SCOR Global Life, Immeuble SCOR, La Defense

Genetic testing – The Future Impact on Insurance Medicine

Prof. Paul Cullen

Assmann Foundation for Prevention
Paris, 20 April 2009

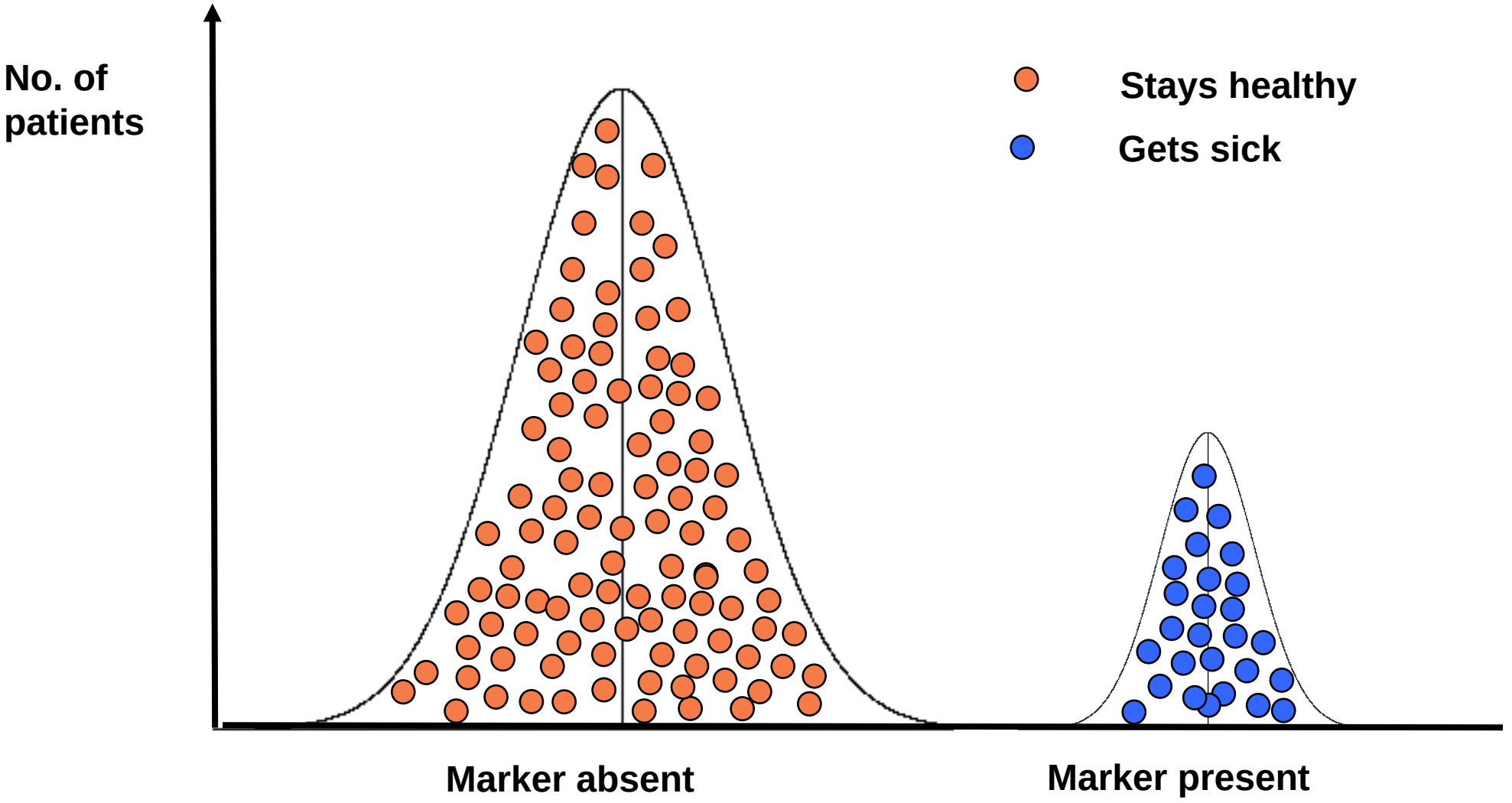
Prediction

Latin praedicere, from prae = before and dicere = to say: *A **prediction** is a statement or claim that a particular event will occur in the future in more certain terms than a forecast… A prediction … [is] valid if the predictor is a knowledgeable person in the field and is employing sound reasoning and accurate data.*

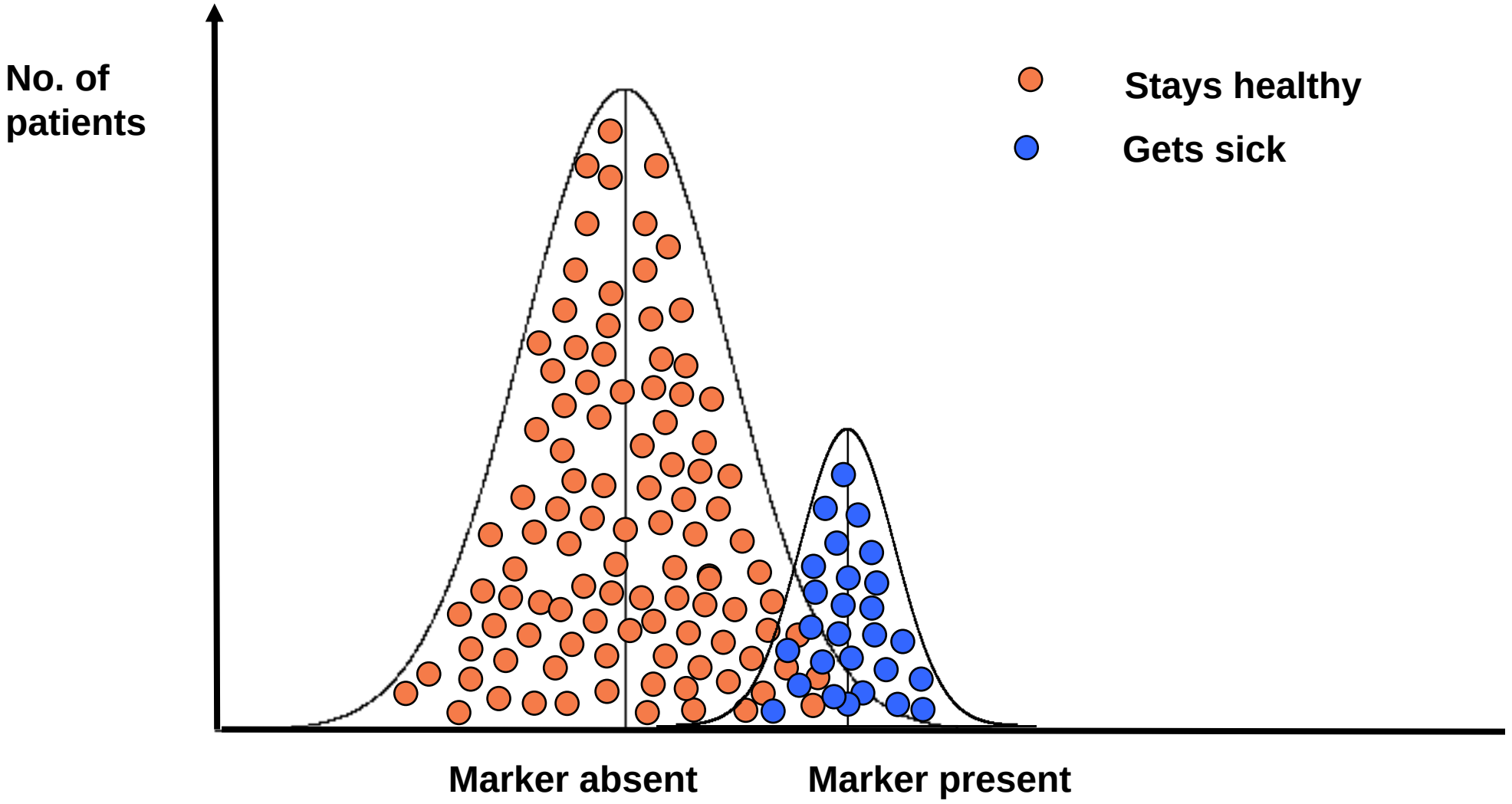
Definition itself contains a substantial element of uncertainty

Wikipedia, 2009

Separation of healthy and sick: ideal case

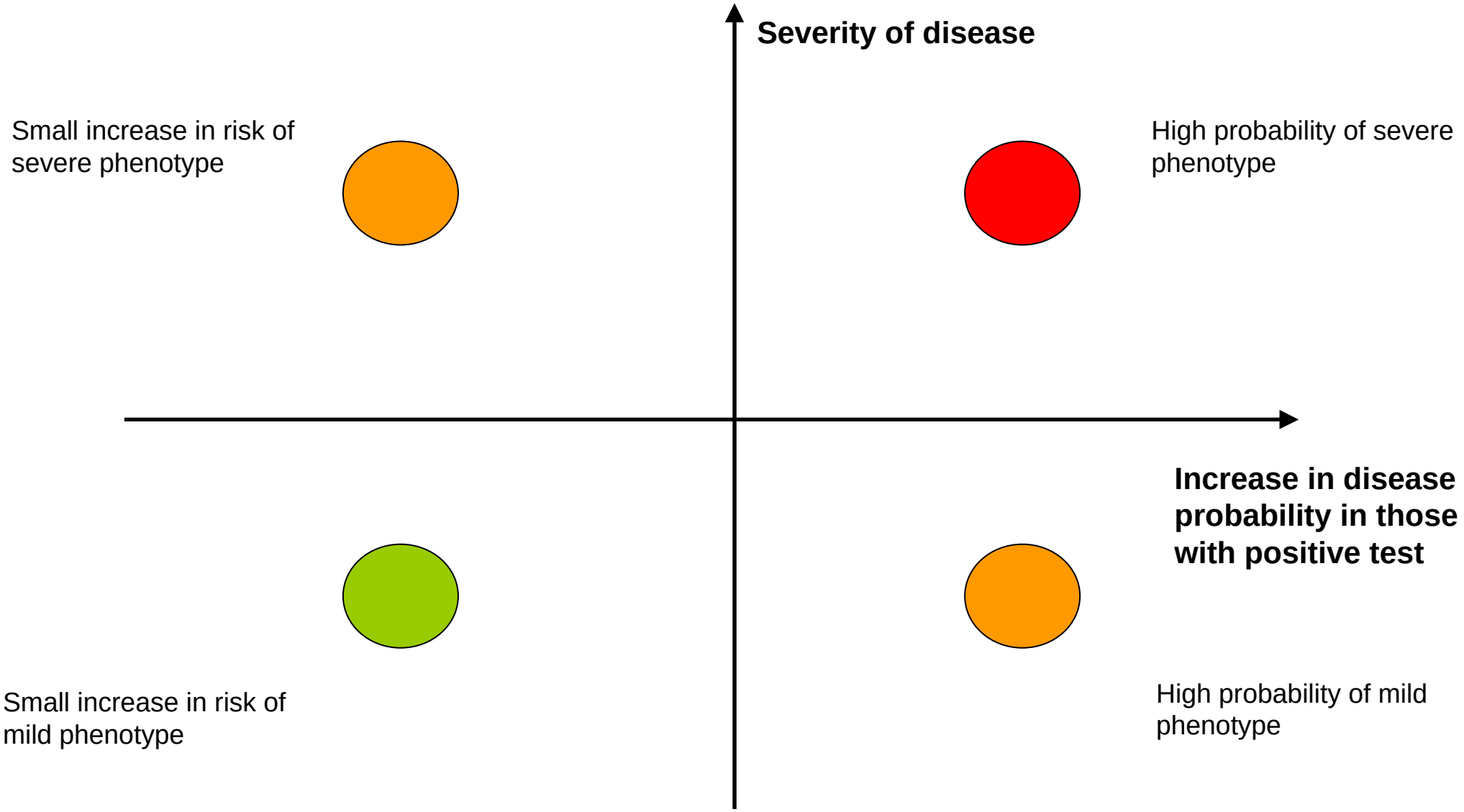


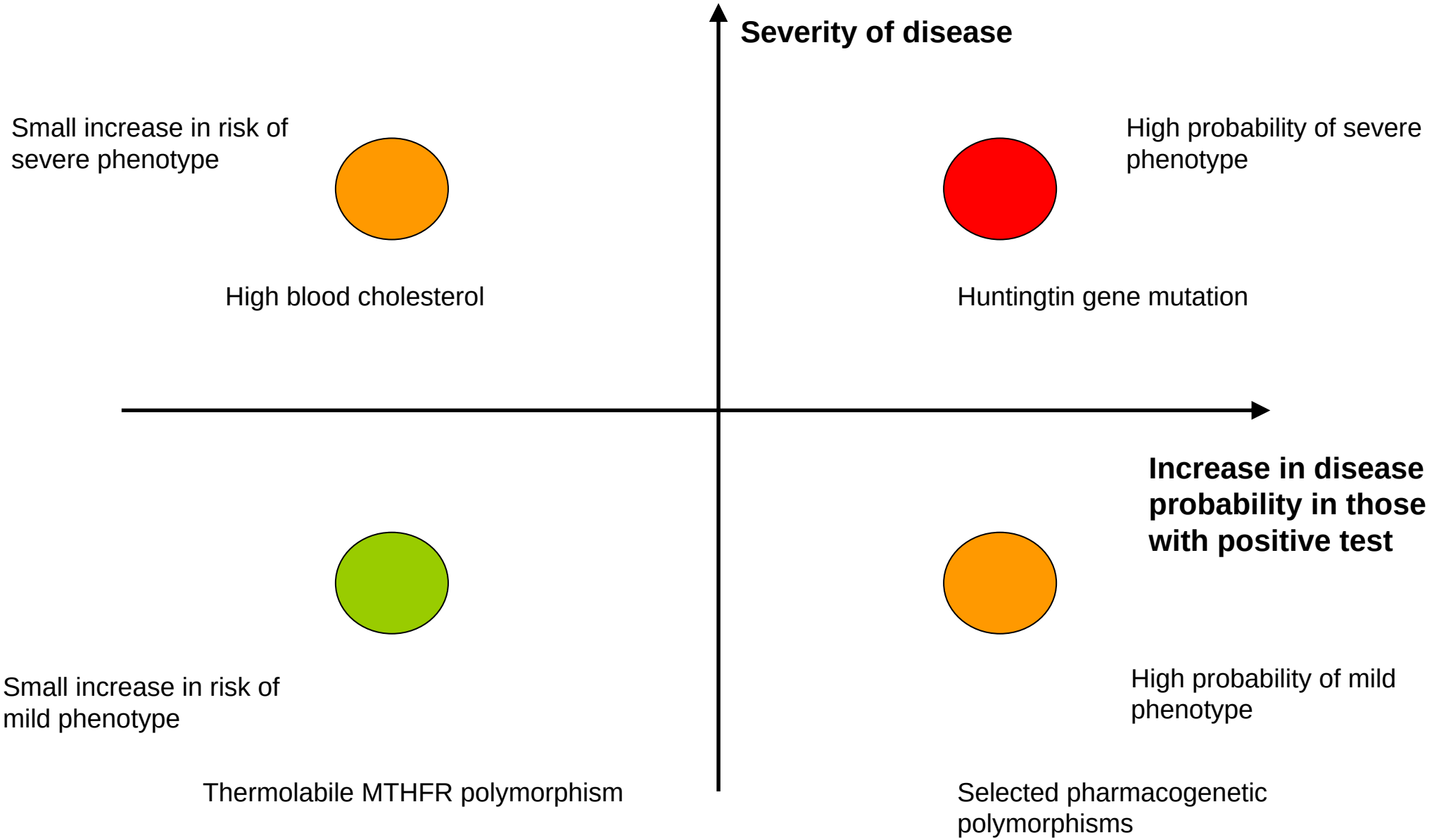
Separation of healthy and sick: reality



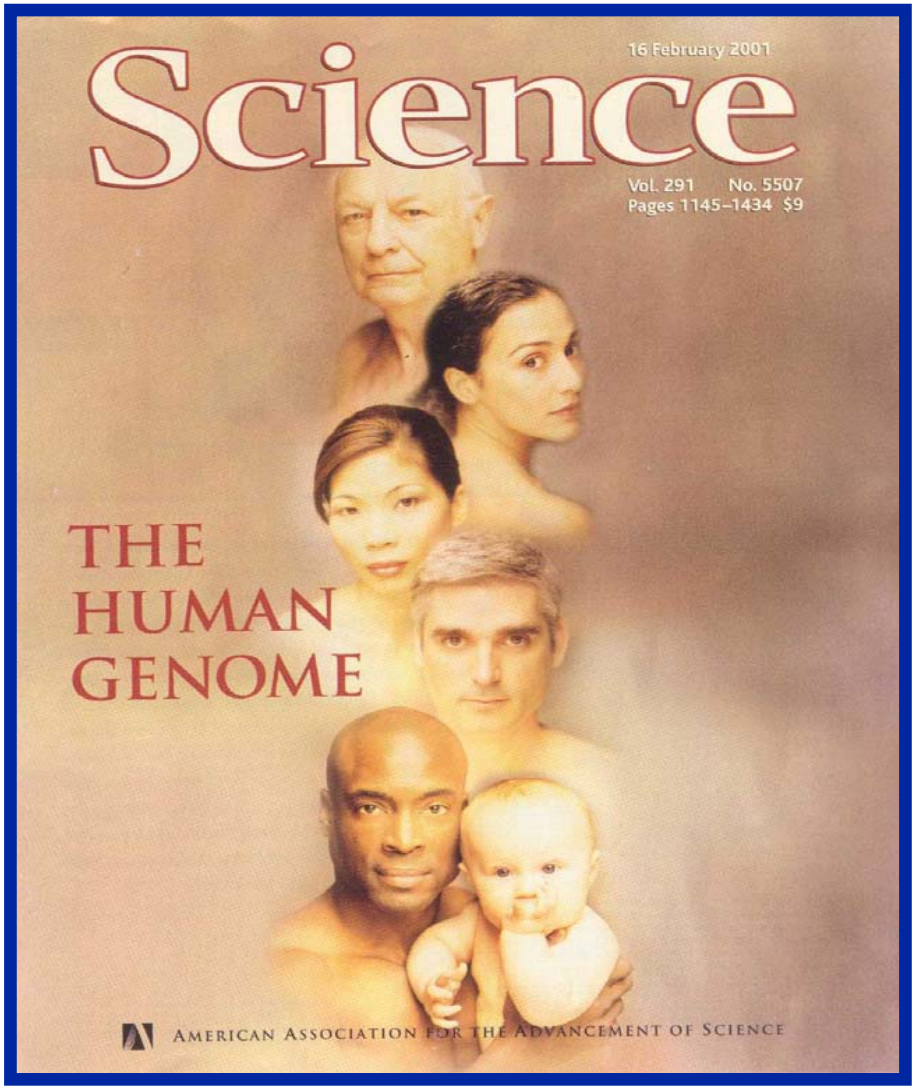
What is a predictive laboratory test?

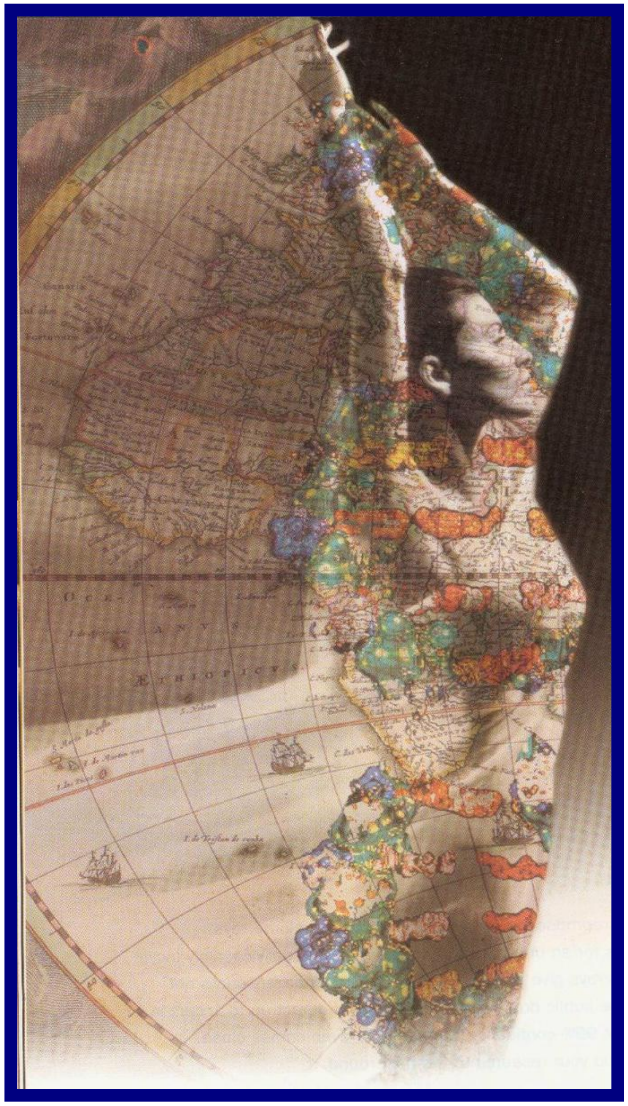
1. Measurement of blood cholesterol
2. Hepatitis C serology
3. Determining APC resistence
4. Factor V-Leiden PCR
5. Detection of mutation in BRCA-1 gene
6. Detection of exess of CAG-triplets in the huntingtin gene


Severity of disease
Small increase in risk of severe phenotype
High probability of severe phenotype
Increase in disease probability in those with positive test
Small increase in risk of mild phenotype
High probability of mild phenotype


Severity of disease
Small increase in risk of severe phenotype
High probability of severe phenotype
High blood cholesterol
Huntingtin gene mutation
Increase in disease probability in those with positive test
Small increase in risk of mild phenotype
High probability of mild phenotype
Thermolabile MTHFR polymorphism
Selected pharmacogenetic polymorphisms

The Human Genome Mapping Project





The raw data from the human genome project will be available to all

THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release March 14, 2000

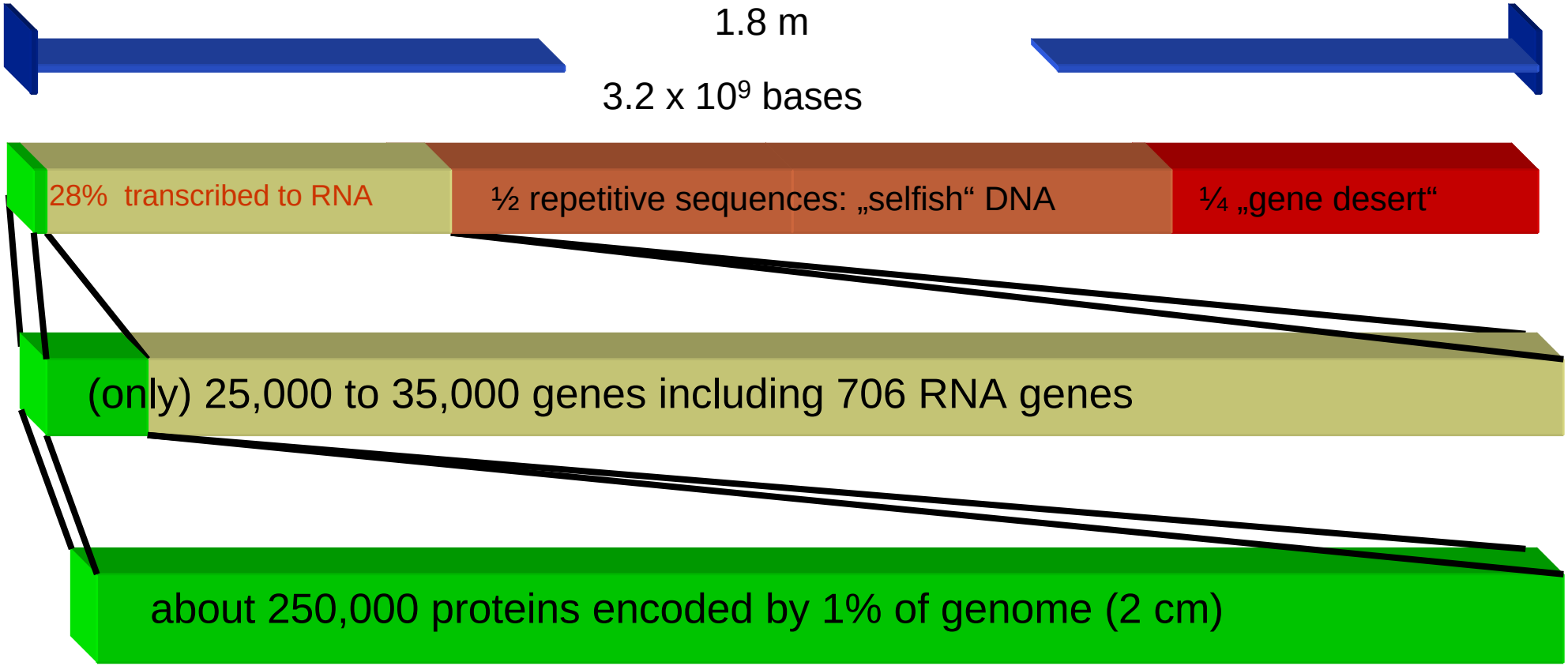
REMARKS BY THE PRESIDENT
AT NATIONAL MEDAL OF SCIENCE AWARD CEREMONY

The East Room

3:23 P.M. EST

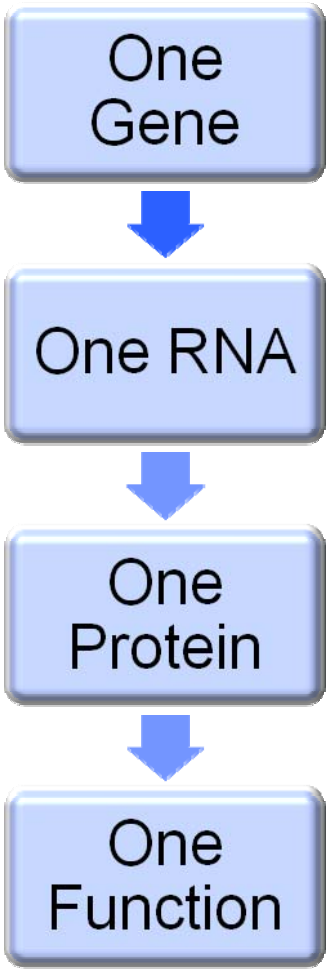
"Today, we [pledge] to lead a global effort to make the raw data from DNA sequencing available to scientists everywhere, to benefit people everywhere."

Principal results of human genome project

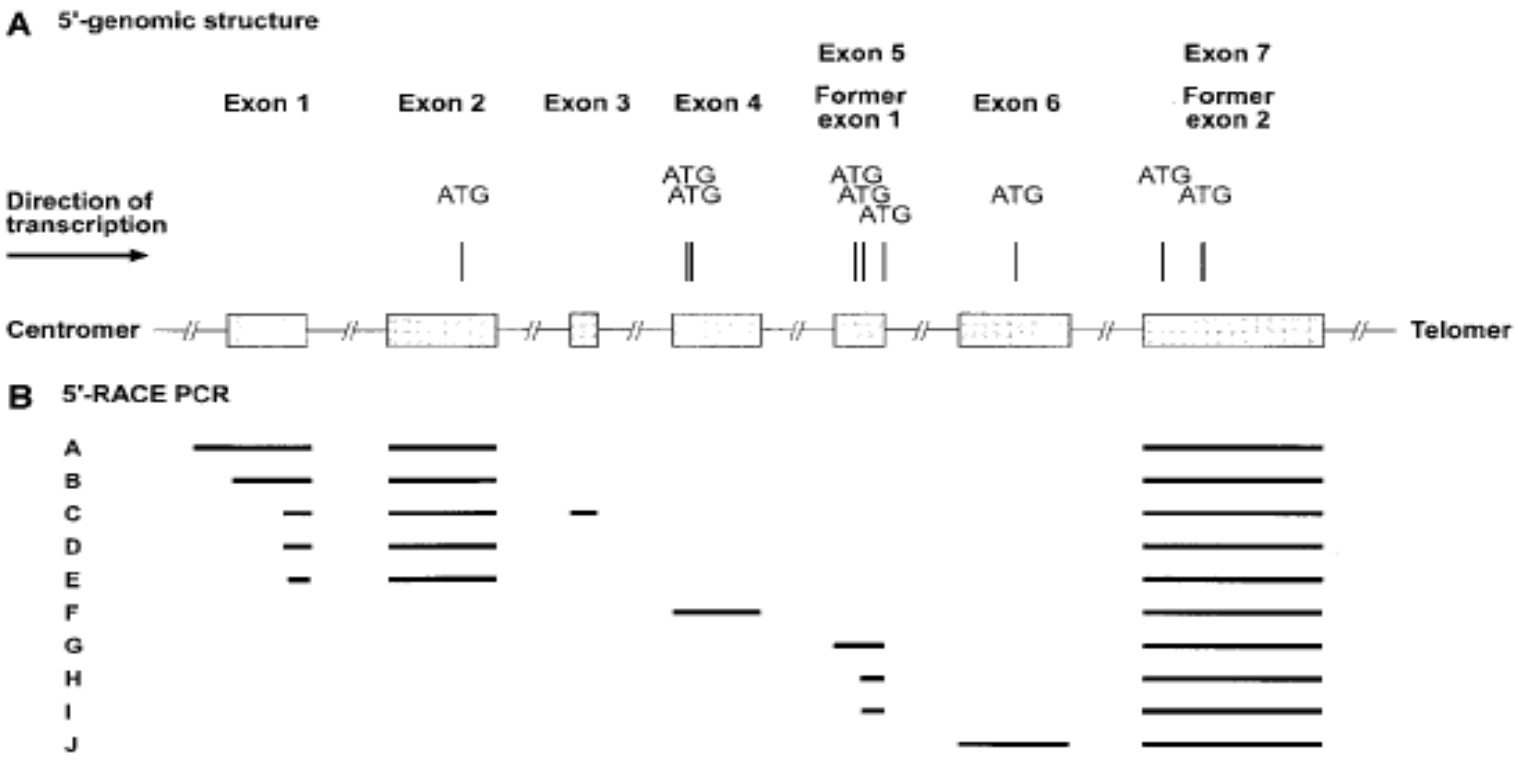


The human genome: a „museum of viral infections“

Original paradigm

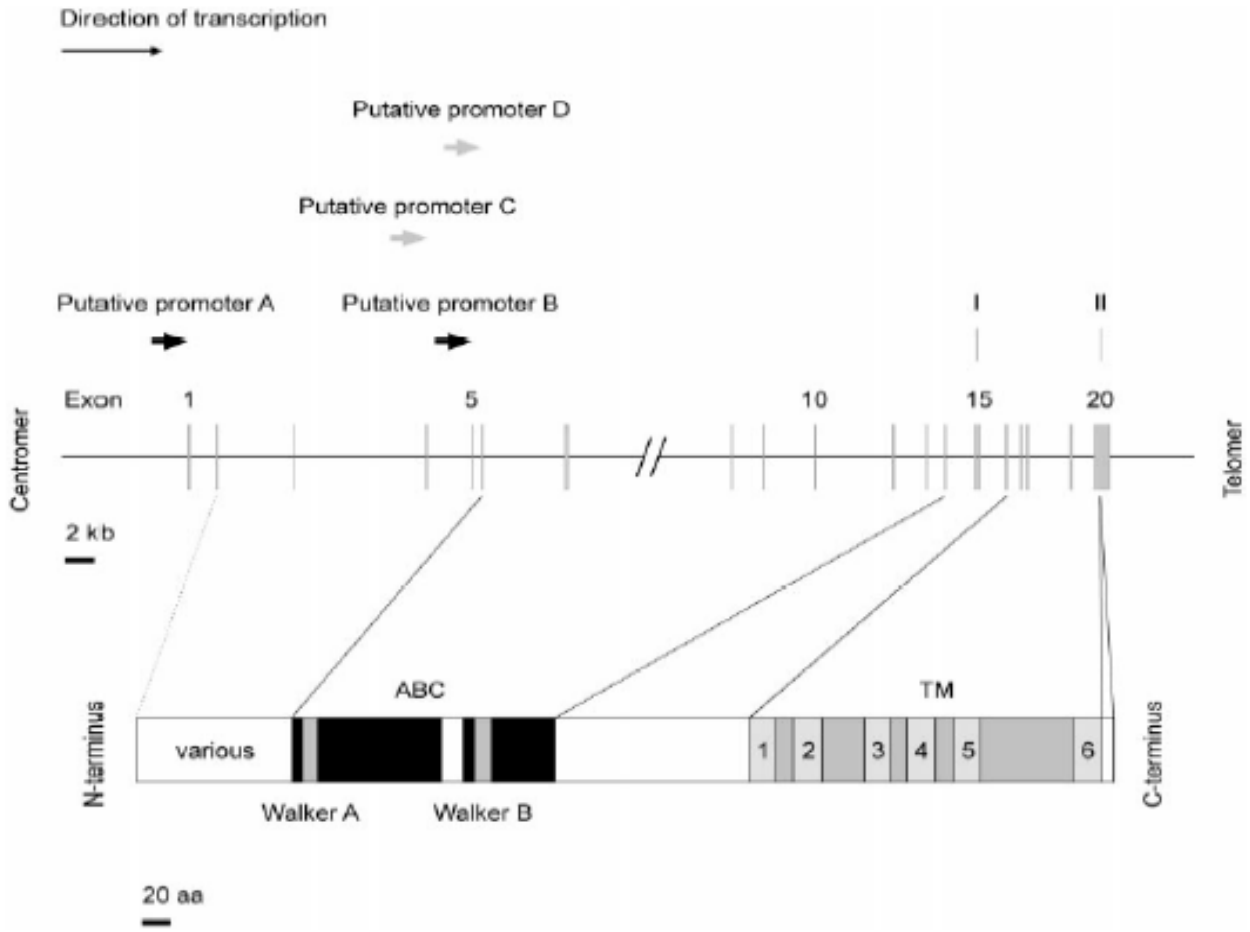


Example of a complex gene: ABCG1



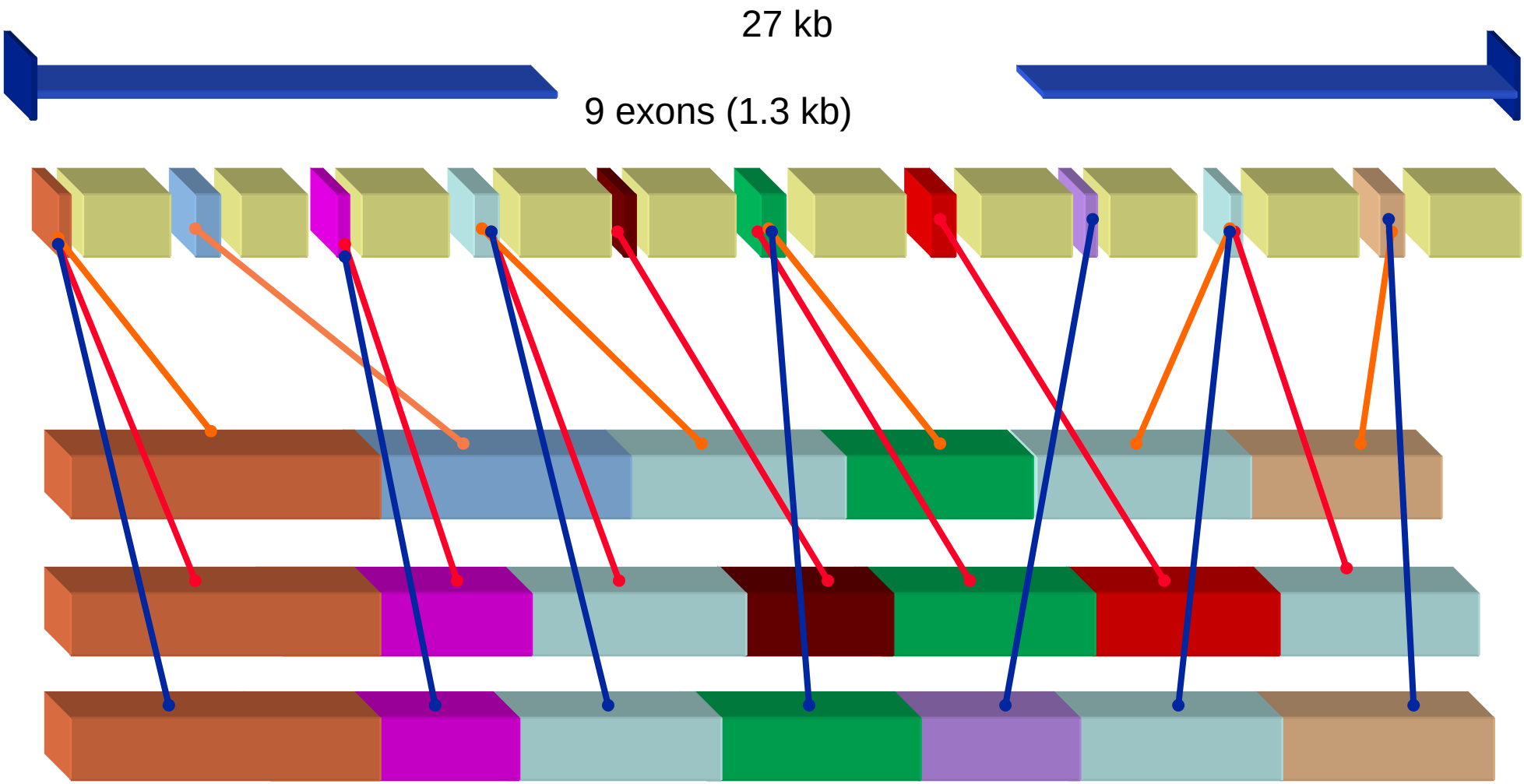
Human ABCG1 sequence. Lorkowski et al. BBRC 280;121, 2001

Example of a complex gene: ABCG1



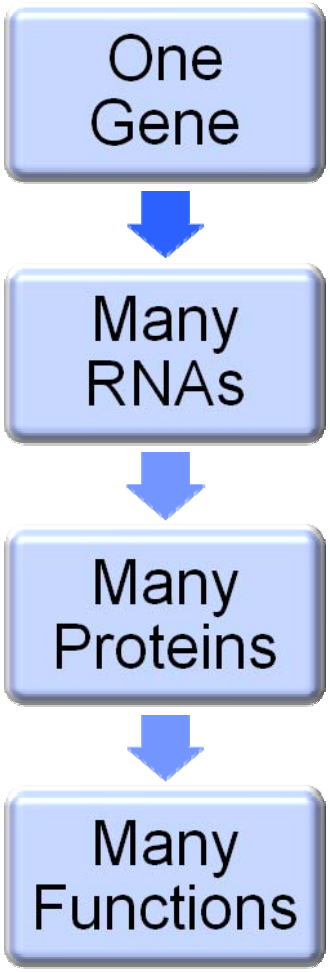
Genomische Struktur und Proteindomäne von ABCG1

The "average gene": diversity through combination

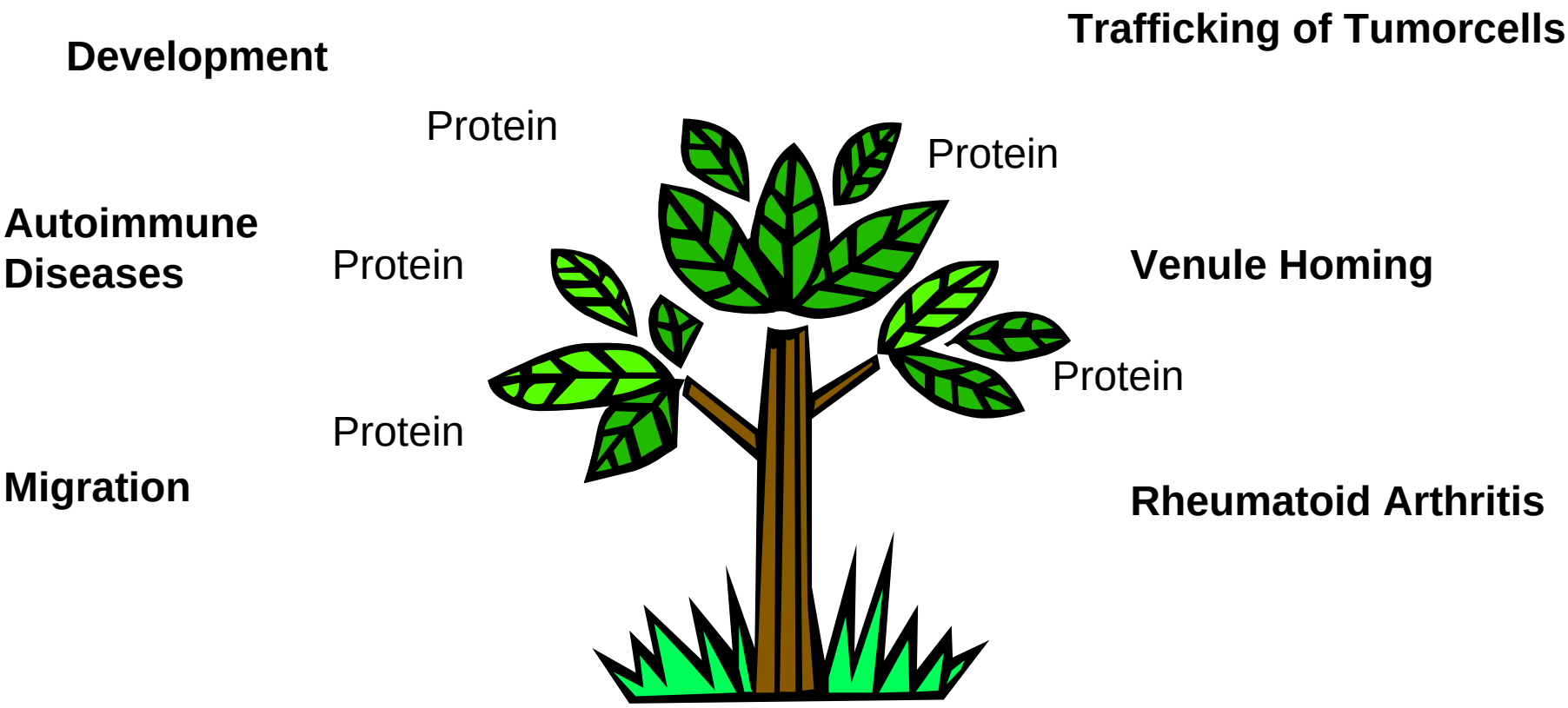


protein with 447 aa's, at least **60%** of genes show alternative splicing

New paradigm

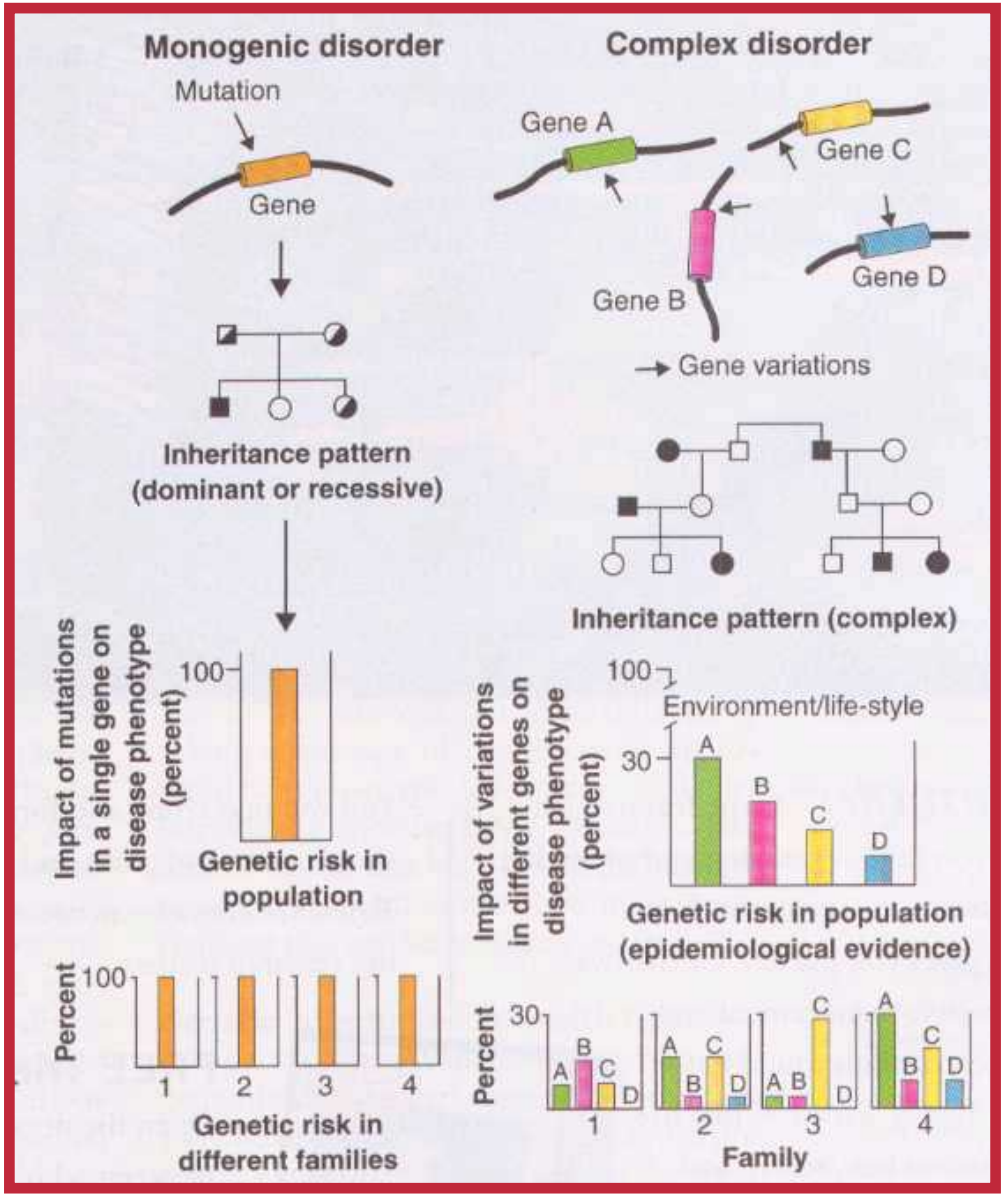


Tree-like nature of DNA→Protein



CD44 Gene: 20 Isoforms

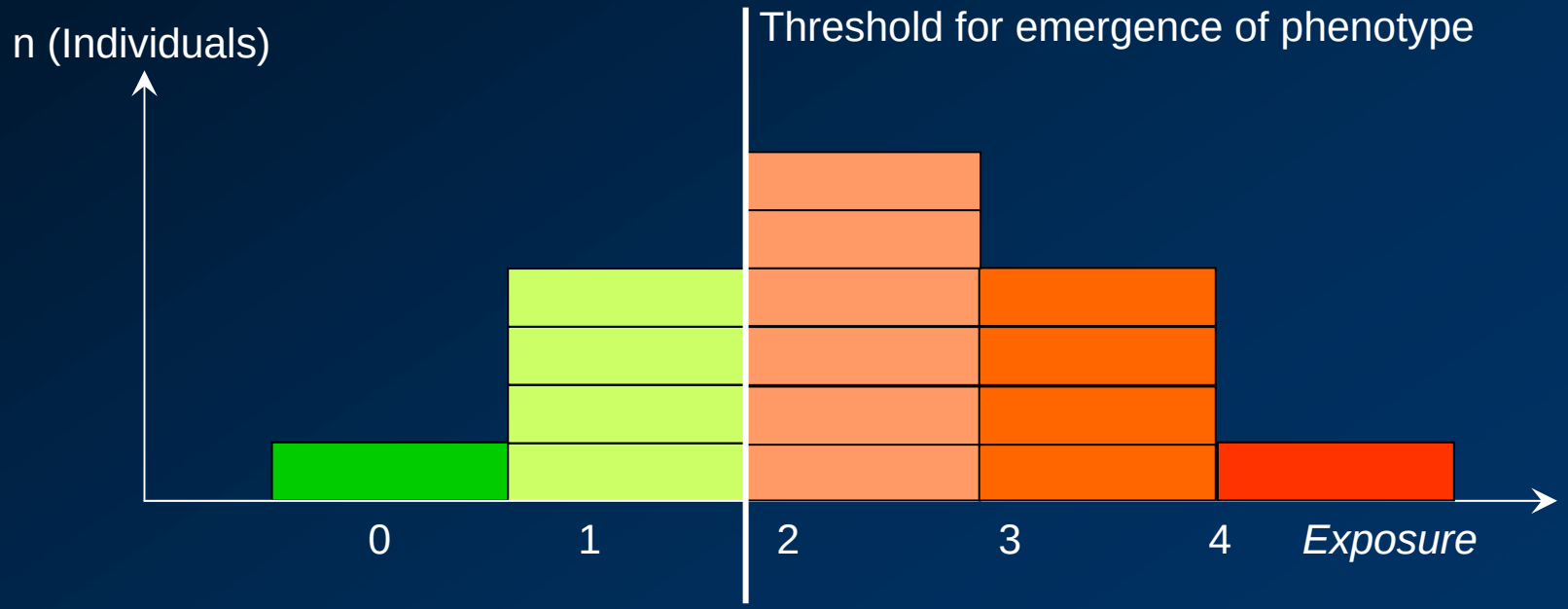
Genes and complex diseases



Peltonen and McKusick, Science 291:1224, 2001

Pathogenesis of multifactorial disease

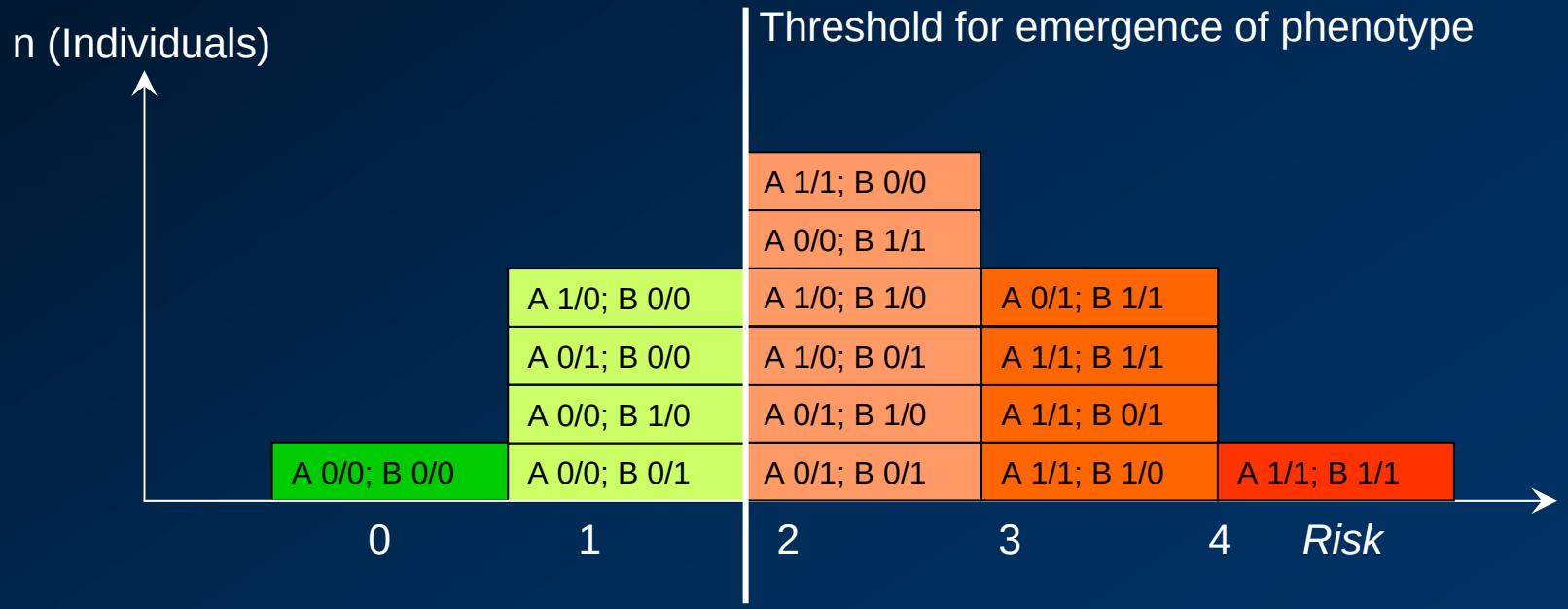
Assumption: Normal distribution of ennvironmental factors
Not accounted for: Sex-specific threshold differences



Pathogenesis of multifactorial disease

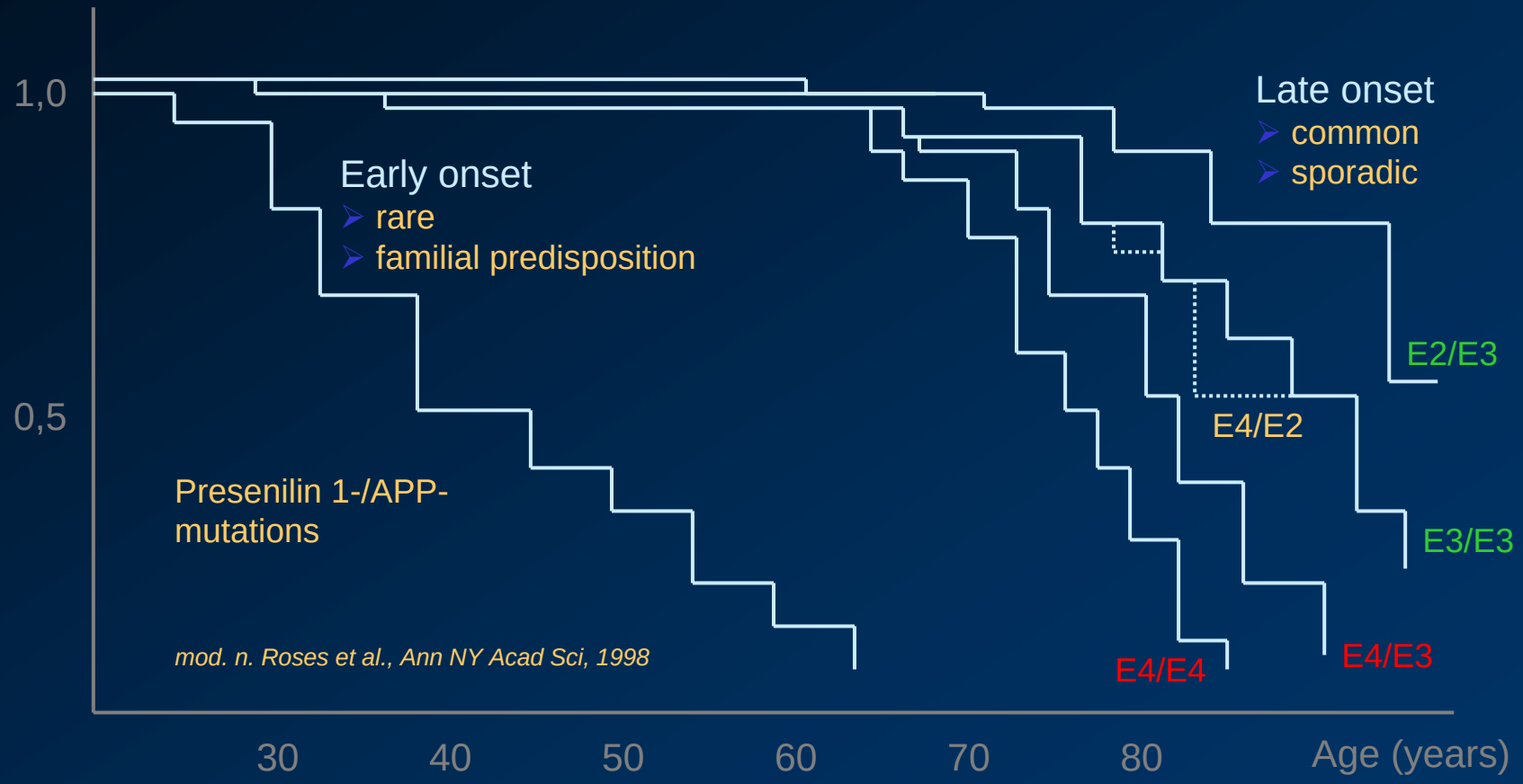
Genetic effects	*Risk*		
	low	*medium*	*high*
Polymorphism A:	0/0	0/1	1/1
Polymorphism B:	0/0	0/1	1/1

Assumption: Normal allele distribution, gene dose effect



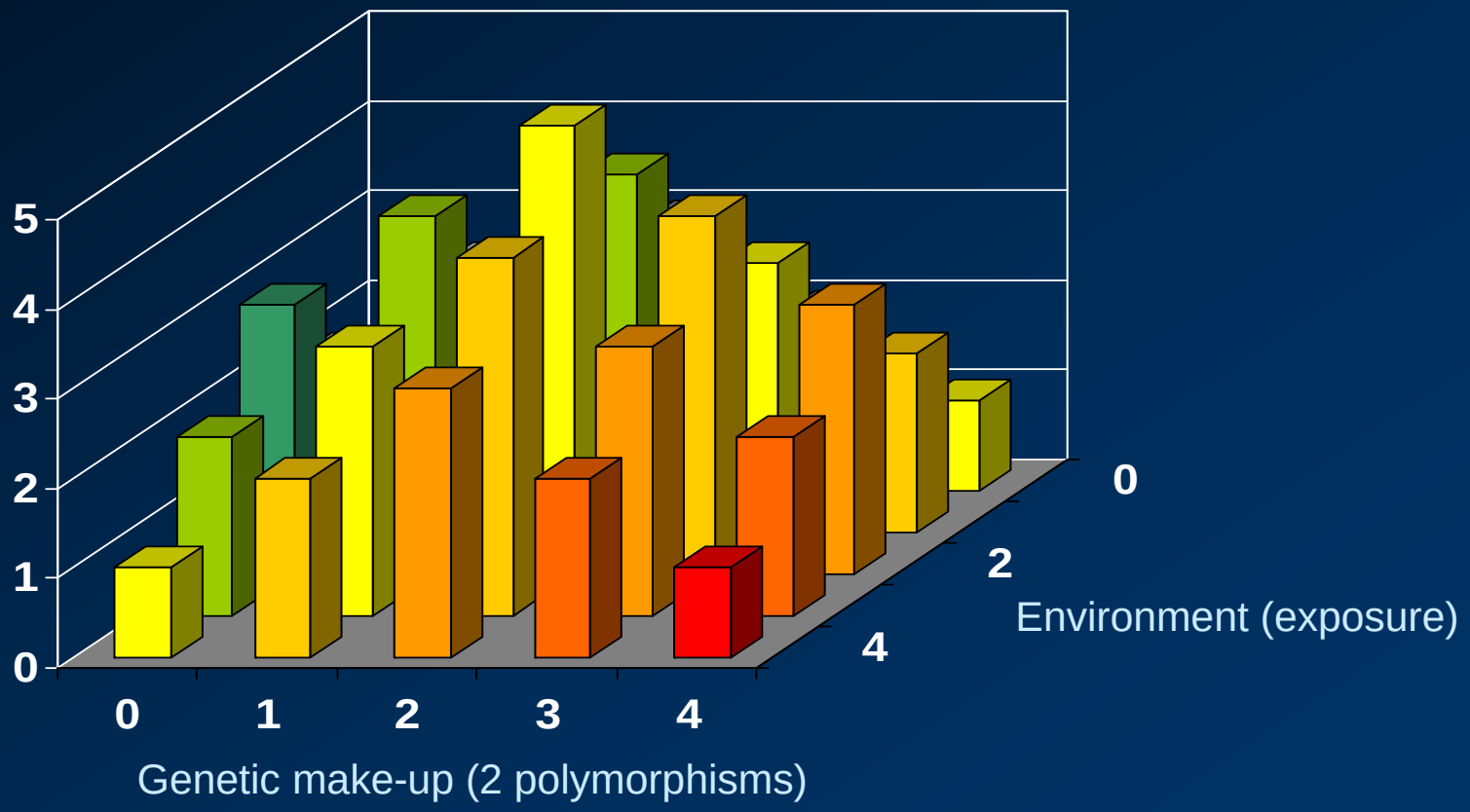
Monogenic vs. multifactorial diseases

Example: Alzheimer‘s disease and the Apo E4 allele

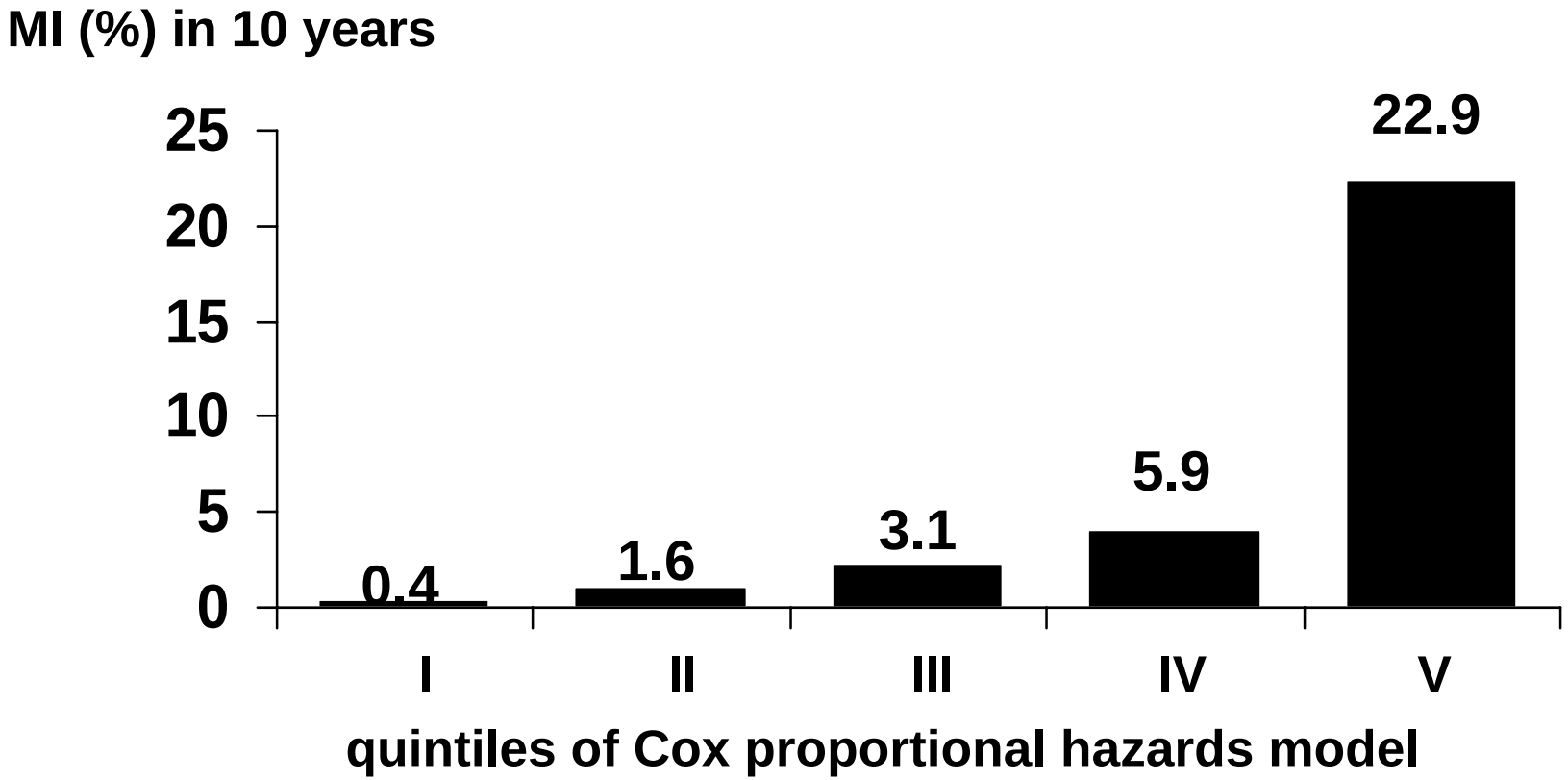


Genetic risk profiles in multifactorial disease

Combination of genetic and environmental effects



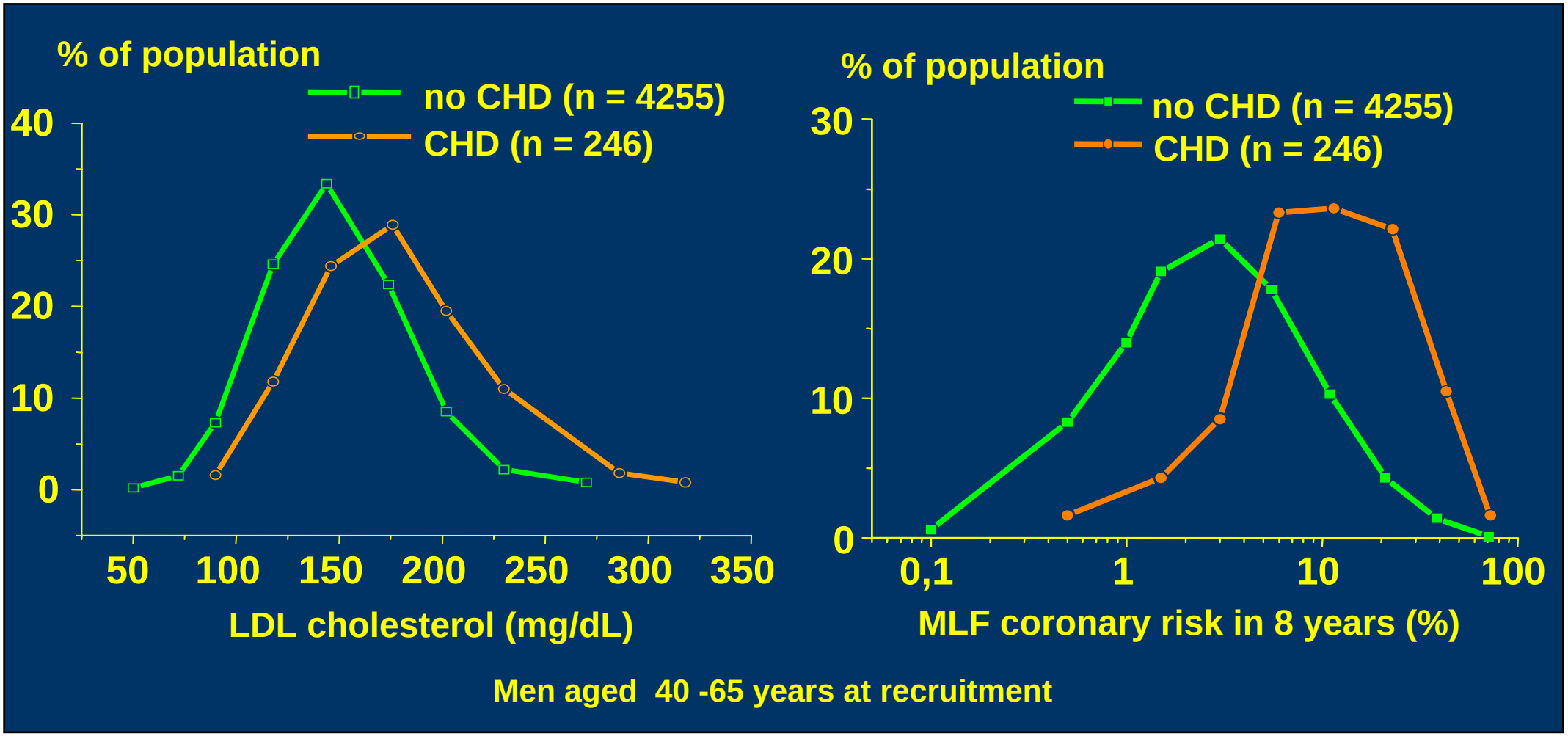
The PROCAM algorithm



Independent variables: age, systolic blood pressure, LDL-C, HDL-C, triglycerides, diabetes mellitus, smoking, positive family history of MI

406 fatal and non-fatal myocardial infarctions among 7,152 men aged between 35 and 65 years

Prediction of coronary risk in PROCAM



Genetic defects do not always cause disease

Defect	Disease	Probability in %
Mutation in the SPINK1 gene	chronic recurring pancreatitis	1-2
APOE4 carrier status	Alzheimer's disease	6-13
HFE gene	Haemochromatosis	10-50
BRCA1, BRCA2 mutations	Ovarian cancer	30-40
BRCA1, BRCA2 mutations	Breast cancer	40-80
Mutation in the retinoblastoma gene	Retinoblastoma	90
Mutation in huntingtin gene	Huntington's chorea	nearly 100

APOE: Apolipoprotein E, HFE: haemochromotosis gene; BRCA: Breast cancer; SPINK: Serine protease inhibitor, Kazal type 1. Source: Richtlinien zur prädiktiven genetischen Diagnostik. Deutsches Ärztebl 2003; Jg. 100, Heft 19, A1297-A1305.

Genetic defects may manifest at any age

Disease	First symptoms	Most common time of appearance
Cystic fibrosis	Meconium ileus	At birth
Phenylketonuria	Developmental delay	First year
Autosomal dominant polycystic kidney disease	Multiple renal cysts	Second decade
Huntington's chorea	Psychiatric disorder	Fourth or fifth decade
Alzheimer's disease	Loss of short-term memory	About sixth decade

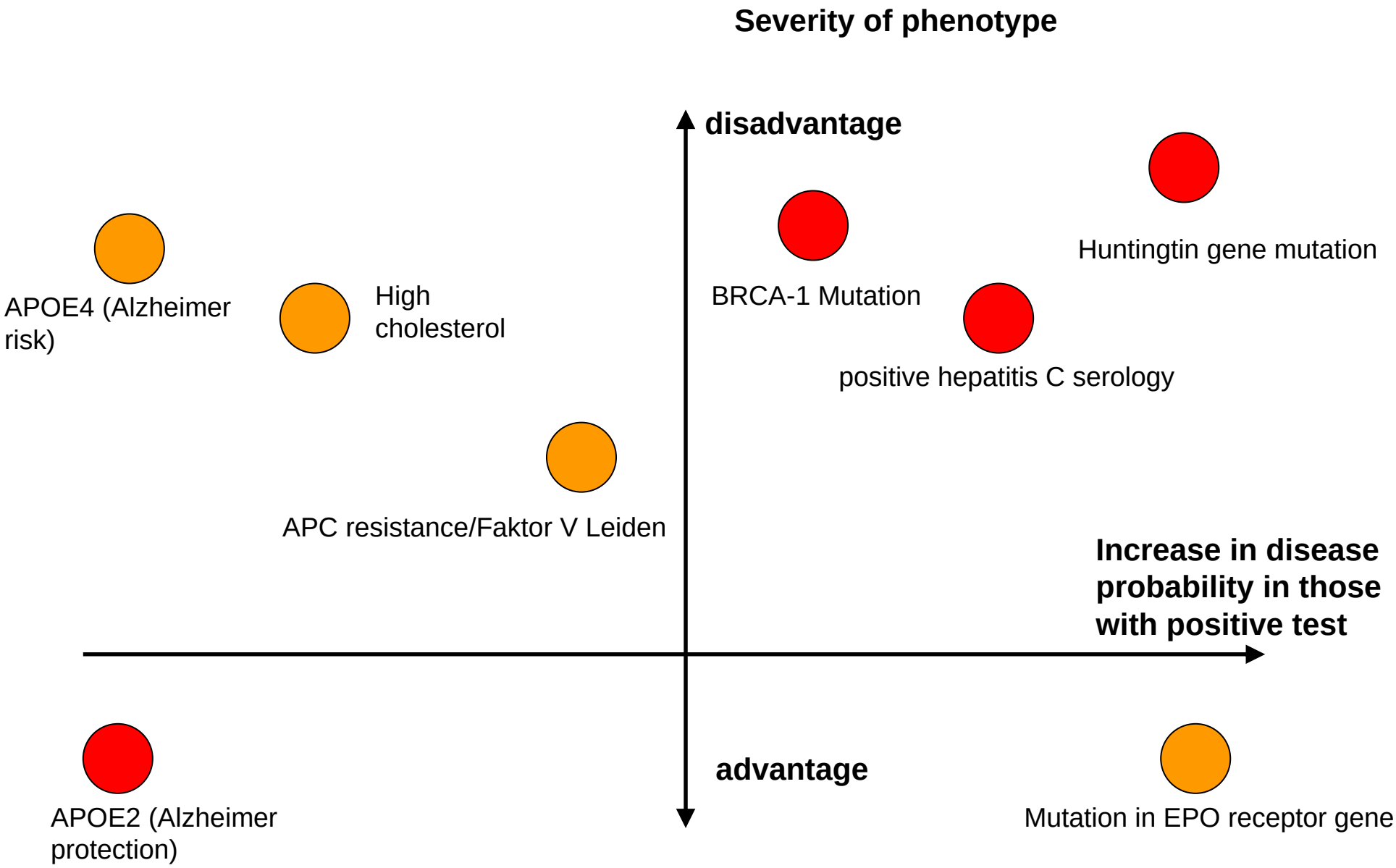
Source: Richtlinien zur prädiktiven genetischen Diagnostik. Deutsches Ärztebl 2003; Jg. 100, Heft 19, A1297-A1305.

Mutations may also confer advantages

Genetic feature	Effect
APOE2 carrier status	reduced risk of Alzheimer's disease
CCR5 delta32 allele	increased resistance to HIV infection
HbS allele	increased resistance to malaria
CFTR (ABCC7) mutations	increased resistance to cholera
Mutation in EPO receptor gene*	enhanced physical performance*

ABCC7: adenosine triphosphate binding cassette protein type C7; APOE: Apolipoprotein E, CCR5: chemokine C-C motf receptor 5, Hb: haemoglobin, CFTR: cystic fibrosis transmembrane conductance regulator. Source: Richtlinien zur prädiktiven genetischen Diagnostik. Deutsches Ärztebl 2003; Jg. 100, Heft 19, A1297-A1305.

Eero Mäntyranta, the Finnish long distance skiier and Olympic gold medallist, carries this mutation


Severity of phenotype
disadvantage
Huntingtin gene mutation
BRCA-1 Mutation
APOE4 (Alzheimer risk)
High cholesterol
positive hepatitis C serology
APC resistance/Faktor V Leiden
Increase in disease probability in those with positive test
advantage
APOE2 (Alzheimer protection)
Mutation in EPO receptor gene

Genetic exceptionalism

Derived from the concept of HIV exceptionalism, Murray in 1997 developed the concept of „genetic eceptionalism“. This concept assumes that genetic information is „special“ because it

- is invariable
- may predict future disease
- may lead to social exclusion or psychological fear
- may be used (misused) for purposes other than that for which it was originally generated, e.g. paternity or forensic testing
- has implications for third parties – usually family members

Source: Murray T, 1997, Genetic exceptionalism and „fuure diaries“: Is genetic information different from other medical information. In M. Rothstein (Ed.). *Genetic secrets: Protecting privacy and confidentiality in the genetic era (pp 60-73).* New Haven, Connecticut, Yale University Press

The argument for genetic exceptionalism

For*

- Genetic tests not only detect existing disease, but also predict future disorders
- Genetic tests provide only statistical probabilities and not certainty regarding the risk or severity of future disease
- Results of genetic testing are of relevance not only to tested person but to his or her relatives
- The results of genetic tests have maor implications for the patient in relation to inheritance of disease

Against

- True to an equal or even greater extent for many other tests such as the HIV test, the PROCAM score, hepatitis serology and many more
- Also true of many results such as heptatis C positivity and risk of developing chronic hepatitis
- Also true of many non-genetic tests. For example, the diangosis of myocardial infarction automatically signals increased risk of heart attack in the patient‘s children
- Many medical results have similar implications irrespective of the method used to generate them (clinical examination, imaging, biochemical testing)

*Position paper of the German Green Party August 2006

Monogenic diseases

1. About 4.000 monogenic diseases known
2. Criteria for testing* only exist for 50 to 100
3. This however covers about 90% of current tests

*Based on the 2005 model project ACCE (Analytical validity, Clinical validity, Clinical utility and Ethical, legal and social implications) of the US Centres of Disease Control. Source: Schmidkte J. Auf dem Prüfstand der Genetiker. Dt. Ärztebl. 2008; Jg. 105, Heft 36, A1830-A1834.

The German Genetic Diagnostics Law

"The purpose of this law is to specify the conditions under which genetic testing and genetic analyses performed as part of genetic testing may be performed and to regulate the use of genetic samples and data. Its aim is to prevent discrimination on the basis of genetic characteristics in fulfilment of the duty of the state to protect human dignity and the right to information autonomy."

*Passed first reading by the German Cabinet on August 27, 2008.

The German Genetic Diagnostics Law

“A predictive genetic test is one that aims to investigate

a) a future disease or disorder of health

b) presence of a genetic carrier status for a disease or disorder of health of offspring”,

while “genetic analysis” refers to

a) analysis of the number or structure of chromosomes

b) analysis of the molecular structure of DNA or RNA

c) protein chemical analysis of the direct products of the nucleic acids.

*Passed first reading by the German Cabinet on August 27, 2008.

Law to Regulate Use of Medical Information

„It is not useful to limit legal regulations to genetic tests while treating in a different fashion the basic requirements of all other forms of laboratory testing.

Thus, there is a need for a Diagnostics Law or a Law to Regulate the Use of Medical Information rather than a pure Genetic Diagnostics Law.“

Kiehntopf M, Deufel T, Pagel C. Gendiagnostikgesetz – Zweifel am Konzept. Dt. Ärztebl. 2008, Jg. 105, Heft 15: A776-A777

The future of genetic testing

1. Genetic testing is becoming routine and will become more widespread in coming years
2. Several companies offering whole-genome screening (e.g. 24andMe)
3. $500 genome will be available within next few years
4. Many countries are planning or have implemented legislation to regulate genetic testing

Genetic testing and disease prediction

1. The type information provided by genetic tests is not fundamentally different from that provided by other forms of predictive testing: there is nothing “special” about genetic tests
2. Knowledge of genetic variation will become an important component of calculating risk
3. Genetic information alone only sufficient for prediction of rare monogenic disorders
4. For most diseases, genetic information must be combined with biochemical and lifestyle information to predict risk

Genetic testing and insurance medicine

1. Genetic testing can be incorporated with biochemical and lifestyle data to define categories of risk
2. With increased availability of genetic testing, more and more clients will possess potentially relevant genetic information prior to taking out insurance
3. There is no fundamental difference between genetic information and other forms of medical information (history, physical examination, lifestyle factors, biochemical tests) in terms of risk prediction