The 5th Science Council of Asia (SCA) Conference (Hanoi, Vietnam, 2005)
Symposium II: Bioscience for Health
Invited Lecture 2 (May 12, 14:45-15:15)

Healthcare in the Era of Genomic Medicine

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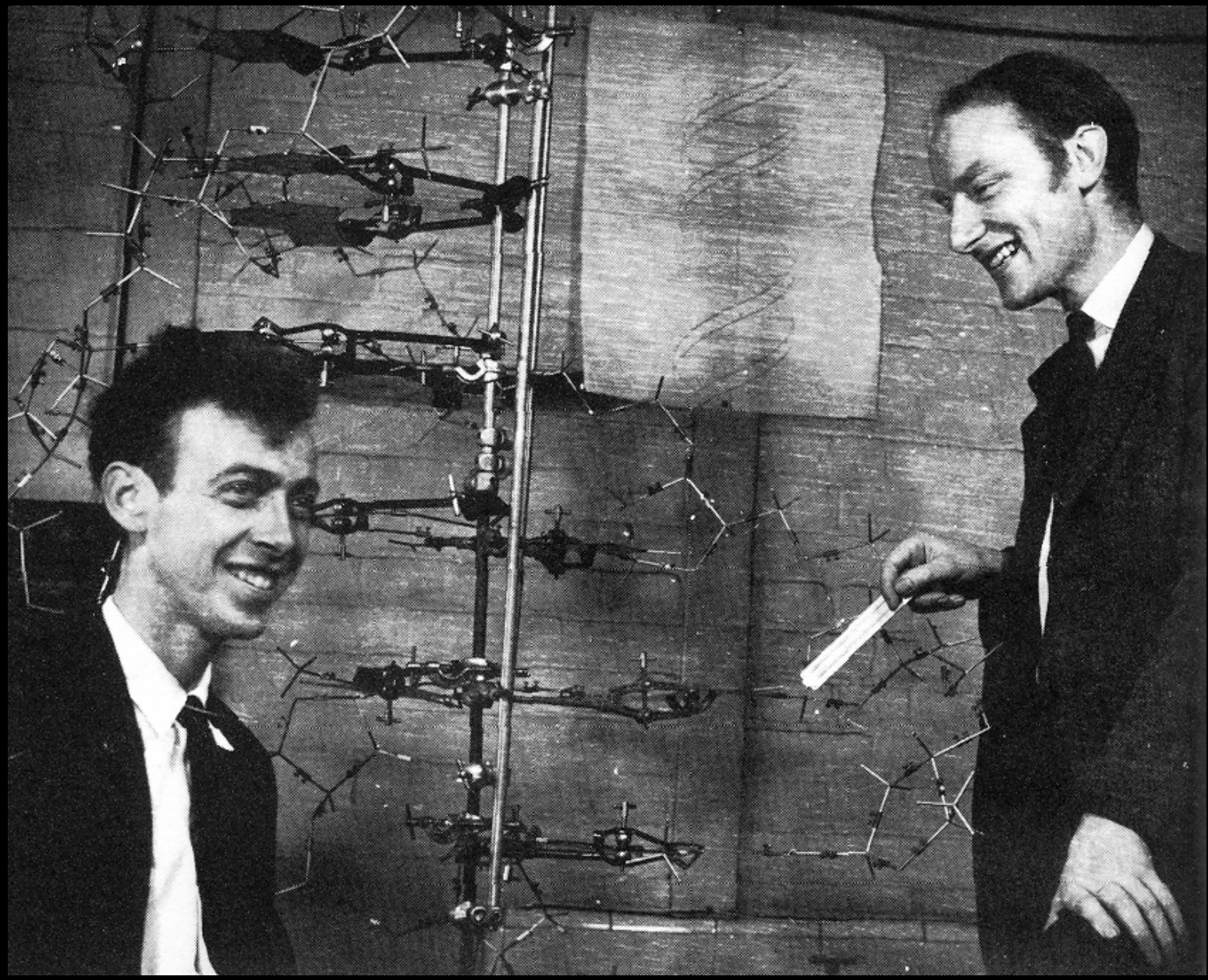
Human Genome Project

Watson & Crick, May 1953

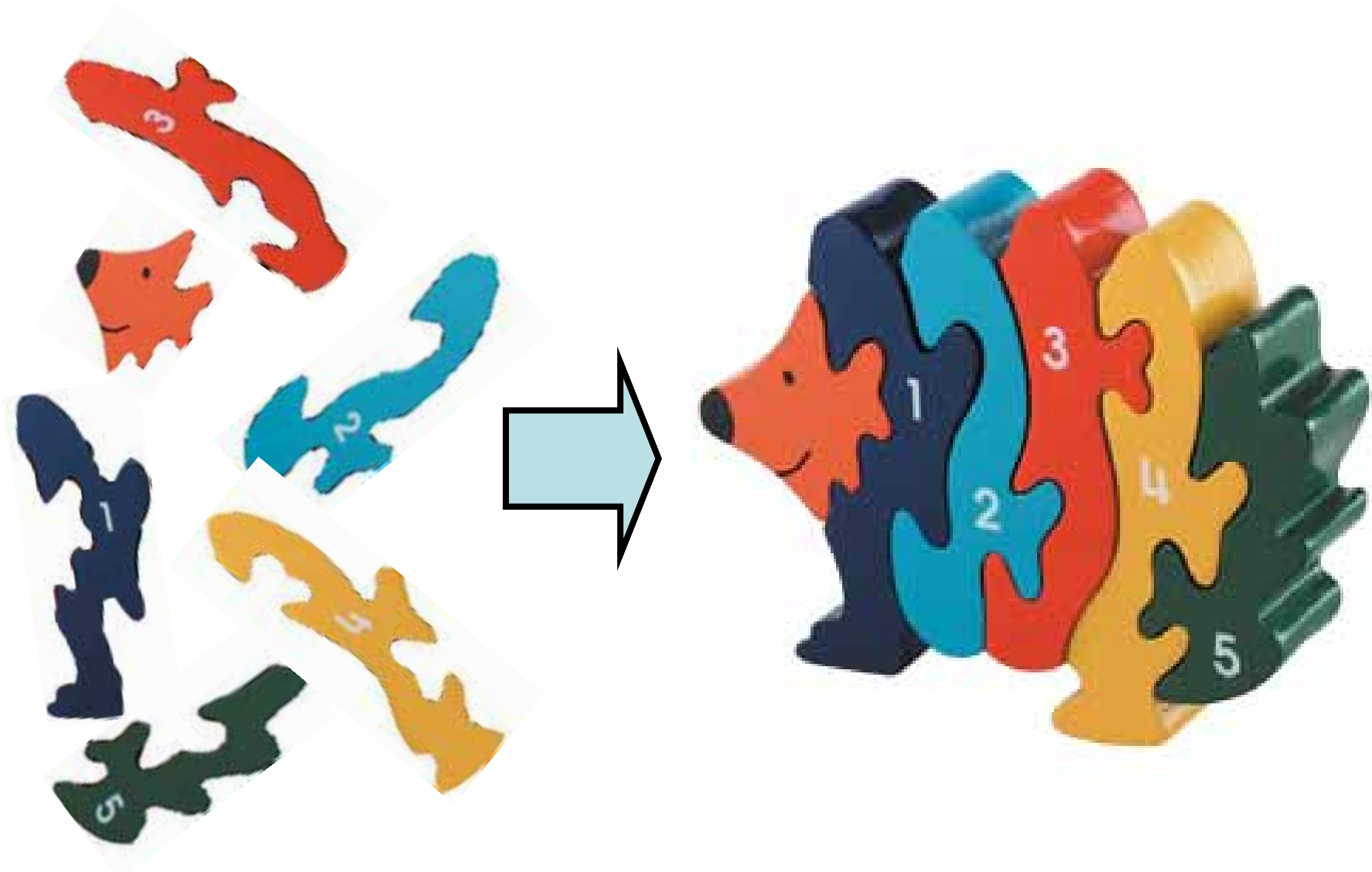



ヒトゲノムとは？

Human Genome Project

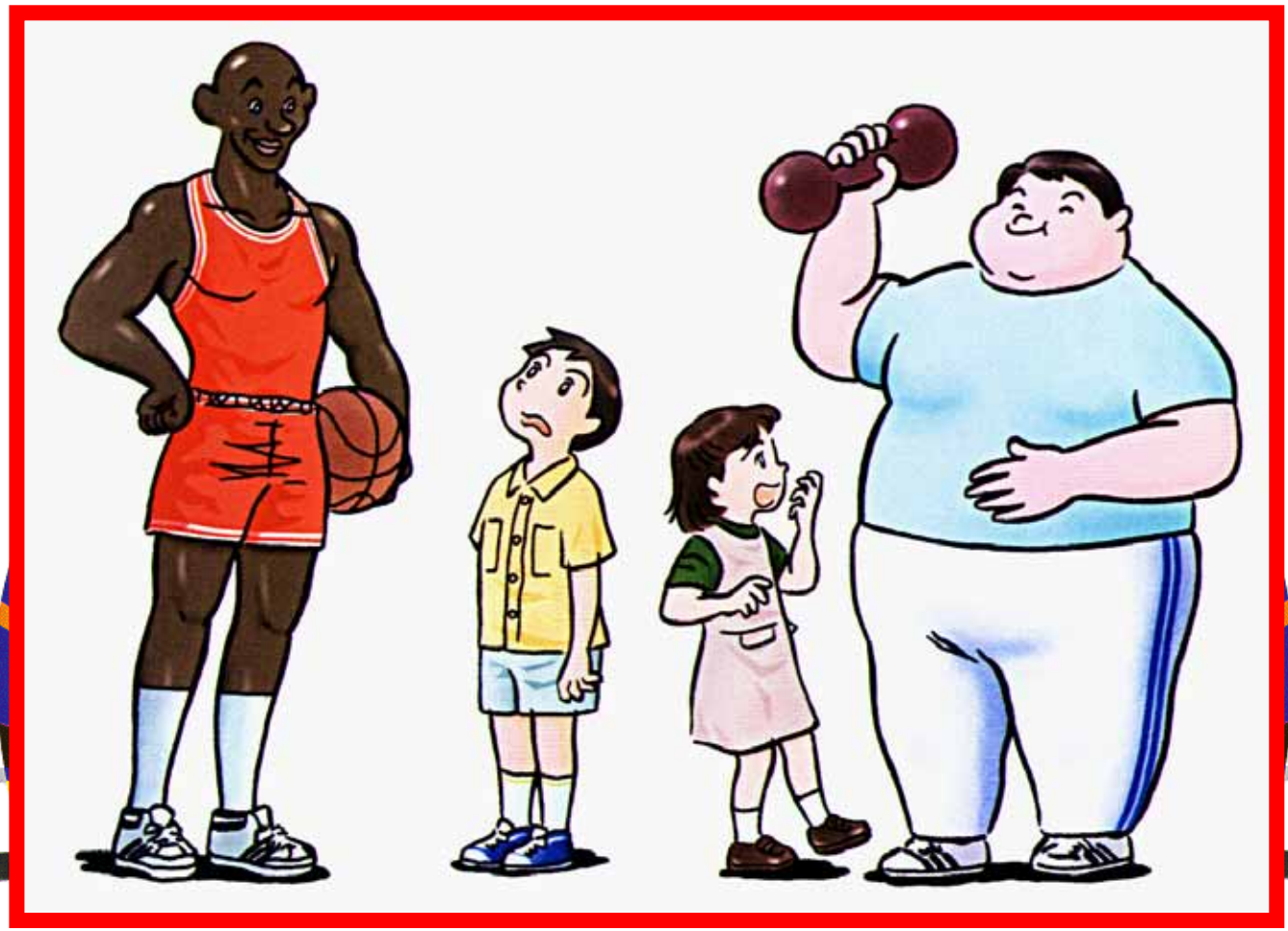
- identify all genes (~30,000) in human DNA
- determine the sequences of the 3 billion base pairs that make up human DNA
- store this information in databases
- use genomic information for ***Genome Science*** and ***Genomic Medicine***
- address the ethical, legal, and social issues (ELSI) that may arise from the project

Human Genome Project has generated complete parts list of human body



Genetic Variation

Single Nucleotide Polymorphism (SNP)

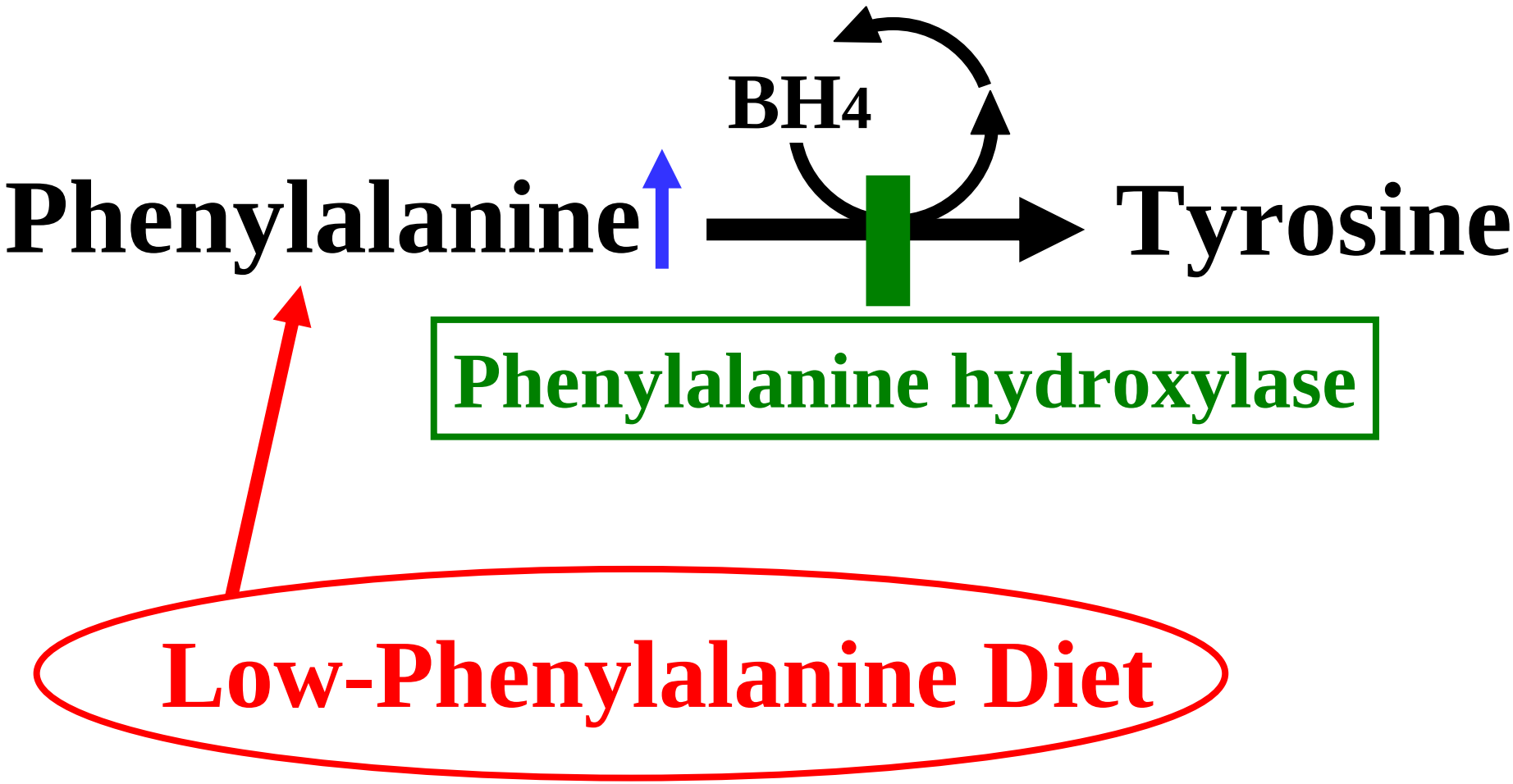


1 in 1,000 nucleotides between individuals

Anticipated Benefits of Genome Research on Healthcare

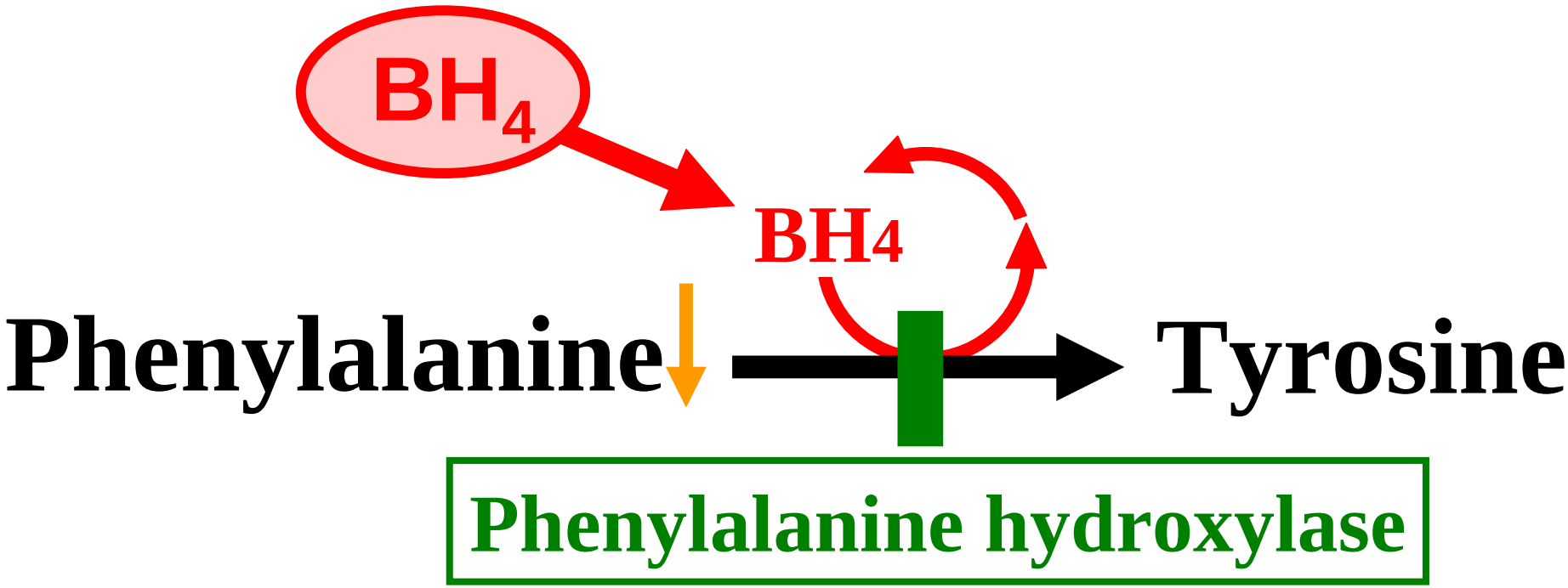
- **improve diagnosis and treatment of disease**
  - ***Mendelian disorders***
- **detect genetic predispositions to disease**
  - ***Common diseases***
- **design custom drugs based on individual genetic profiles**
  - ***pharmacogenomics***
- **use gene therapy and control systems as drugs**

Phenylketonuria (PKU)



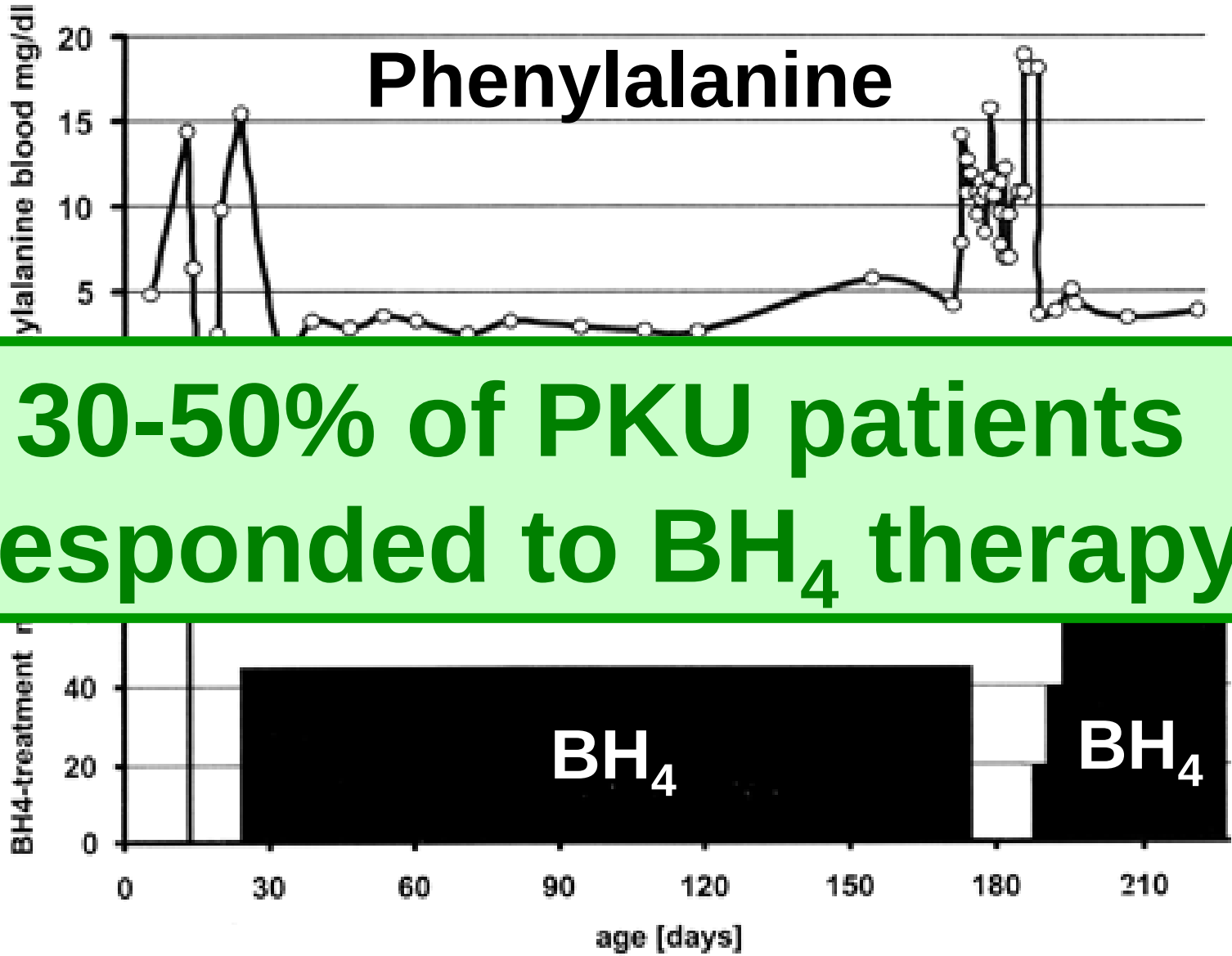
Low-Phenylalanine Diet

Phenylketonuria (PKU)



BH_4-responsive phenylalanine hydroxylase deficiency

(Kure S, et al. J Pediatr. 135:375-8, 1999)



30-50% of PKU patients responded to BH_4 therapy

(Trefz & Blau, Pediatrics 112:1566-9, 2003)

Anticipated Benefits of Genome Research on Healthcare

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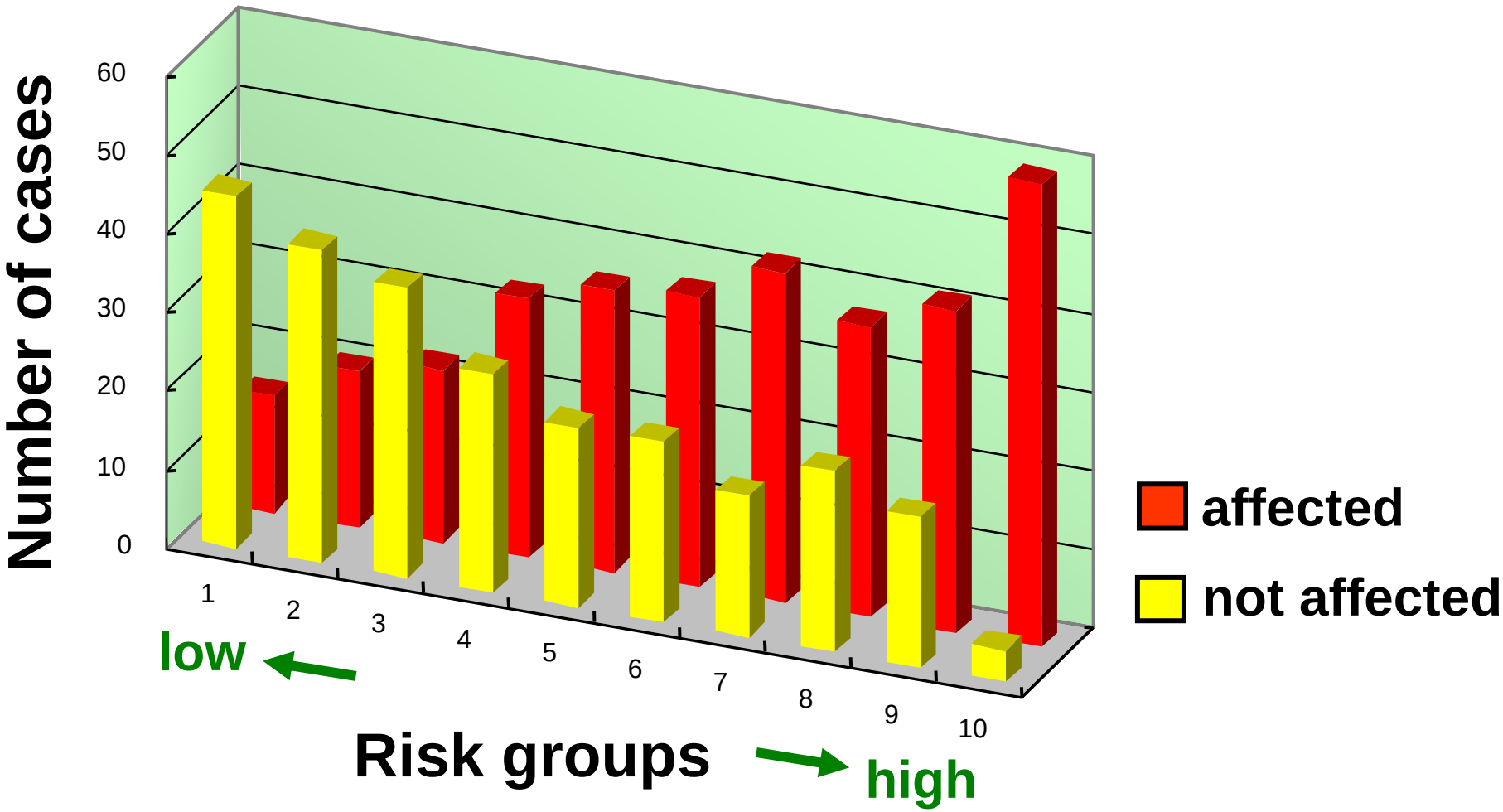
Genes associated with bronchial asthma in Japanese population

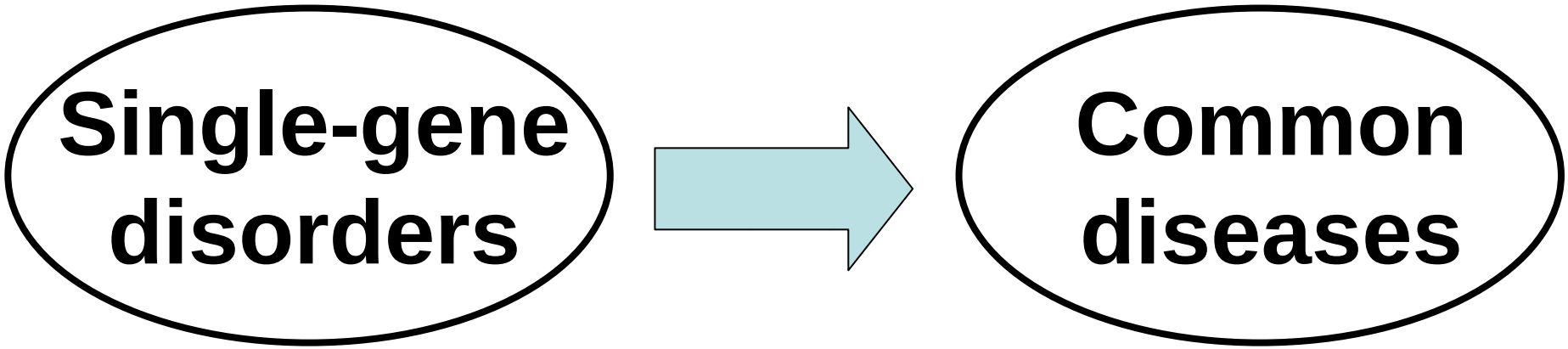
Gene		Locus
IL1RN	Interleukin-1 receptor antagonist protein	2q14
CTLA4	Cytotoxic T-lymphocyte protein 4	2q33
PGDS	Prostaglandin-H2 D-isomerase	4q21-22
IRF1	Interferon regulatory factor 1	5q31
IL4	Interleukin-4	5q31
IL13	Interleukin-13	5q31
UGRP1	Uteroglobin-related protein 1	5q31-34
IL12B	Interleukin-12B	5q31-33
ADRB2	Adrenergic receptor, beta 2	5q32-34
LTC4S	Leukotriene C4 synthetase	5q35
TNF	Tumor necrosis factor alpha	6p21
PAFAH	Platelet activating factor acetylhydrolase	6p21
EOTAXIN1	Eotaxin-1	7q11
C5	Complement 5	9q33
IKAP	IKK complex-associated protein	9q34
FCER1B	High affinity IgE receptor beta chain	11q13
AICDA	Activation induced cytidine deaminase	12p13
C3AR1	Complement 3a receptor	12p13
STAT6	Signal transducer and activator of transcription 6	12q13
IFNG	Interferon-gamma	12q21
NOS1	Nitric oxide synthetase 1	12q24
FLAP	Five-lipoxygenase activating protein	13q12
CYSLTR2	Cysteinyl leukotriene receptor 2	13q14
IL4RA	Interleukin-4 receptor alpha	16p12
NOS2A	Nitric oxide synthetase 2	17cen-q11
RANTES	Regulated upon activation, and normal T-cell expressed and presumably secreted	17q11-q12
TBX21	T-box 21	17q21
TBXA2R	Thromboxane A2 receptor	19p13
C3	Complement 3	19p13
C5R1	Complement 5a receptor	19q13

Prediction of risk for childhood asthma using logistic regression analysis

(Japanese children)



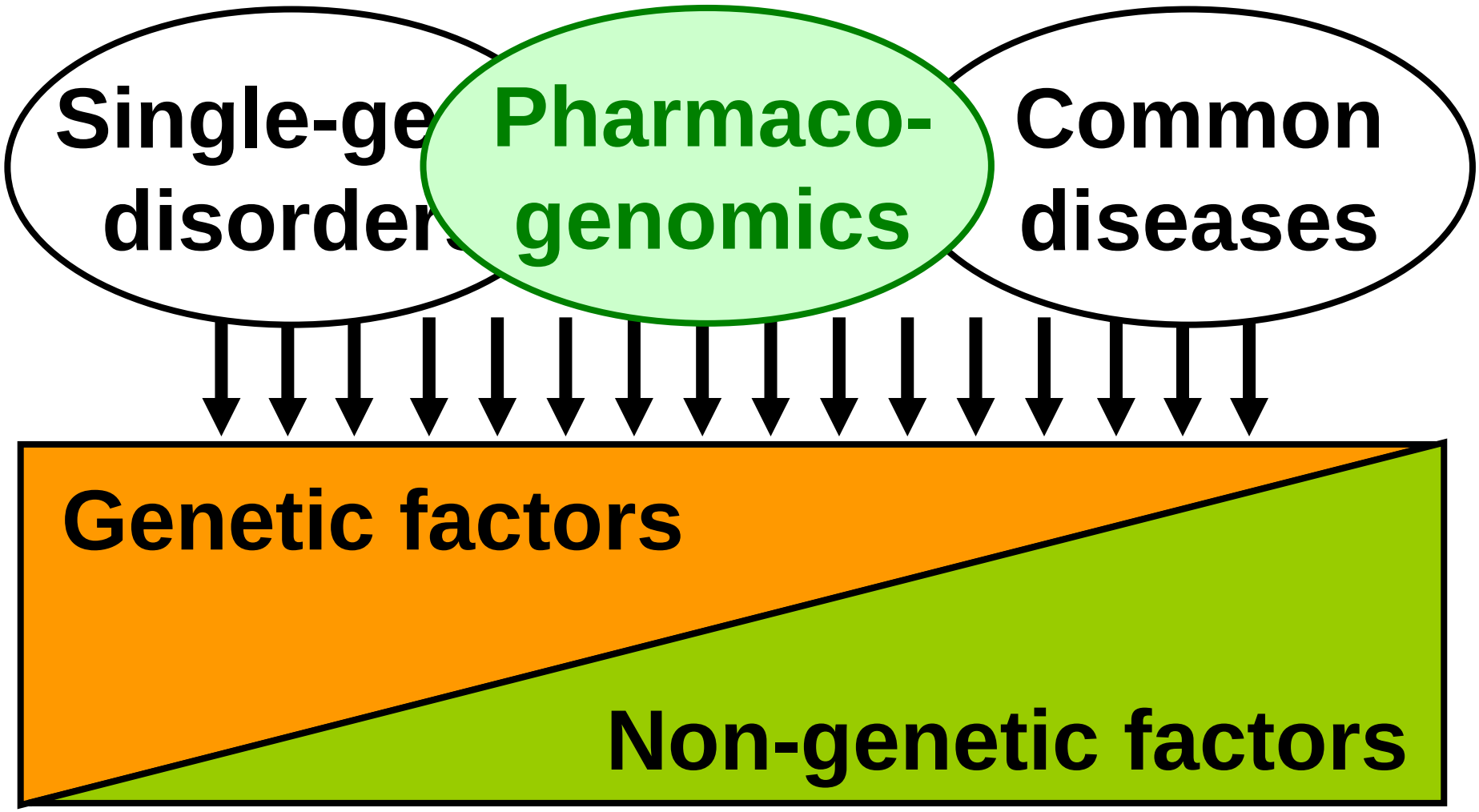
Paradigm shift ?



Phenylketonuria
Thalassemia
Gaucher disease
Muscular dystrophy
Hemophilia

Asthma
Diabetes mellitus
Hypertension
Rheumatoid arthritis

Single-gene and common diseases represent points on a continuum

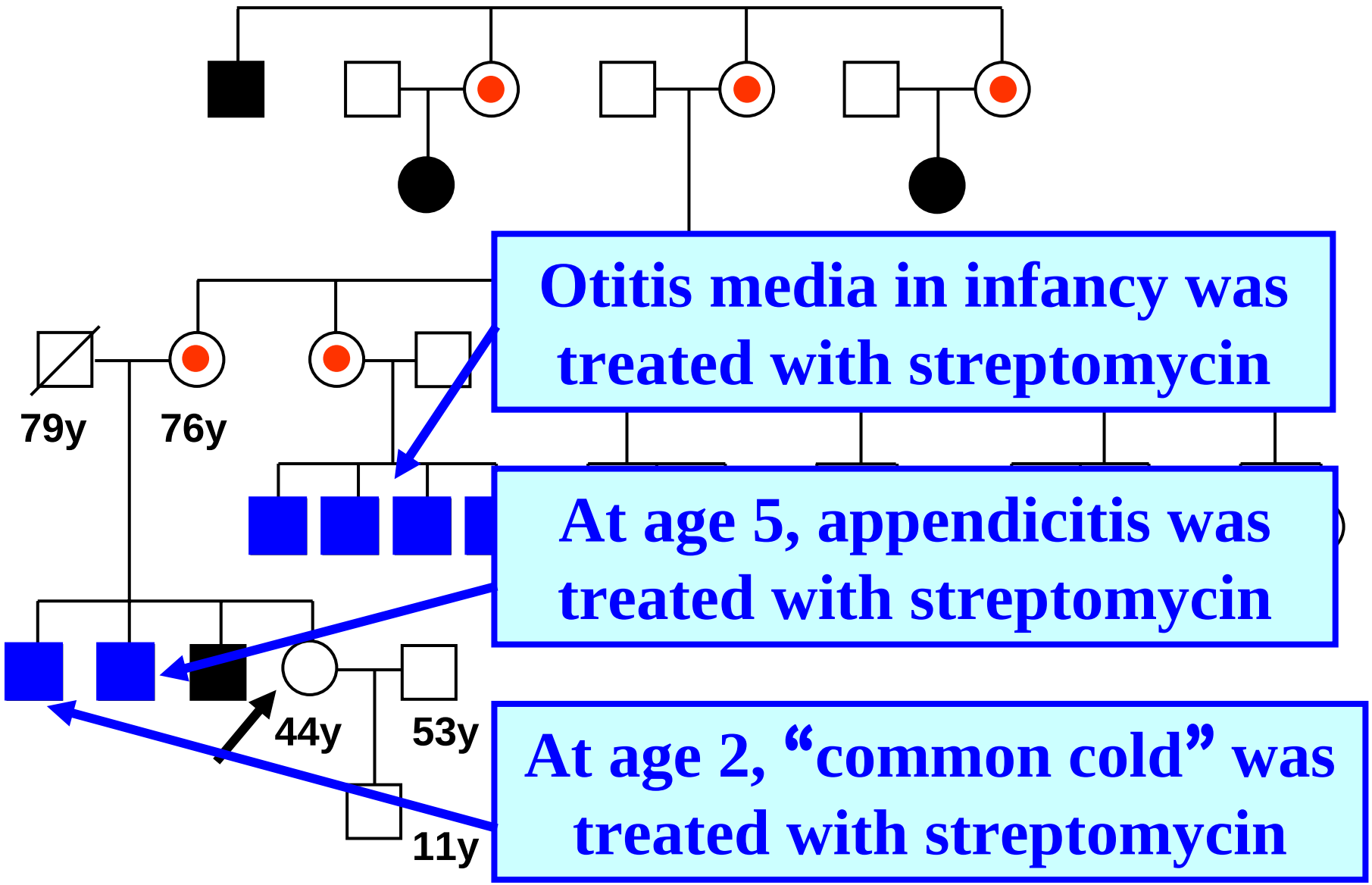


What is Pharmacogenetics? (Pharmacogenomics)

The use of genetic analysis to predict drug response

- **Efficacy**: how well a medicine works in a patient
- **Safety**: whether there are any adverse side effects

A pedigree of deafness



Aminoglycoside antibiotics* cause hearing loss to individuals with a mitochondrial 1555A>G mutation

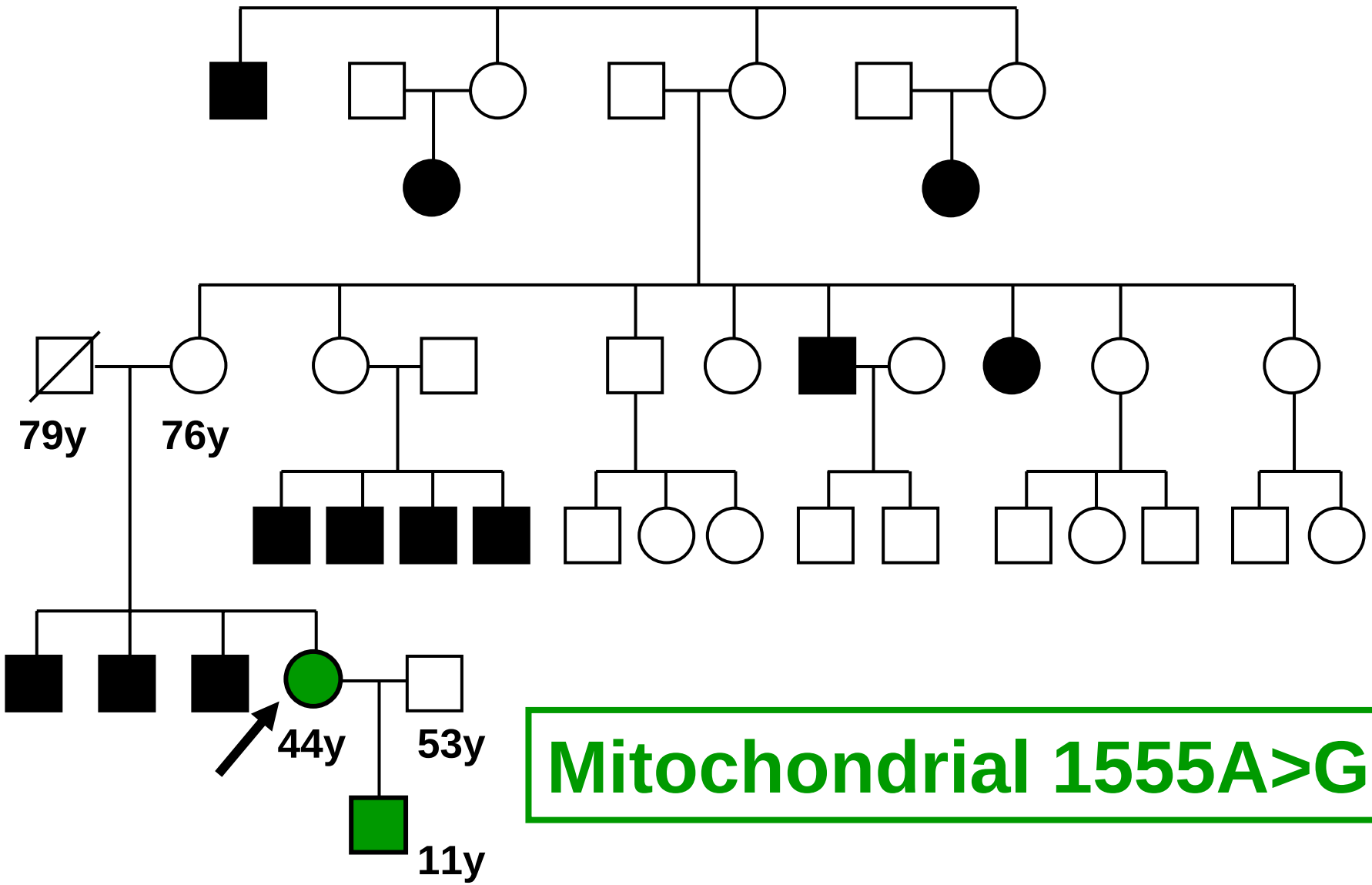
(*Nature Genetics 4:289-94, 1993*)

*Streptomycin, Gentamicin, Amikacin, Tobramycin etc.

Aminogycoside antibiotics are widely used to treat serious bacteral infection

They are commonly prescribed for newborns (such as gentamicin) to treat bacterial infections

A pedigree of deafness



Mitochondrial 1555A>G

薬　剤　カ　ー　ド

お 名 前　　○　○　○　○　殿

生年月日　　年　月　日

この方は、アミノグリコシド系抗生物質 の
投与により難聴をきたす可能性が高いため、診療時の
ご配慮をお願い致します。

東北大学病院遺伝科(TEL:022-717-8140)

（診察時、このカードを医師にお見せ下さい）

Medical Alert

Name: _____

Birth Date: _____

Do NOT administer aminoglycoside antibiotics to this person.
It would cause irreversible hearing loss.

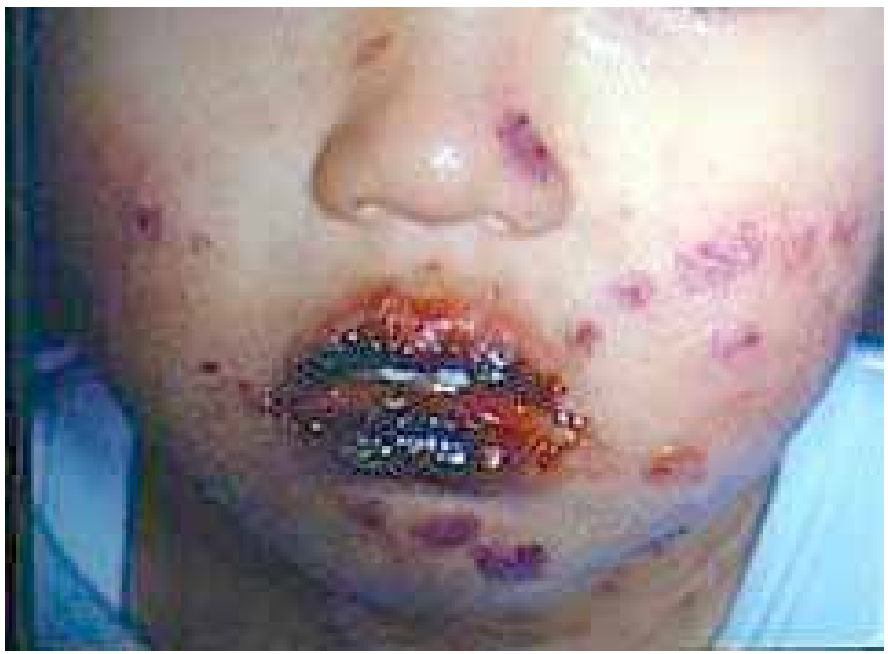
Department of Medical Genetics
Tohoku University School of Medicine
Sendai, Japan
(TEL: +81-22-717-8140)

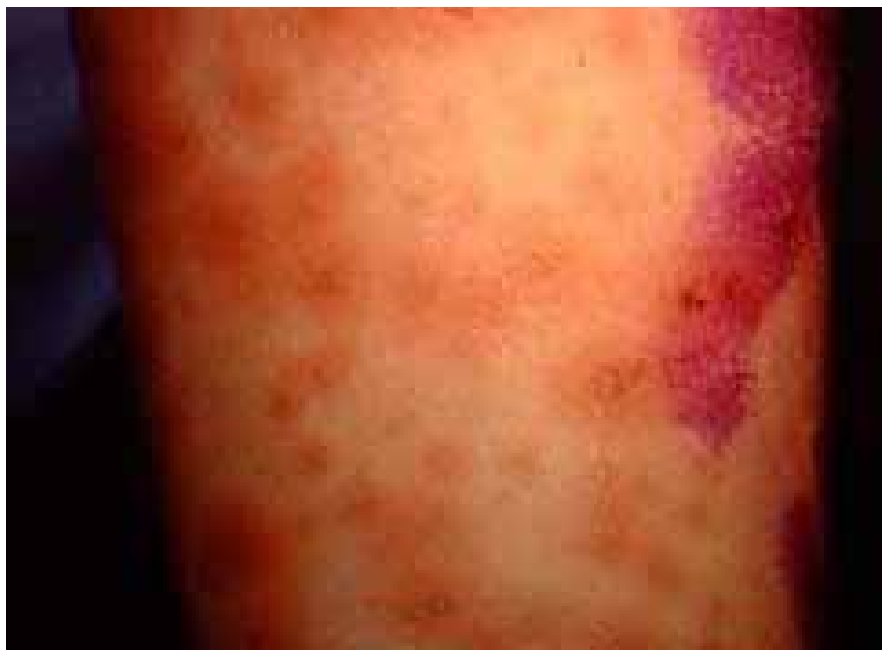
Aminoglycoside antibiotics

- Amikacin
- Gentamicin
- Kanamycin
- Neomycin
- Netilmicin
- Streptomycin
- Tobramycin

Stevens-Johnson syndrome

- **Life-threatening reactions of the skin to particular types of medication**





Genetic marker for Stevens-Johnson syndrome caused by carbamazepine (CBZ)

HLA-B*1502 allele was detected in:

- **100% of CBZ-SJS individuals**
- **3% of CBZ-tolerant individuals**
- **8.6% of normal individuals**

(Han Chinese)

(Chung et al. Nature 428:486, 2004)

One drug fits all

↓

Personalized medication

U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Guidance for Industry

Pharmacogenomic Data Submissions

DRAFT GUIDANCE

November 2003
Procedural

Nature Medicine
6:487, 2000

“Here’s my sequence …”

How do we detect pharmacogenomic SNPs?

Requirements for Point-of-Care Genetic Testing

- **Simple**
  - **Readily performed by non-expert**
- **Rapid**
  - **Genotyping on the spot**
- **Inexpensive**
  - **No expensive instrumentation**
- **Reliable**
  - **No errors allowed**

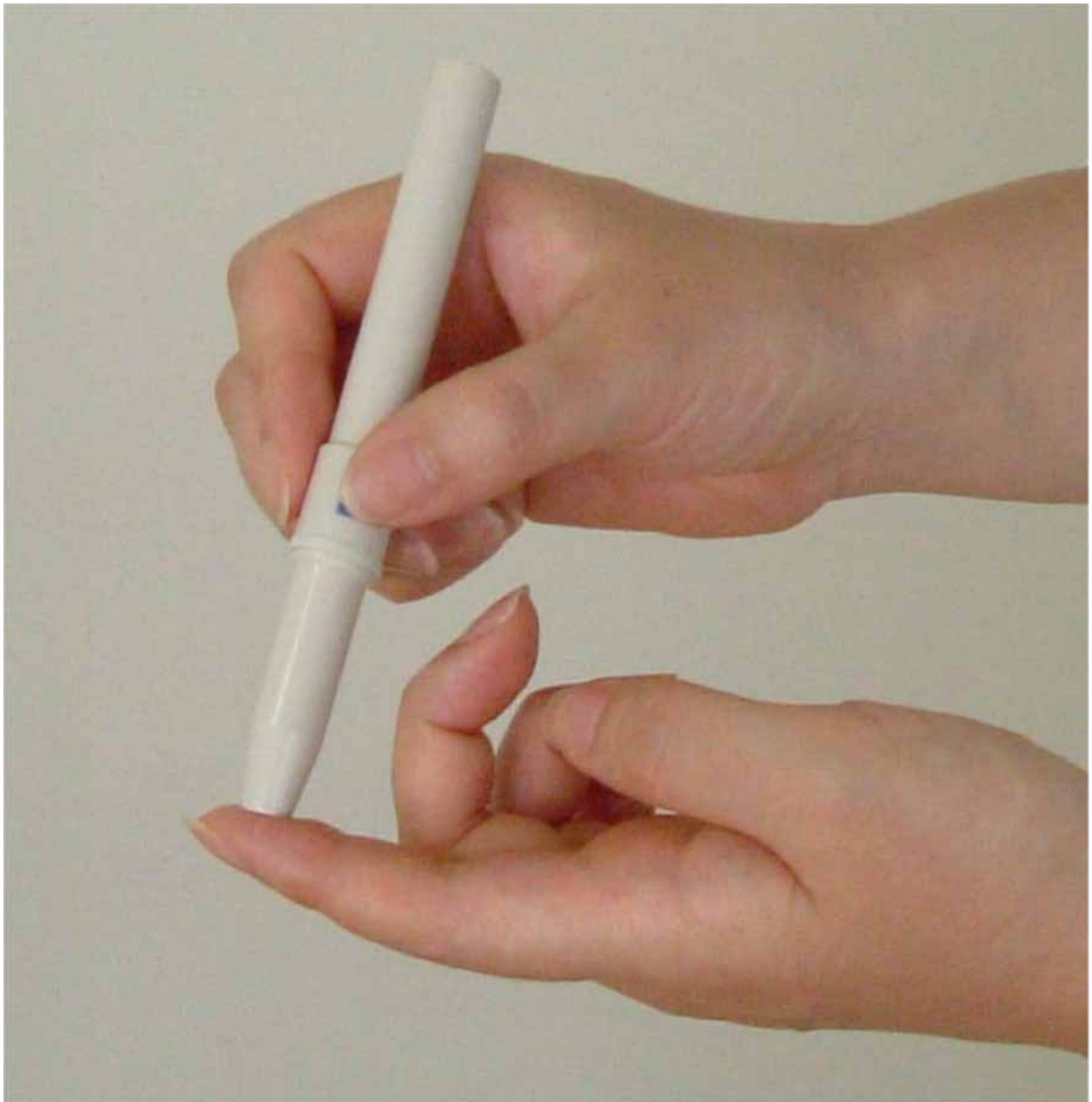
CASSOH

Competitive
Allele-**S**pecific
Short
Oligonucleotide
Hybridization

(*Human Mutation*, 22:166-172, 2003)

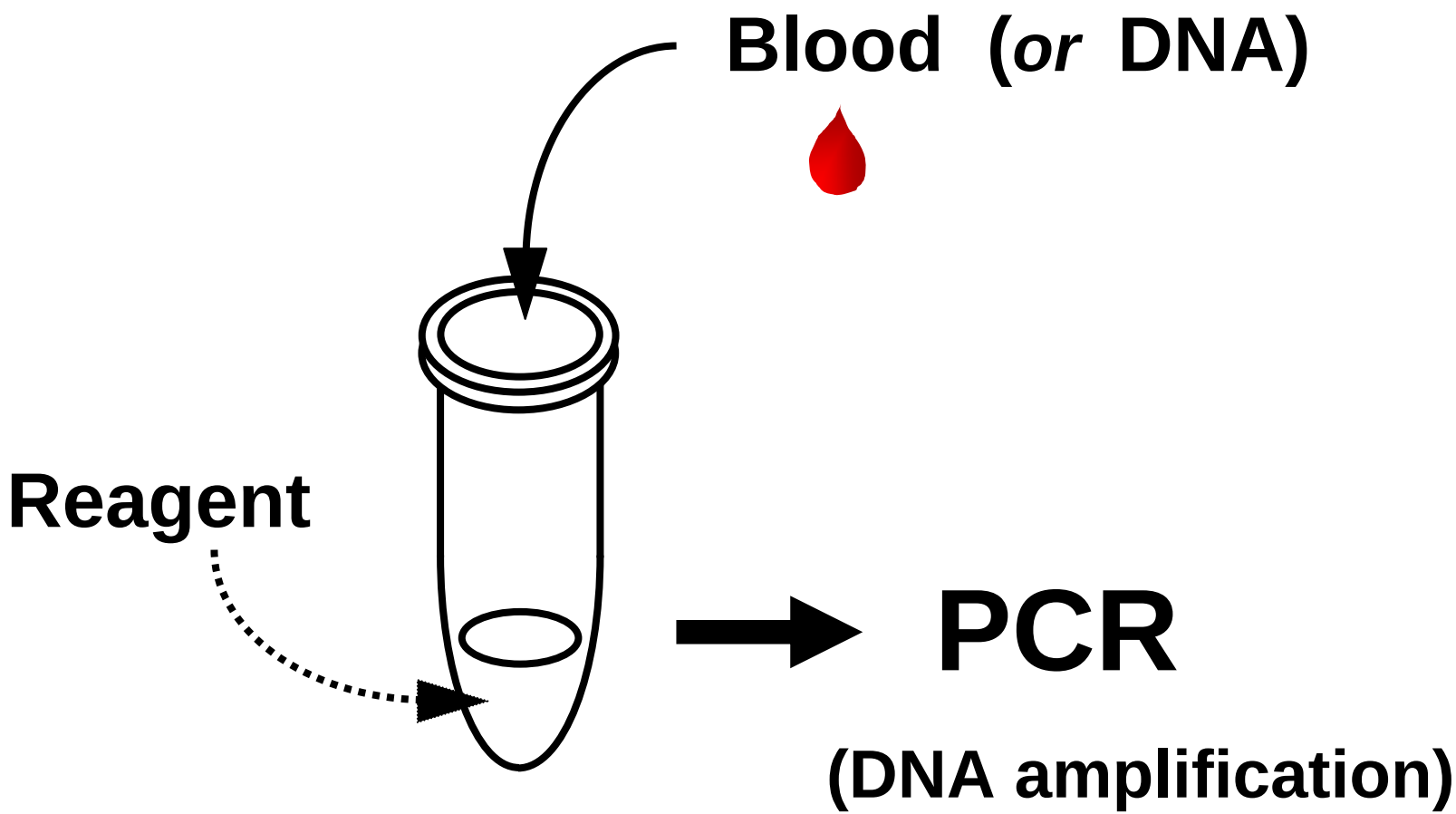
CASSOH

Step 1



CASSOH

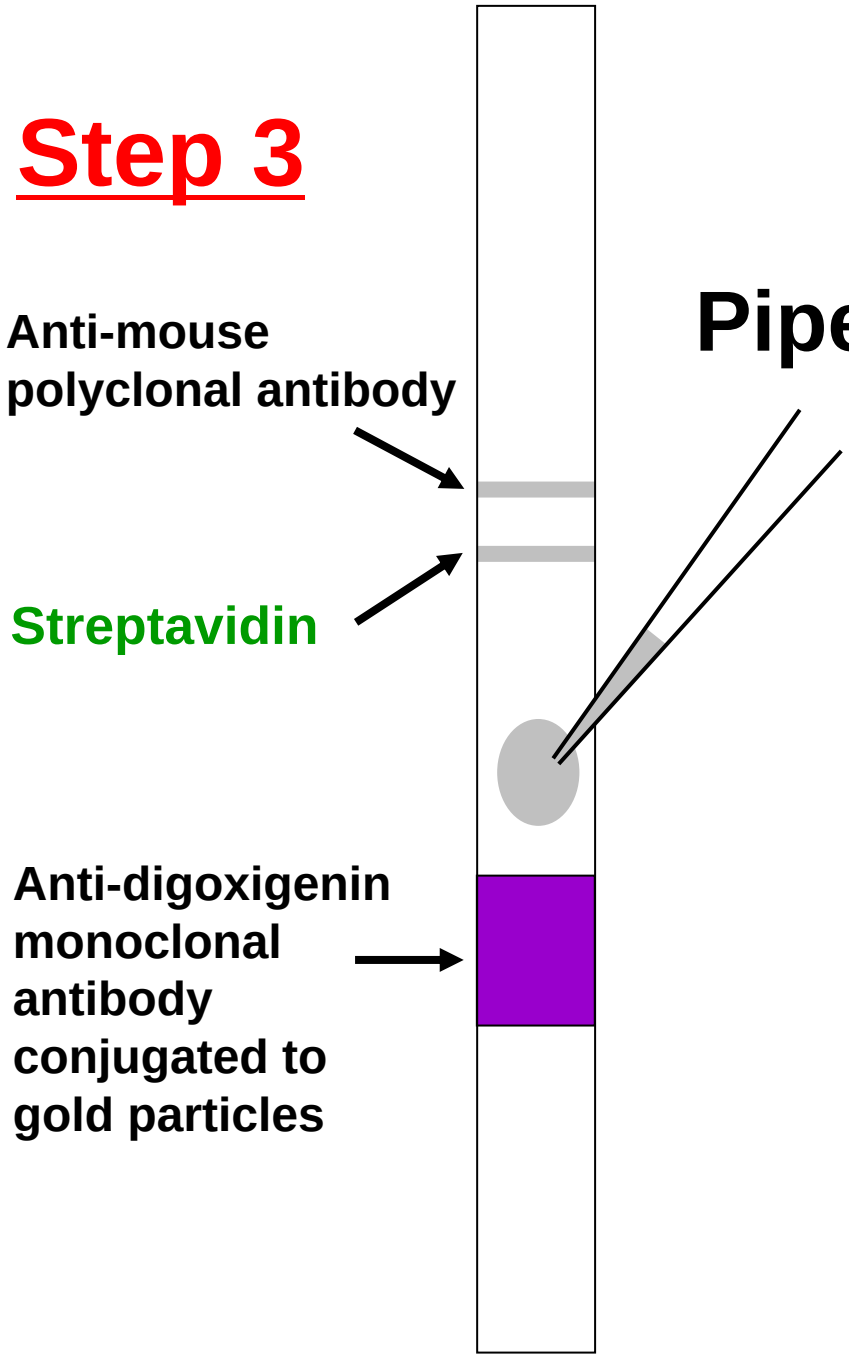
Step 2



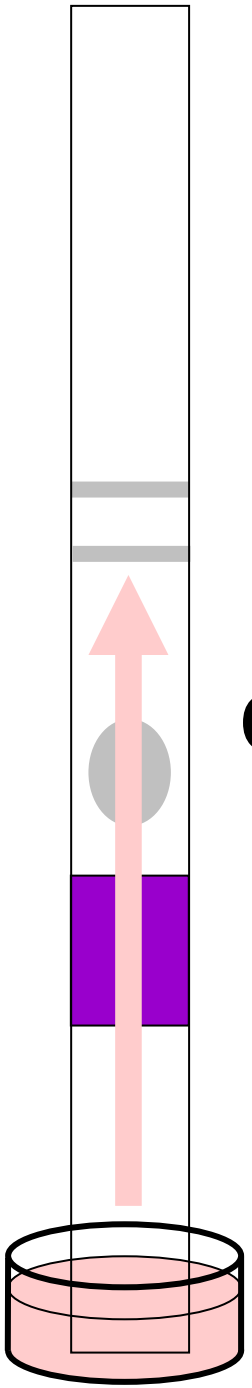
CASSOH

Step 3

Pipette 5 µl of PCR product

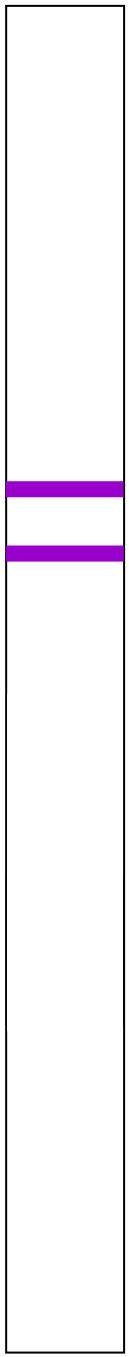


CASSOH



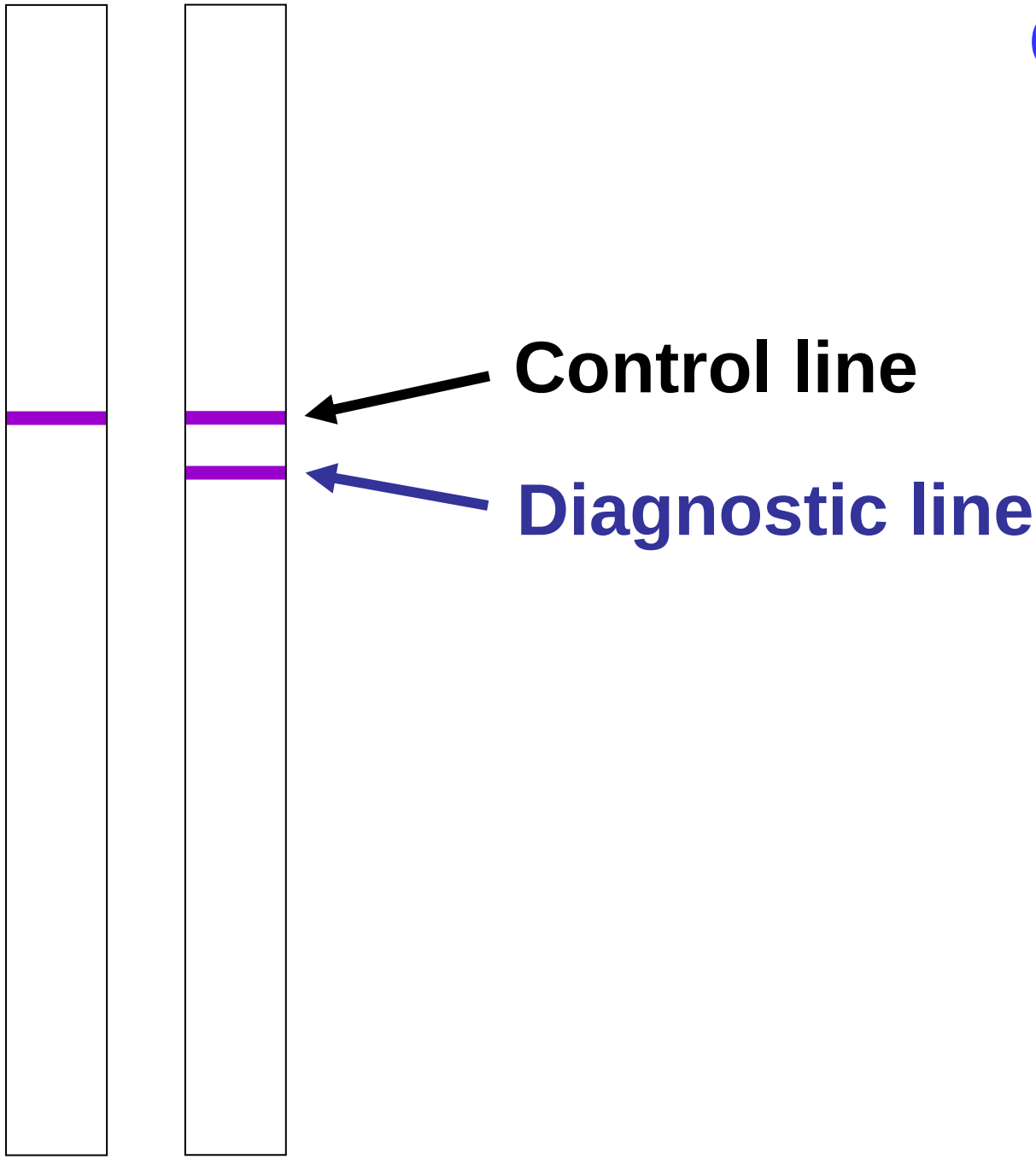
Chromatography

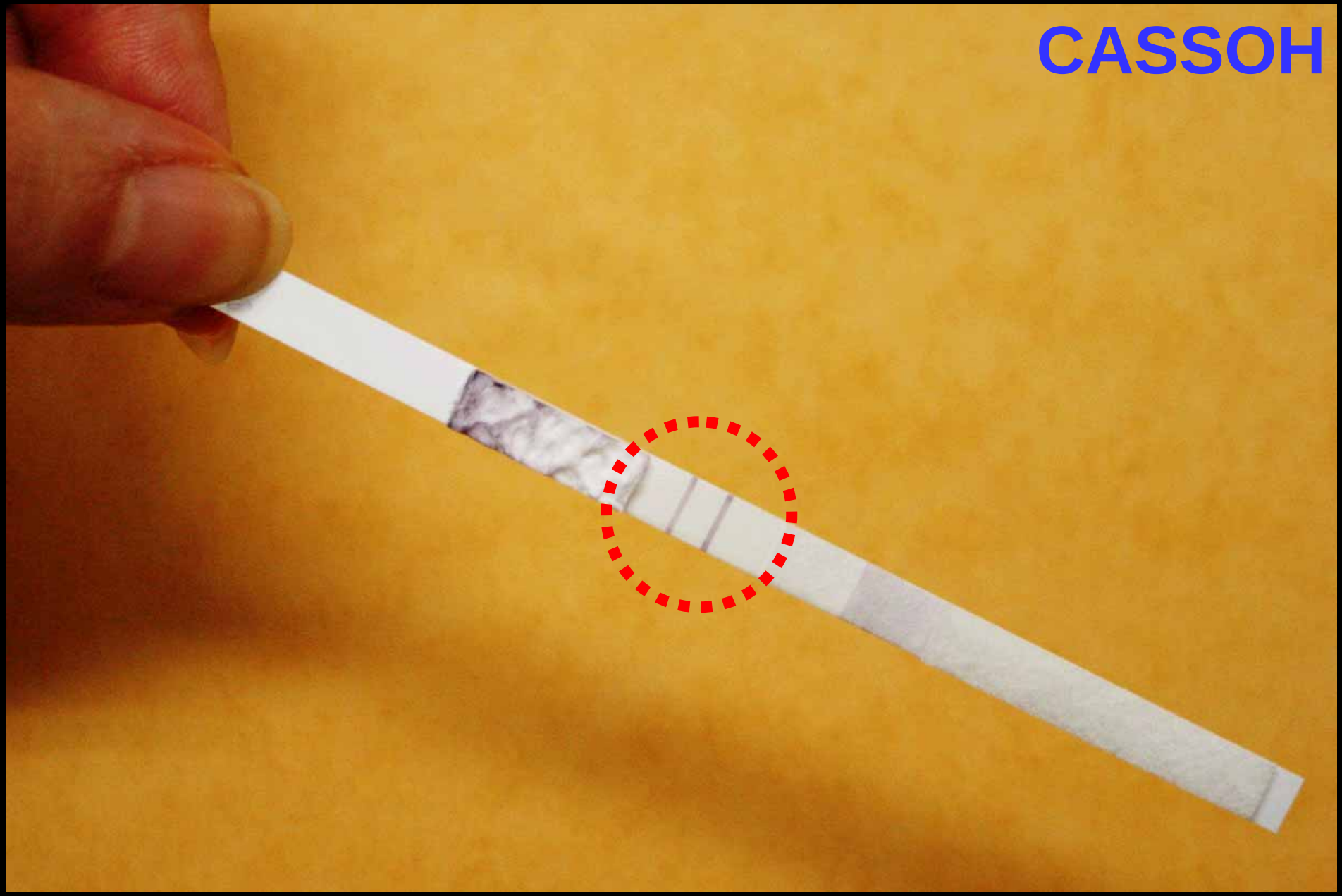
CASSOH

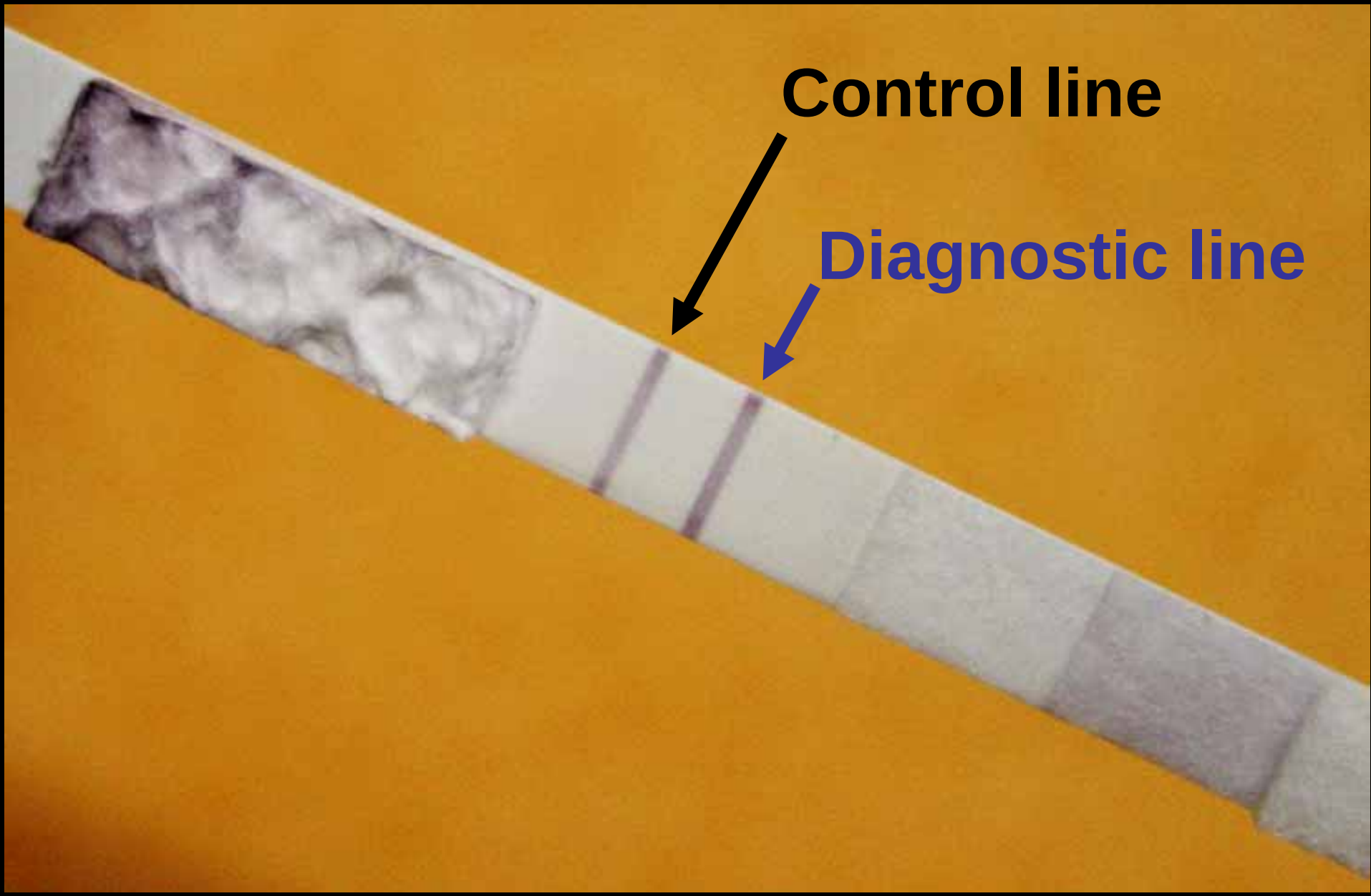


Stand at room temp. for 5 min.

CASSOH




CASSOH


Control line
Diagnostic line

Application of CASSOH to pharmacogenetic SNPs

Gene	SNP	Phenotype
ALDH2	1459G>A	Alcohol intolerance
CYP2C19	681G>A	Poor metabolizer of omeprazole, diazepam
NAT2	341T>C	Poor metabolizer of isoniazid (INH)
NAT2	590G>A	
NAT2	857G>A	
TPMT	719A>G	Poor metabolizer of 6-MP and AZP
UGT1A1	211G>A	Poor metabolizer of irinotecan
Mitochondria	1555A>G	Hearing loss by aminoglycoside antibiotics

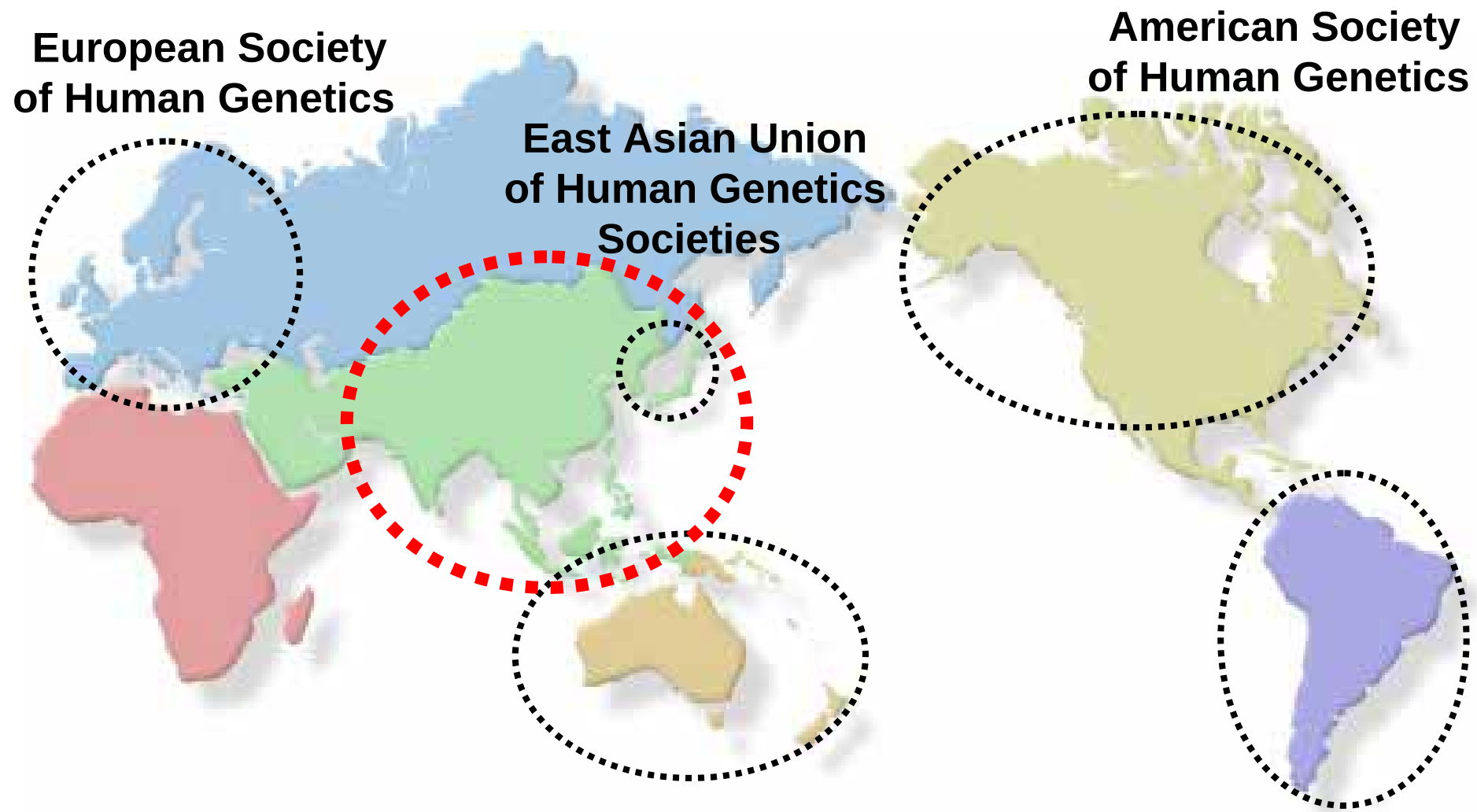
Ethnic difference in drug metabolism

Gene	Mutation/allele	Phenotype	Frequency*	
			Caucasians	Orientals
N-acetyl transferase (NAT2)	T341C	Slow acetylator	>28%	7%
	C282T/G857A	Rapid acetylator	>5%	10-18%
Cytochrome P450 2D6 (CYP2D6)	C188T (P34S)	Poor metabolizer (mild)	3%	50%
	*4	Poor metabolizer	20%	<1%
Cytochrome P450 2C19 (CYP2C19)	m1 and m2	Poor metabolizer	2.5-6%	15-23%

*Numbers are for homozygous individuals.

(Nature Biotechnology 16 Supplement, 1998)

International Federation of Human Genetics Societies (IFHGS)



Genomic Medicine
Ethical, Legal, and Social Issues

- fairness in the use of genetic information
- privacy and confidentiality
- psychological impact and stigmatization
- genetic testing
- reproductive issues
- education, standards, and quality control
- commercialization
- conceptual and philosophical implications

Healthcare in the Era of Genomic Medicine