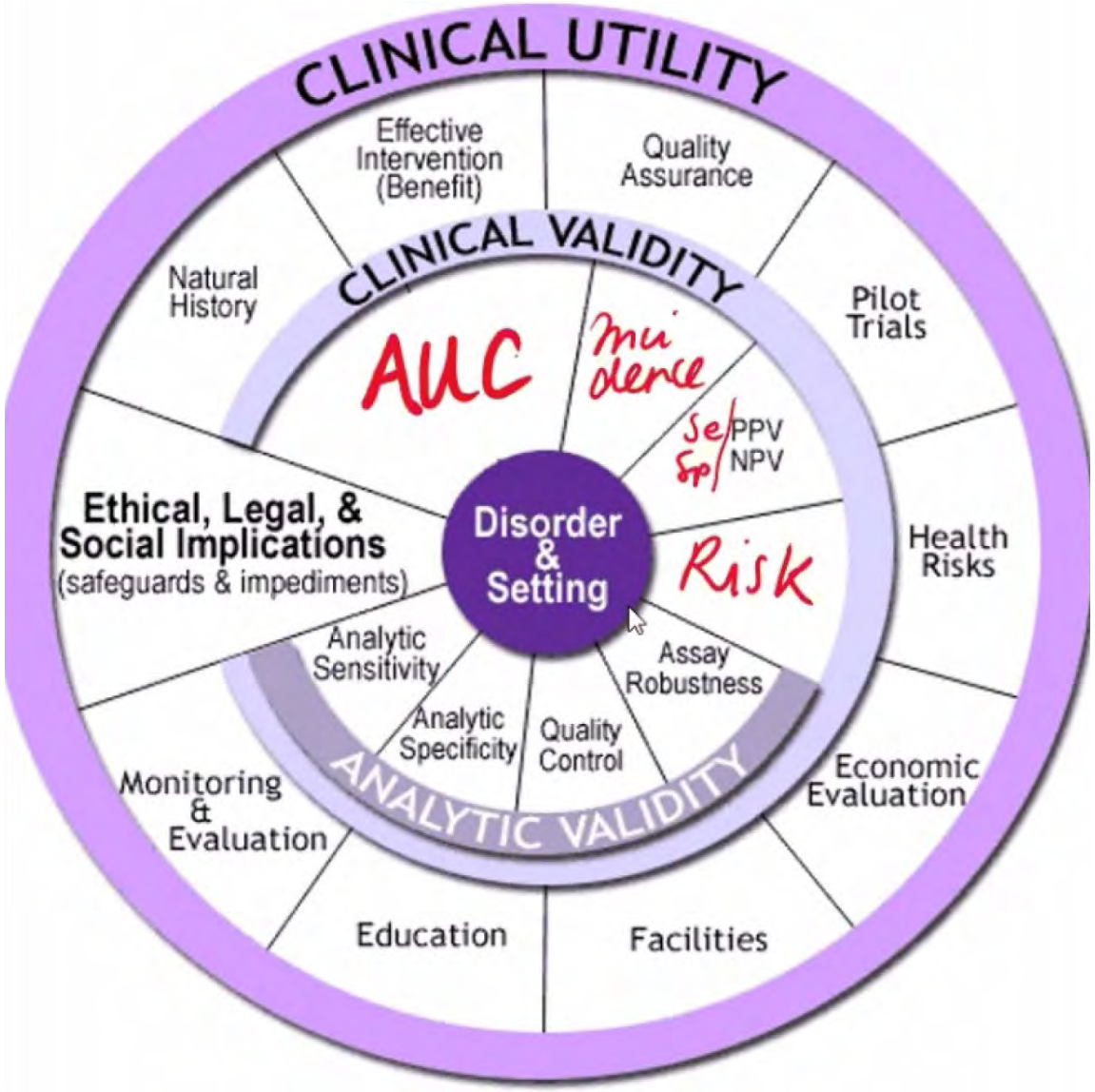
Figure. Odds Ratio Between Combined Pathogenic Variants in Each Gene and Breast Cancer Among White Women With Breast Cancer and Reference Controls

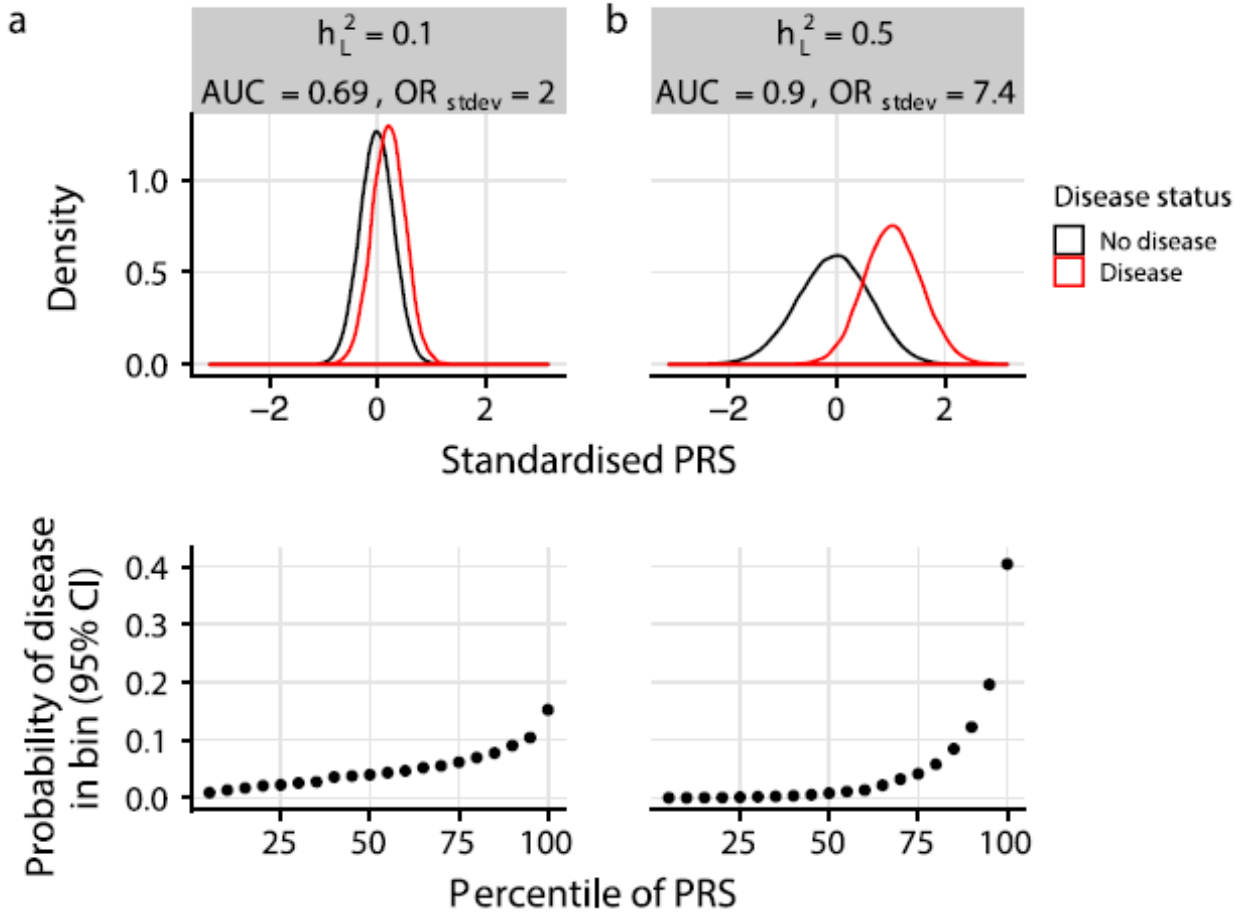


JAMA Oncology Published online April 13, 2017

Panel-based clinical testing among 65 057 patients with breast cancer

«Clinical Validity» und PRS

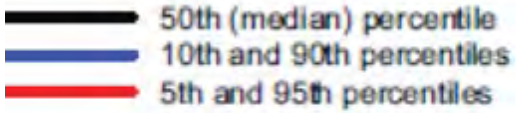




Human Molecular Genetics, 2019, Vol. 28, No. R2

Beispiel PRS und Brustkrebsrisiko bei BRCA1/BRCA2-Trägern

PRS investigated and outcome	BRCA1 carriers				BRCA2 carriers			
	No. of controls	No. of cases	OR (95% CI)	P[a]	No. of controls	No. of cases	OR (95% CI)	P[a]
Continuous[b]	380	70	1.73 (1.28 to 2.33)	<.001	933	141	1.60 (1.34 to 1.91)	<.001
Continuous: adjusted for FH[c]	380	70	1.74 (1.29 to 2.35)	<.001	933	141	1.59 (1.32 to 1.90)	<.001



"Population-based prostate and female breast cancer PRS are associated with a wide range of absolute breast and prostate cancer risks for male BRCA1 and BRCA2 carriers. These findings warrant further investigation ..."

tate cancer risks for male BRCA1 and BRCA2 carriers. Despite the modest estimated AUCs, our results demonstrate that because

Caveats:

- Berechnung des absoluten Risikos unter der Annahme, dass sich die PRS-Odds Ratio über ganzen PRS-Bereich log linear verhält
- Stichproben-Grösse / nur "Europäer"
- Notwendigkeit der Validierung in grossen, prospektiven Studien

Breast and Prostate Cancer Risks for Male BRCA1 and BRCA2 Pathogenic Variant Carriers Using Polygenic Risk Scores

JNCI J Natl Cancer Inst (2022) 114(1): djab147

Beispiel Gen-spezifischer PRS und Brustkrebs-Risiko

J Clin Oncol 00. © 2021 by American Society of Clinical Oncology

Risk of Breast Cancer Among Carriers of Pathogenic Variants in Breast Cancer Predisposition Genes Varies by Polygenic Risk Score

Knowledge Generated

PRS showed particular importance of risk stratification among carriers of PVs in moderate penetrance genes such as *CHEK2* and *ATM*. The risks associated with change in PRS were smaller among carriers of *BRCA1* or *BRCA2* but no other effect modification by PRS was observed for carriers of PVs in the other genes tested.

Relevance

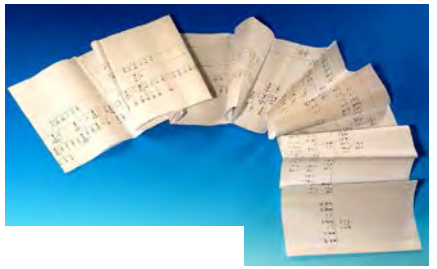
PRS yielded a meaningful risk gradient among both carriers and noncarriers of PVs in BC predisposition genes and may be particularly important for women with PVs in *ATM* and *CHEK2*. The incorporation of PRS into risk prediction models may help to determine the potential benefit of breast magnetic resonance imaging and the age of BC screening initiation.

TABLE 3. Lifetime Absolute BC Risk (by age 80 years) of BC for Different Pathogenic Variant Carriers With Respect to Different PRS Percentile and BC Family History Status

Lifetime Absolute Risk (95% CI)	No Family History				Family History of BC (First-Degree Relative)			
	10th Percentile PRS	Median PRS	Mean PRS	90th Percentile PRS	10th Percentile PRS	Median PRS	Mean PRS	90th% PRS
Noncarrier	6.7 (6.6 to 6.9)	11.1 (11.1 to 11.2)	12.1 (12.0 to 12.1)	18.3 (17.9 to 18.7)	9.1 (8.6 to 9.6)	14.8 (14.2 to 15.5)	15.9 (15.3 to 16.6)	23.9 (22.9 to 25.0)
BRCA1 carrier	36.1 (26.4 to 48.5)	41.2 (32.6 to 52.0)	41.4 (32.8 to 52.2)	46.9 (33.9 to 62.7)	45.4 (33.9 to 59.2)	51.1 (41.2 to 62.7)	51.3 (41.4 to 62.6)	57.3 (42.8 to 72.9)
BRCA2 carrier	43.8 (33.6 to 56.3)	49.3 (40.7 to 59.4)	49.5 (41.0 to 59.5)	55.3 (42.0 to 70.1)	53.9 (42.4 to 66.9)	59.8 (50.7 to 69.9)	59.9 (50.8 to 69.8)	65.9 (51.8 to 79.3)
ATM carrier	12.8 (10.3 to 15.9)	20.5 (16.7 to 25.2)	21.9 (18.0 to 26.6)	32.3 (26.8 to 38.8)	17.0 (13.7 to 21.1)	26.7 (21.9 to 32.5)	28.2 (23.3 to 34.0)	40.9 (34.2 to 48.5)
CHEK2 carrier	15.2 (12.6 to 18.2)	24.1 (20.3 to 28.5)	25.5 (21.6 to 30.0)	37.3 (32.0 to 43.4)	20.0 (16.7 to 24.0)	31.1 (26.3 to 36.6)	32.6 (27.8 to 38.0)	46.6 (40.3 to 53.4)
PALB2 carrier	21.5 (15.4 to 29.7)	33.2 (24.2 to 44.2)	34.6 (25.7 to 45.3)	49.2 (37.6 to 62.1)	27.9 (20.1 to 38.0)	41.9 (31.3 to 54.3)	43.1 (32.7 to 54.7)	59.5 (46.8 to 72.0)

NOTE. The results for the other genes are in Data Supplement 2.
Abbreviations: BC, breast cancer; PRS, polygenic risk score.

BAG-Empfehlungen zur bildgebenden Überwachung bei Brustkrebs



Bundesamt für Gesundheit BAG
Direktionsbereich Kranken- und Unfallversicherung

Referenzdokument «Überwachungsprotokoll»
zu Artikel 12*d* Absatz 1 Buchstabe d der Krankenpflege-Leistungsverordnung (KLV) - Stand 01/2021

? →

Grund für die Überwachung	Alter / Bildgebungsmodalität (MRI = Kernspintomografie, MG = Mammografie)											
	20 - 29		30 - 39		40 - 49		50 - 59		60 – 69		70 - 75	
	MRI	MG	MRI	MG	MRI	MG	MRI	MG	MRI	MG	MRI	MG
Lebenszeitrisiko mässig erhöht (17 – 29%)	kein Screening		kein Screening		-	jährlich	-	jährlich	-	alle 2 Jahre	-	alle 2 Jahre
Lebenszeitrisiko stark erhöht (≥30 %)	kein Screening		jährlich[1)]	jährlich[2), 3)]	jährlich[1)]	jährlich	jährlich[1)]	jährlich	alle 2 Jahre[1), 4)]	alle 2 Jahre[4)]	-	alle 2 Jahre
BRCA1/2-Mutation	jährlich ab 25 J[5)]	-	jährlich	jährlich	jährlich	jährlich	jährlich	jährlich	jährlich	jährlich	-	alle 2 Jahre
STK11-Mutation	jährlich ab 25J[5)]	-	jährlich	jährlich[3)]	jährlich	jährlich	jährlich	jährlich	jährlich	jährlich	-	alle 2 Jahre
TP53-Mutation	jährlich	-	jährlich	-	jährlich	-	jährlich	-	jährlich	-	kein Screening	

Caveats von Cecile Janssens

Every model is a simplification of reality

Different study population → different performance

Keep generalizability in mind when choosing study population

Martens & Janssens, *Curr Epidemiol Rev, 2020*

Wide age range in study population → higher AUC

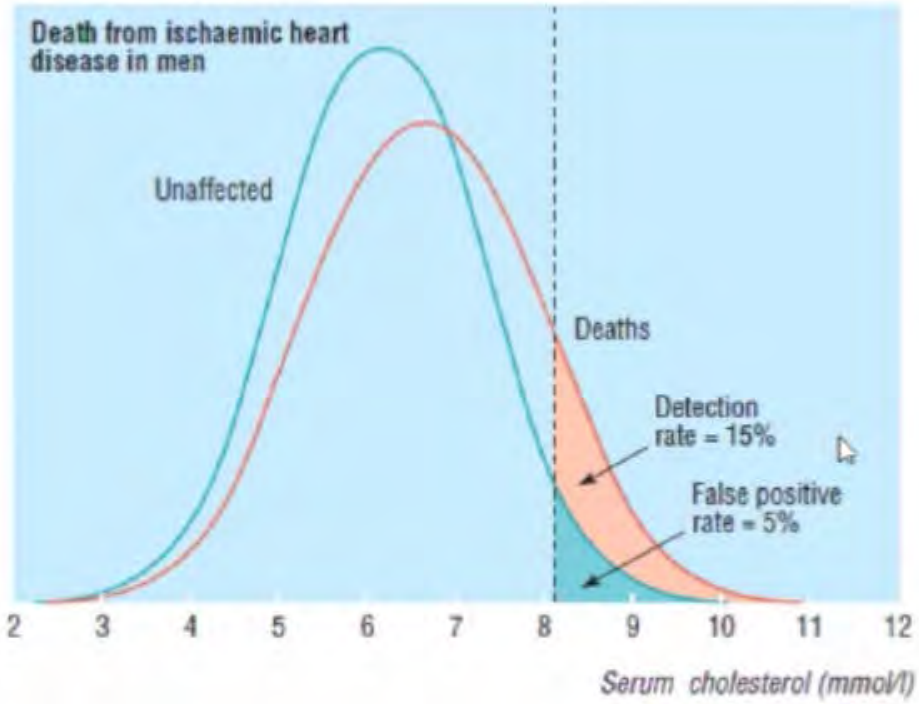
Higher heritability → higher max AUC

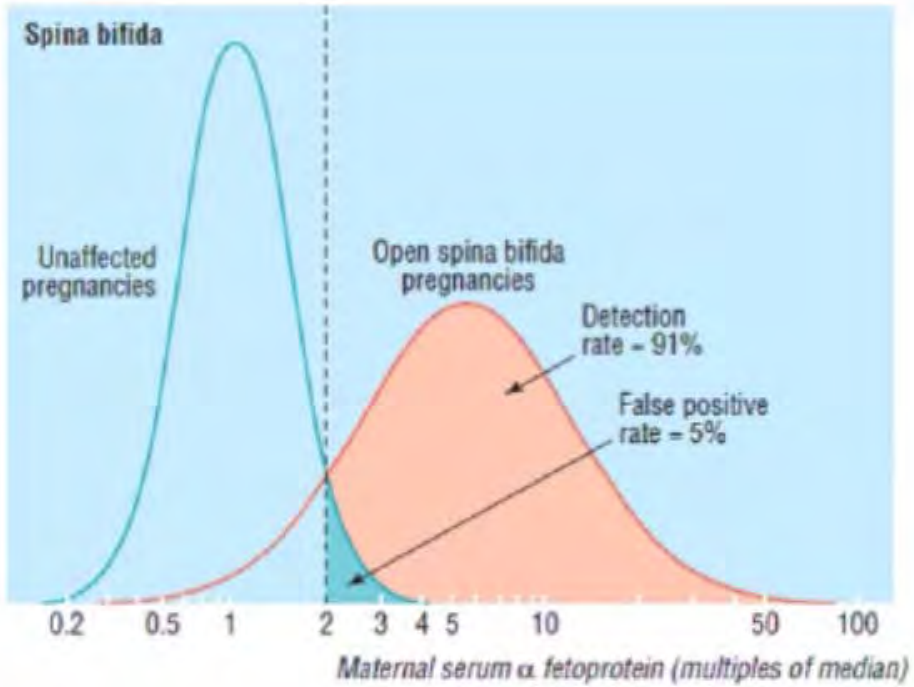
Heritability depends on the environment
Genetic effects may differ with age and age at onset

UK Biobank has wide age range (40-70yr)

Models that include age are a strong predictor of age-related diseases

Wann ist ein Screening-Test lohnenswert?





Summary points

To be a worthwhile screening test, a risk factor must be strongly associated with a disorder

N J Wald, A K Hackshaw, C D Frost
BMJ VOLUME 319 11 DECEMBER 1999

Sinnhaftigkeit von polygenen Risiko-Scores

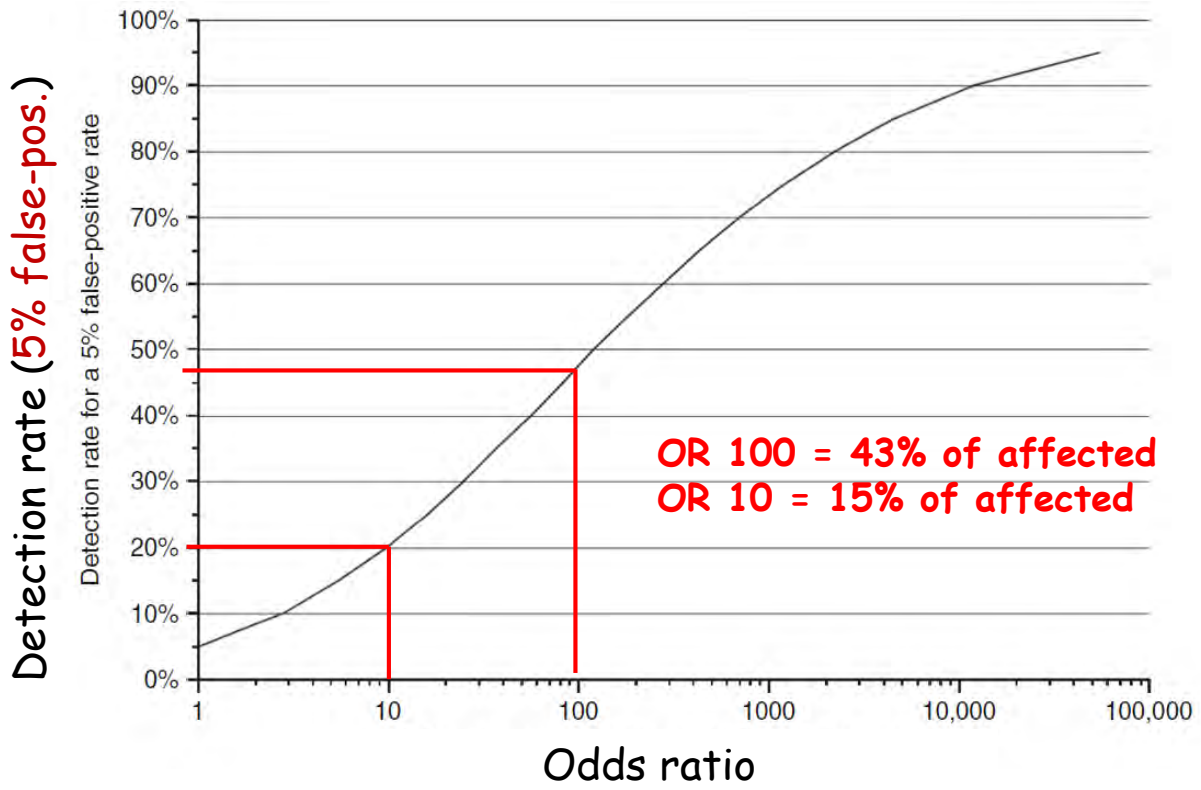
Ätiologie ≠ Risiko-Vorhersage / Bevölkerungssreening

The illusion of polygenic disease risk prediction

Nicholas J. Wald, FRS [1] and Robert Old, PhD[1]

A problem at the interface of genomic medicine and medical screening is that genetic associations of etiological significance are often interpreted as having predictive significance. Genome-wide association studies (GWAS) have identified many thousands of associations between common DNA variants and hundreds of diseases and benign traits. This knowledge has generated many publications with the understandable expectation that it can be used to derive polygenic risk scores for predicting disease to identify those at sufficiently high risk to benefit from preventive intervention. However, the expectation rests on the incorrect assumption that odds ratios derived from polygenic risk scores that are important etiologically are also directly useful in risk prediction and population screening.

Genetics in Medicine (2019) 21:1705–1707; https://doi.org/10.1038/s41436-018-0418-5

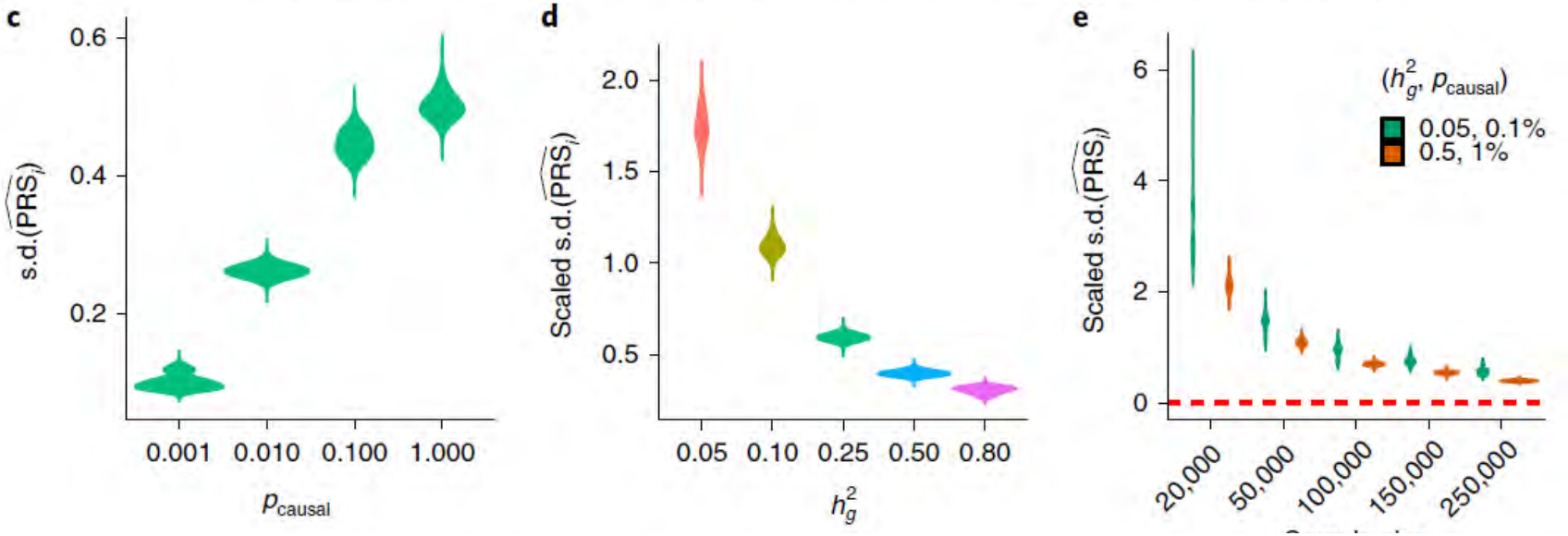


Estimating odds ratios or hazard ratios is appropriate and customary in etiological studies but can be deceptive, and conceal the poor discriminatory power of predictive scores.

Unsicherheit bei der Abschätzung individueller PRS einbeziehen

NATURE GENETICS | VOL 54 | JANUARY 2022 | 30–39 |

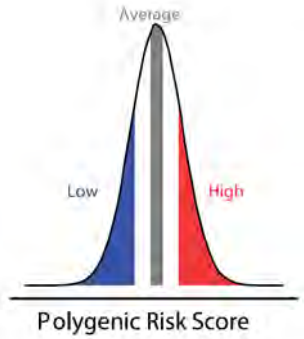
Large uncertainty in individual polygenic risk score estimation impacts PRS-based risk stratification



Polygenicity | Heritability | GWAS-Stichprobengrösse

estimate the variance of an individual's PRS and can yield well-calibrated credible intervals via posterior sampling. For 13 real traits in the UK Biobank ($n = 291,273$ unrelated 'white British'), we observe large variances in individual PRS estimates which impact interpretation of PRS-based stratification; averaging across traits, only 0.8% (s.d. = 1.6%) of individuals with PRS point estimates in the top decile have corresponding 95% credible intervals fully contained in the top decile. We provide an analytical

Polygene Risiko-Scores in der Onkologie:
Ready for prime time?



Vielversprechend

- **Hoffnung**: Potential zur personalisierteren Krebsrisiko-Vorhersage
  => Einbezug in Entscheidungen zum klinischen Management
  - aktuell Verwendung in Screening-Studien zur Krebsrisiko-Stratifizierung
  - Verwendung in multifaktoriellen Krebsrisiko-Prädiktionsmodellen

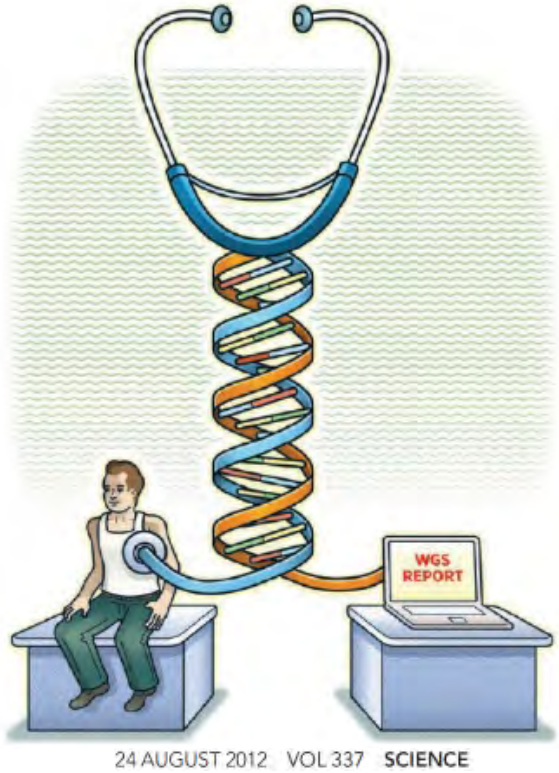
Aber

- Grundsatz-Frage: **Illusion**? (ätiologisch bedeutsam ≠ prädiktiv)
- «**Inflation**» von Scores (unterschiedliche SNPs und Modelle)
- **Populations-Bias** (...Nicht-Europäer...); **Kommerzialisierung** («direct to consumer»)
- Validierung in grossen **prospektiven Studien mit Langzeit-Follow-Up** nötig =>
  Clinical Validity & Clinical Utility?

Persönliches Fazit: Aktuell Verwendung nur im Studien-Rahmen

Polygene Risiko-Scores

Quo vaditis?



24 AUGUST 2012 VOL 337 SCIENCE

The international journal of science / 24 March 2022

nature

The alarming rise of complex genetic testing in human embryo selection

Companies are marketing polygenic risk scores as part of IVF well before the potential benefits – and dangers – are fully understood.

"These tests demand a broader societal discussion."

For now, prospective parents seeking IVF should not be offered polygenic risk scores for diseases unless they are part of rigorous clinical trials. Professional societies should make this clear to their members – as some have already done – and should publish guidelines on how to counsel participants in such trials to avoid giving them false hopes or fears about their children's health. Genetic counsellors must be trained to do the same.