Genomic Medicine, -genomics and personalized medicine

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Introduction of personalized medicine

Certain changes in genes cause an increased risk of development of specific diseases and how an individual responds to certain medications *is determined in part by genetic factors.*

Personalized medicine, then, is a lifelong, individually tailored health care approach to the detection, prevention and treatment of disease based on knowledge of an *individual's precise genetic profile*.

Genomics

- The study of the structure and function of the genome.

Genomic Medicine

Comes largely from knowledge emanating from the Human Genome Project

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

GENOMIC MEDICINE

Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D., *Editors*

Breast and Ovarian Cancer

Richard Wooster, Ph.D., and Barbara L. Weber, M.D.

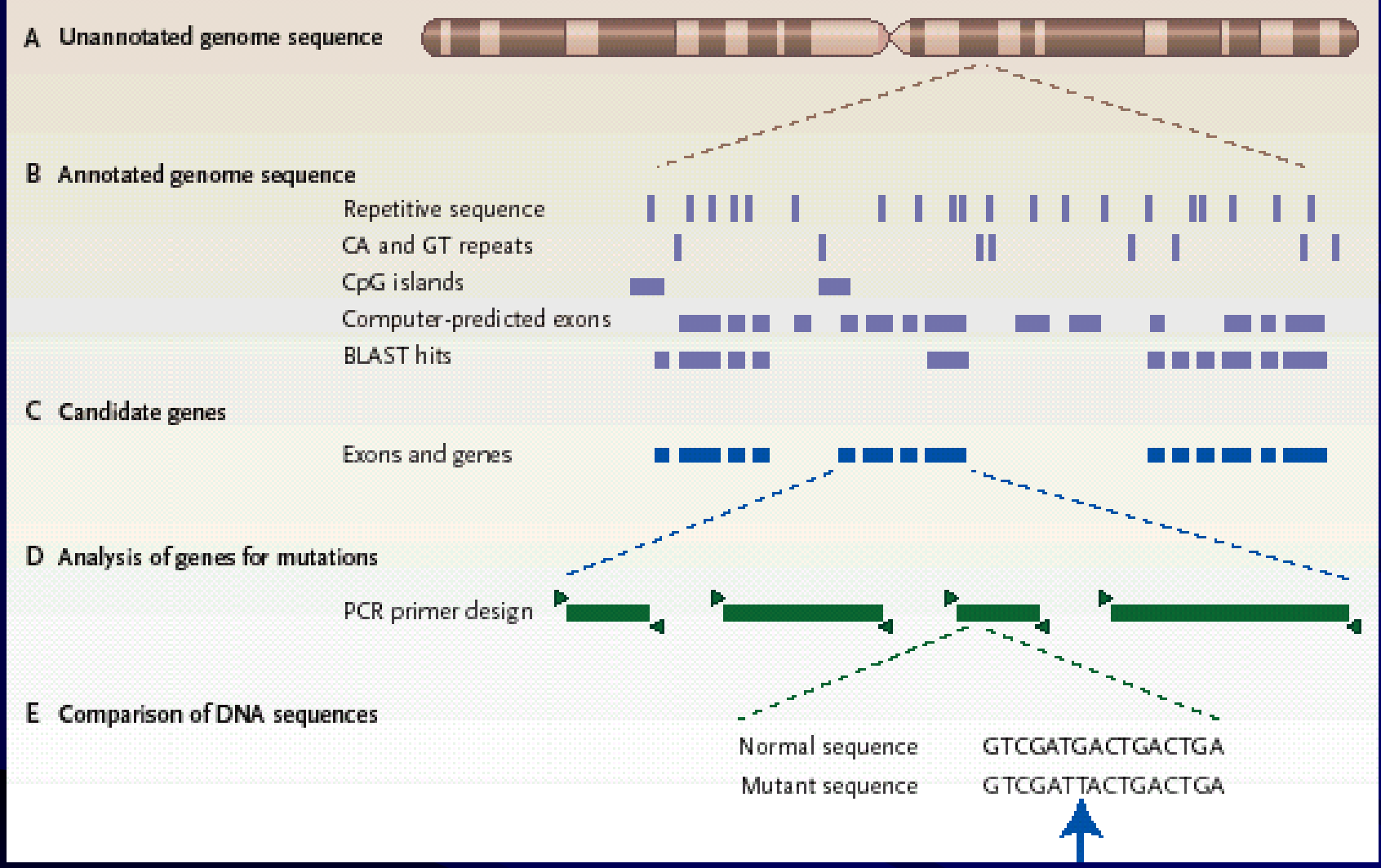


Figure 2. Effect of Sequencing the Human Genome on Gene-Discovery Strategies.

The annotated DNA sequence of the human genome can be used to locate genes, repeat sequences, and other features and has revolutionized the identification of cancer genes. A sequence without annotation is of limited utility (Panel A). As shown in Panel B, an annotated sequence shows genetic markers such as CA and GT repeats along with other data, such as CpG islands, known genes, genes predicted to exist on the basis of computational models, and Basic Local Alignment Search Tool (BLAST) matches. Using publicly available data (http://www.ensembl.org, http://www.ncbi.nlm.nih.gov, and http://www.genome.ucsc.edu), it is possible to jump from a genetic region of interest to the identification of candidate genes in a matter of seconds and download the relevant data (Panel C). With these data in hand, experiments, such as those involving the polymerase chain reaction (PCR), can be designed to analyze the genes for mutations (Panel D). The final step in the identification of genes is to compare the sequence from patients with the disease of interest with the normal reference sequence to discover the mutations (Panel E).

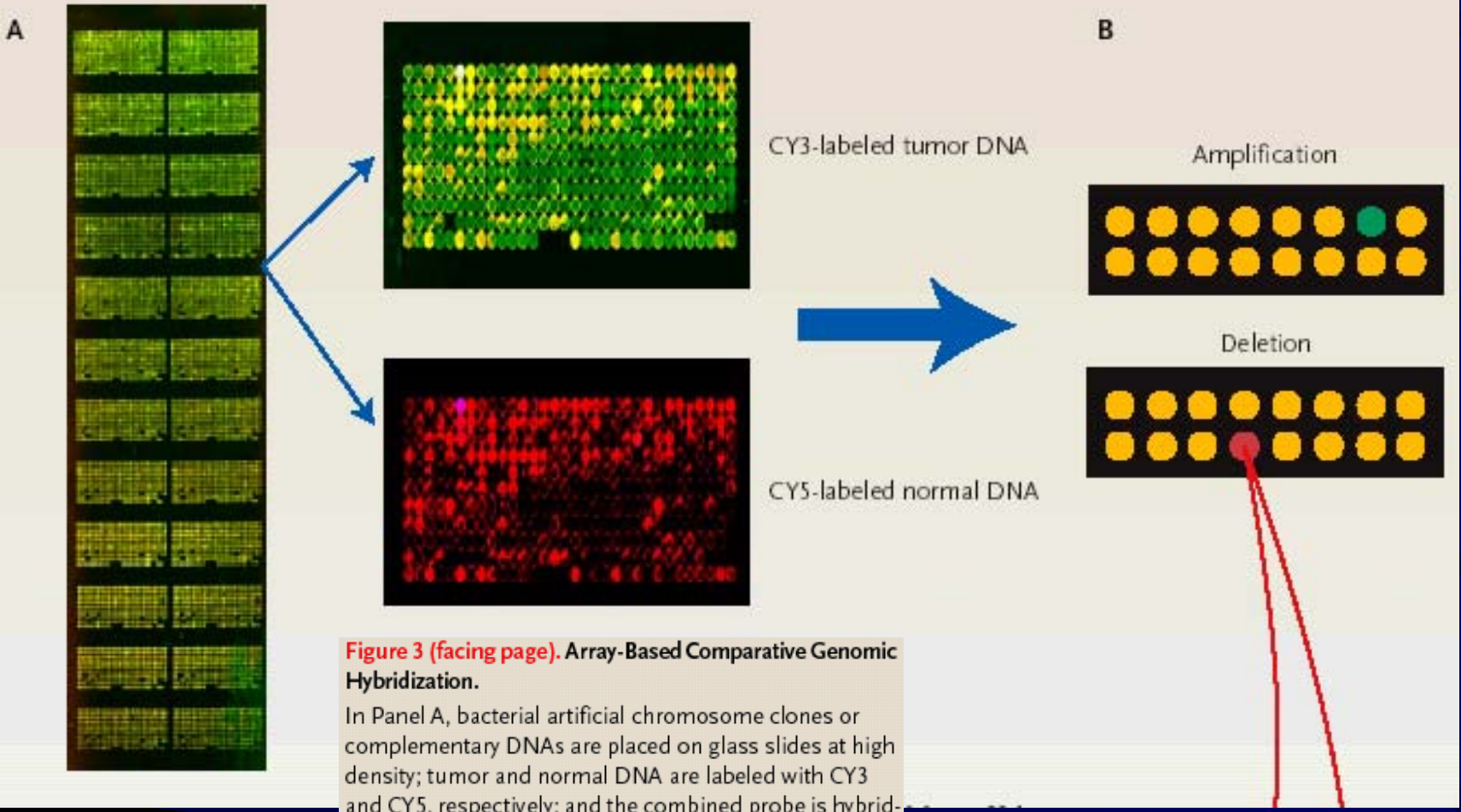
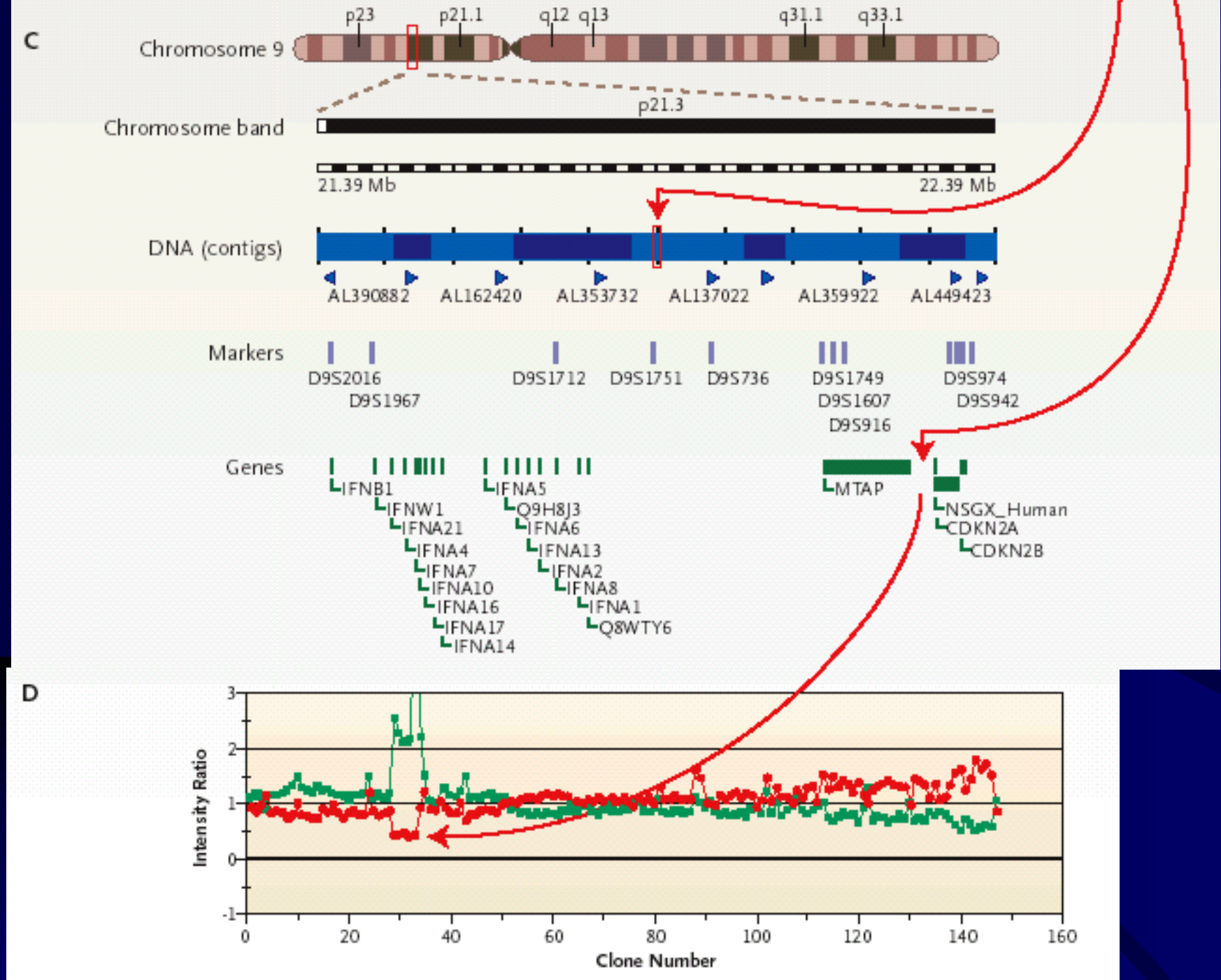


Figure 3 (facing page). Array-Based Comparative Genomic Hybridization.

In Panel A, bacterial artificial chromosome clones or complementary DNAs are placed on glass slides at high density; tumor and normal DNA are labeled with CY3 and CY5, respectively; and the combined probe is hybridized to the array. The array is analyzed with use of a laser scanner that reads each color channel individually and then calculates an intensity ratio for each spot. In Panel B, spots with intensity ratios greater than 1.25 (green spots) represent increases in copy number (amplification), and those with intensity ratios of less than 0.75 (red spots) represent decreases in copy number (deletion). Each spot is a DNA segment that can be linked directly to the human genome sequence (Panel C), thus defining changes in the number of copies of a specific gene. In Panel D, the plotting of intensity ratios for the chromosome 9 bacterial artificial chromosome clones on the array in linear order identifies a homozygous loss


C
Chromosome 9
p23
p21.1
q12
q13
q31.1
q33.1
Chromosome band
p21.3
21.39 Mb
22.39 Mb
DNA (contigs)
AL390882
AL162420
AL353732
AL137022
AL359922
AL449423
Markers
D9S2016
D9S1967
D9S1712
D9S1751
D9S736
D9S1749
D9S1607
D9S916
D9S974
D9S942
Genes
IFNB1
IFNW1
IFNA21
IFNA4
IFNA7
IFNA10
IFNA16
IFNA17
IFNA14
IFNA5
Q9H8J3
IFNA6
IFNA13
IFNA2
IFNA8
IFNA1
Q8WTY6
MTAP
NSGX_Human
CDKN2A
CDKN2B
D
Intensity Ratio
3
2
1
0
-1
0
20
40
60
80
100
120
140
160
Clone Number

SNP markers

- SNPs are very common in the human population.
- SNPs can be found that are *linked* to any disease alleles.
- These mutations are likely to be neutral - they have no direct effect on phenotype
- Linked SNPs can be used as markers for the disease in diagnostic tests.

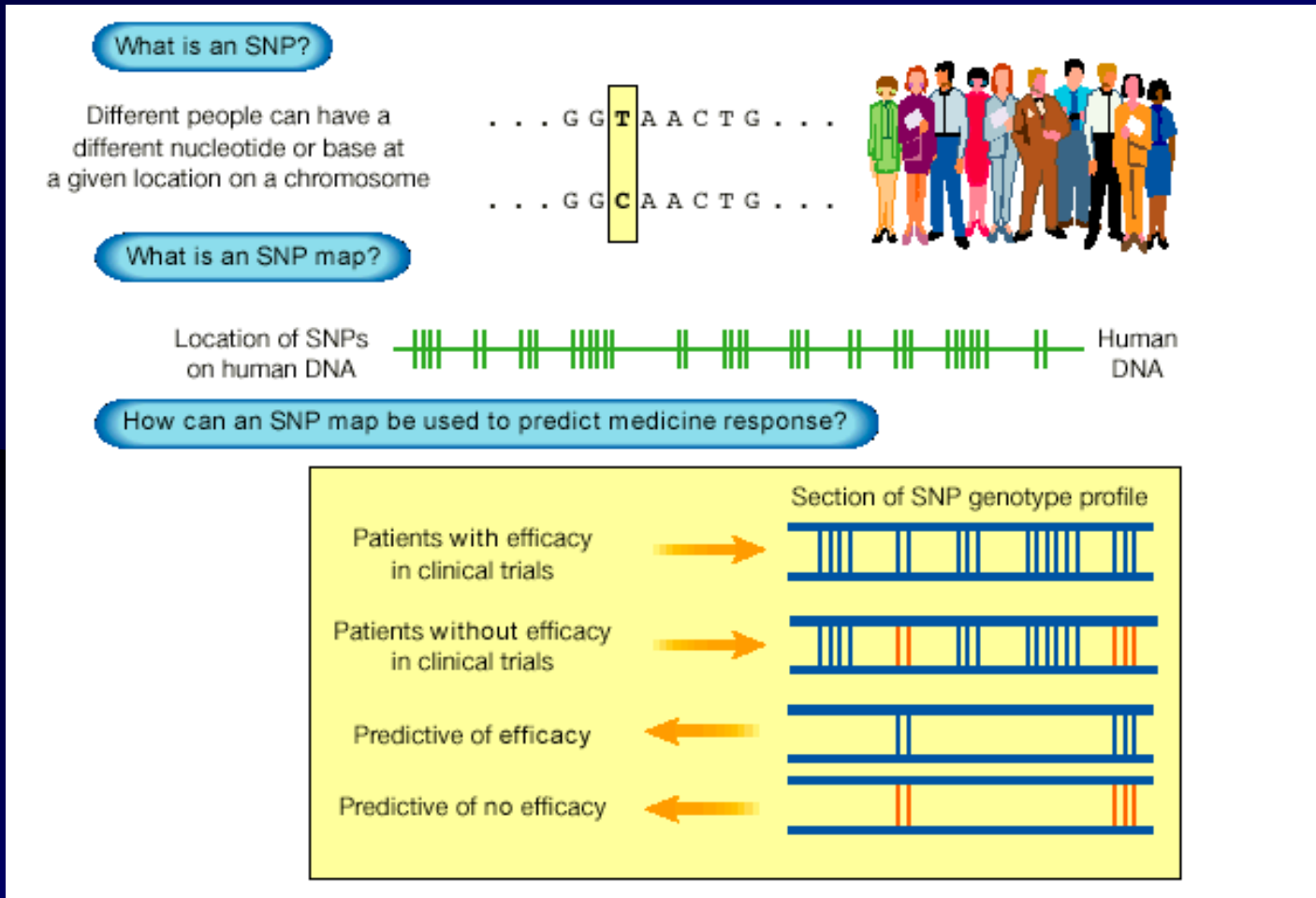
SNP Topics

1. SNP Genotyping and Haplotyping
   - detection, high-throughput genotyping, haplotyping, the haplotype map

2. SNP Applications
   - pharmacogenomics, diagnostic genomics, functional proteomics and therapeutic genomics

SNP Mapping

- Identify SNP sites along the genome to track disease genes.
- A human SNP map would specify the contributions of individual genes to diseases and other phenotypes.



Haplotype Map

- The map's purpose is to relate human genetic variation with disease predisposition, specifically common or complex disorders.

- For specific genomic locations (chosen to avoid recombination and recurrent mutation), a small number of SNP patterns (haplotypes) were found that account for 80%-90% of the entire human population.

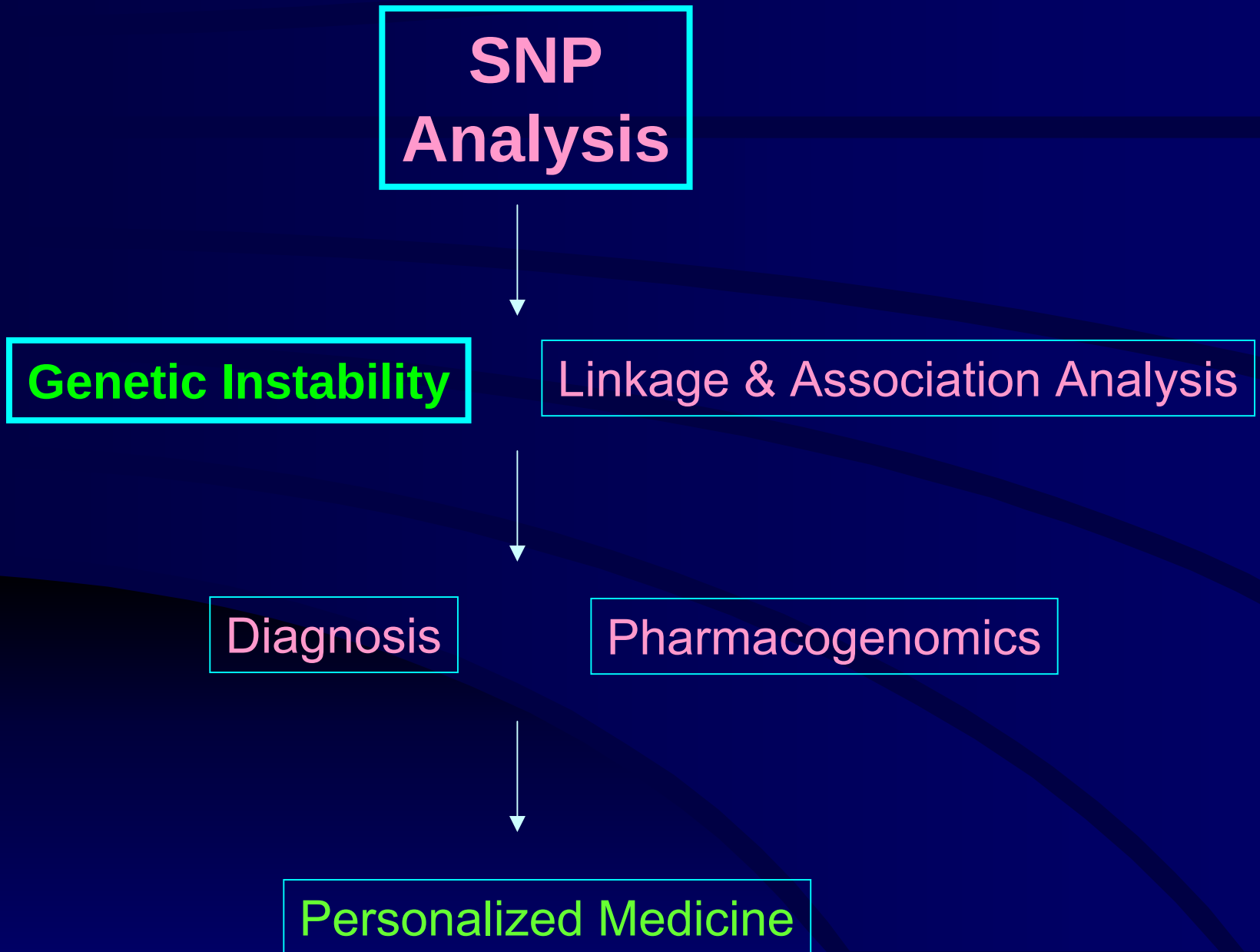
Complex promoter and coding region β_2-adrenergic receptor haplotypes alter receptor expression and predict *in vivo* responsiveness

Connie M. Drysdale*†, Dennis W. McGraw*‡, Catharine B. Stack†, J. Claiborne Stephens†, Richard S. Judson†, Krishnan Nandabalan†, Kevin Arnold†, Gualberto Ruano†, and Stephen B. Liggett‡§¶

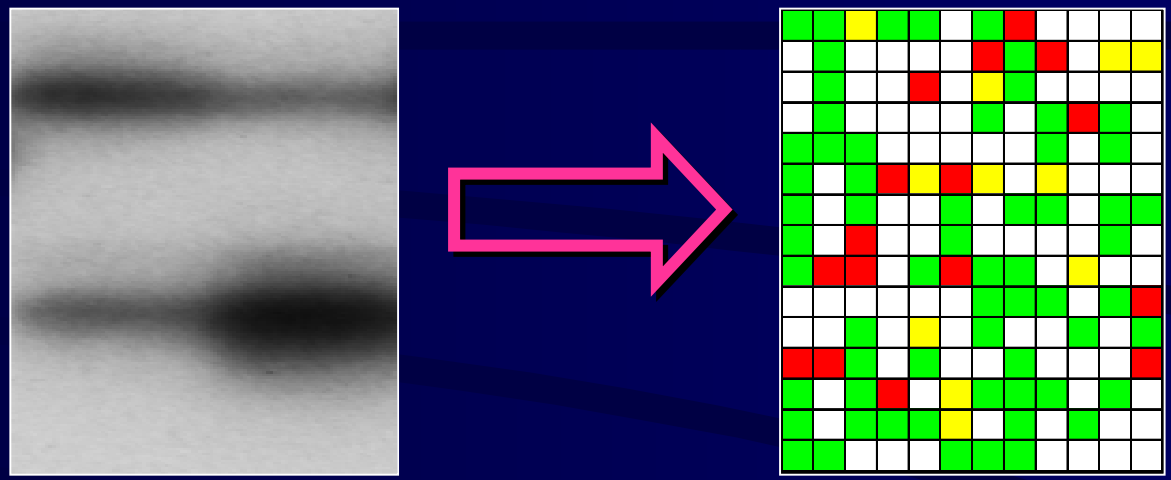
PNAS | September 12, 2000 | vol. 97 | no. 19 | 10483–10488

Nucleotide:	-1023	-709	-654	-468	-406	-367	-47	-20	46	79	252	491	523
Alleles:	G/A	C/A	G/A	C/G	C/T	T/C	T/C	T/C	G/A	C/G	G/A	C/T	C/A
Haplotype													
1	A	C	G	C	C	T	T	T	A	C	G	C	C
2	A	C	G	G	C	C	C	C	G	G	G	C	C
3	G	A	A	C	C	T	T	T	A	C	G	C	C
4	G	C	A	C	C	T	T	T	A	C	G	C	C
5	G	C	A	C	C	T	T	T	G	C	G	C	C
6	G	C	G	C	C	T	T	T	G	C	A	C	A
7	G	C	G	C	C	T	T	T	G	C	A	T	A
8	G	C	A	C	C	T	T	T	A	C	A	C	A
9	A	C	G	C	T	T	T	T	A	C	G	C	C
10	G	C	G	C	C	T	T	T	G	C	A	C	C
11	G	C	G	C	C	T	T	T	G	C	G	C	C
12	A	C	G	G	C	T	T	T	A	C	G	C	C
Location:	5'	5'	5'	5'	5'	5'	AA19 BUP Cys/Arg	5'	AA16 Gly/Arg	AA27 Gln/Glu	syn	AA164 Thr/Ile	syn

SNP Applications



from Analogue to Digital

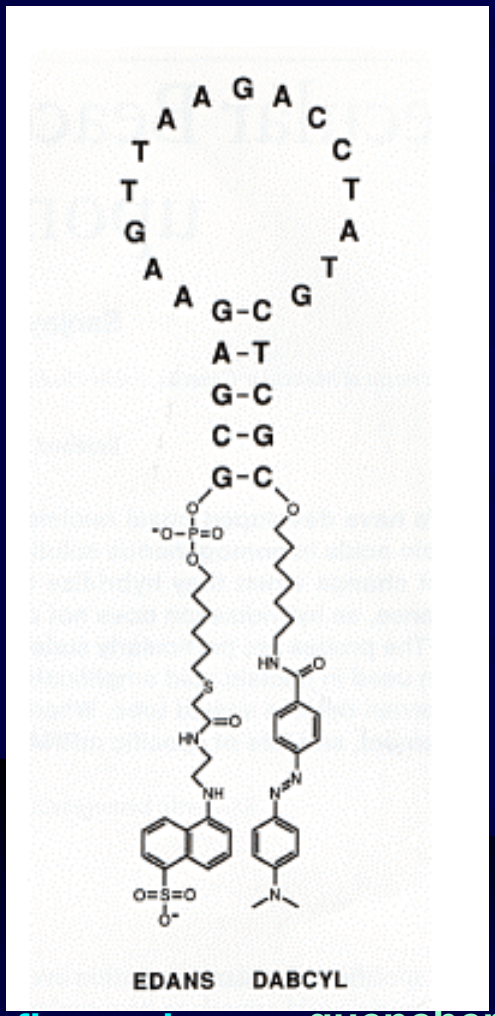


Microsatellite marker

SNP marker

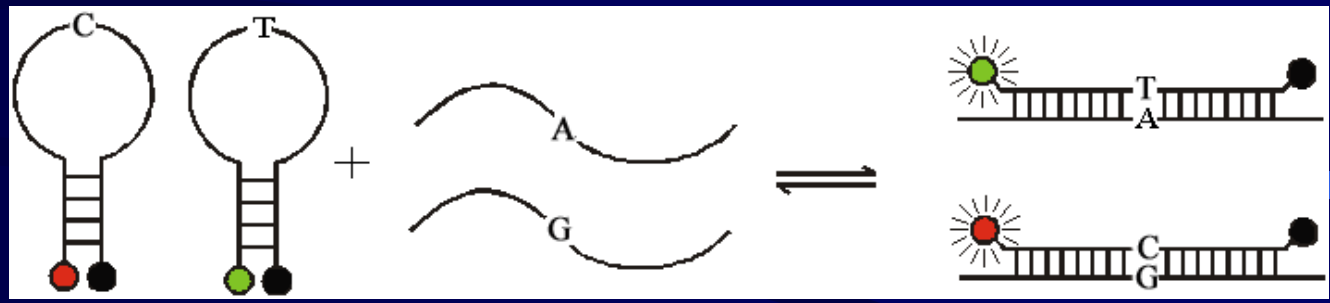
Digital SNP analysis

Molecular Beacons



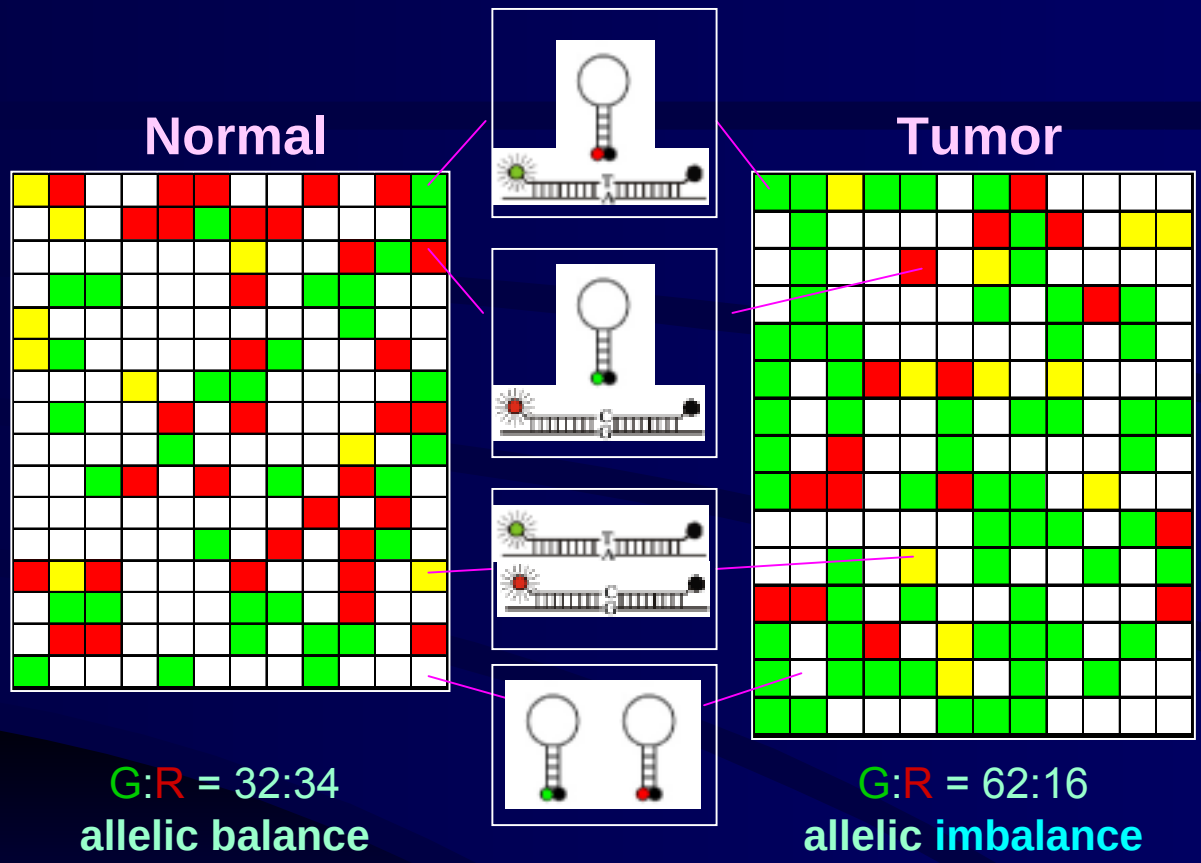
fluorophore quencher

SNP-specific Molecular Beacon



Sanjay Tyagi and Fred Kramer (1996)
Nature Biotechnology 14: 303-308

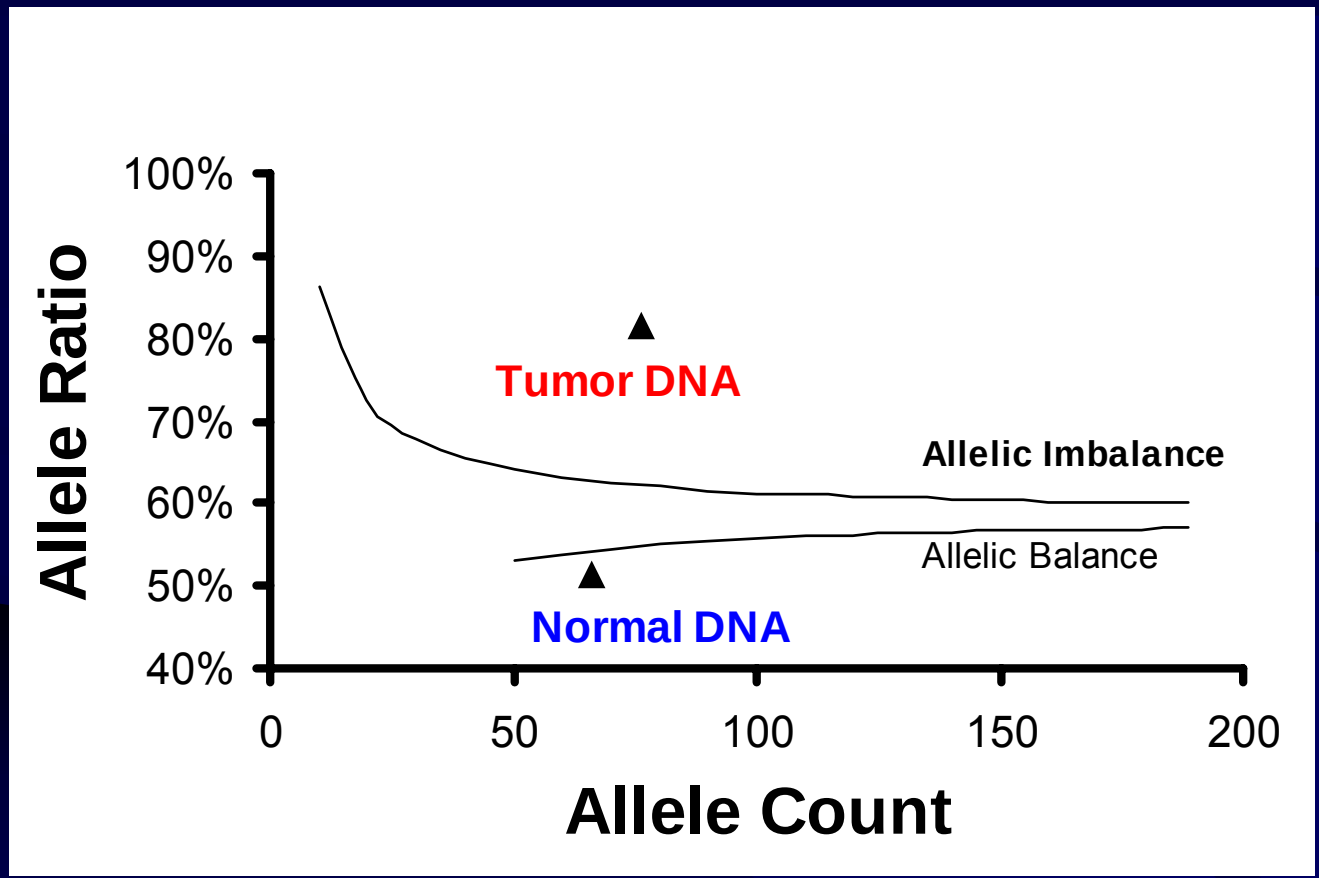
Assess genetic abnormality by counting alleles



Sequencial probability ratio test

(SPRT analysis)-

determines allelic imbalance



Advantages of Digital SNP Analysis

1. is *not biased by the preferential DNA degradation of larger alleles*.
2. can precisely determine the number of alleles examined in each experiment.
3. A statistical method, *SPRT*, can be employed to conclude *whether allelic imbalance is present in the background DNA*.
4. allelic imbalance can be detected *more sensitive* by Digital SNP analysis than microsatellite markers in colorectal carcinomas.

[Science. *244:* 207-11, 1989. & Nat Biotechnol. *19:* 78-81., 2001.]

Assessment of Plasma DNA Levels, Allelic Imbalance, and CA 125 as Diagnostic Tests for Cancer

Hsueh-Wei Chang, Shing M. Lee, Steven N. Goodman, Gad Singer, Sarah K. R. Cho, Lori J. Sokoll, Fredrick J. Montz, Richard Roden, Zhen Zhang, Daniel W. Chan, Robert J. Kurman, Ie-Ming Shih

J National Cancer Institute 94 (22), 1697-1703. (2002)

Allelic status in plasma DNA of ovarian cancer patients

Patient No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Stage	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3
Chromosome 1p / SNP 8118																											
Chromosome 5q / SNP 1756																											
Chromosome 7p / SNP 273																											
Chromosome 8p / SNP 1085																											
Chromosome 12q / SNP 852																											
Chromosome 15q / SNP 1861																											
Chromosome 17p / SNP p53																											
Chromosome 18p / SNP 331																											
Plasma DNA (ng/ml)	18	266	65	199	38	3	1309	264	15	8	17	186	23	42	61	92	210	26	6	10	94	746	36	28	131	8	110
Fraction of tumor DNA	0.3	N/A	N/A	0.5	0.3	0.4	0.3	0.4	0.3	0.3	0.5	0.3	0.4	N/A	N/A	0.7	0.7	0.4	N/A	0.5	0.3	0.7	0.3	0.3	0.3	0.3	0.9
CA125 (U/ml)	X	167	X	18	25	X	580	11	19	15	46	28	115	8	X	1260	76	36	X	220	875	X	9	30	270	16	3185

Patient No.	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
Stage	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4
Chromosome 1p / SNP 8118																											
Chromosome 5q / SNP 1756																											
Chromosome 7p / SNP 273																											
Chromosome 8p / SNP 1085																											
Chromosome 12q / SNP 852																											
Chromosome 15q / SNP 1861																											
Chromosome 17p / SNP p53																											
Chromosome 18p / SNP 331																											
Plasma DNA (ng/ml)	2	146	38	3	67	149	5	338	491	103	92	147	65	285	20	538	39	25	40	14	78	35	895	2481	18	504	1190
Fraction of tumor DNA	0.4	0.4	0.4	N/A	0.5	0.7	0.4	0.6	0.4	0.6	0.6	0.7	0.7	0.7	0.4	0.9	0.3	0.5	0.3	0.3	0.4	0.6	0.7	0.9	0.4	0.7	0.7
CA125 (U/ml)	8	84	X	29	600	75	15	250	377	66	979	13	979	209	19	231	643	319	788	X	X	580	365	66	38	2397	304

Allelic balance

Allelic imbalance

Undetermined

Homozygous (non-informative)

Vol. 8, 2580–2585, August 2002 Clinical Cancer Research

Detection of Allelic Imbalance in Ascitic Supernatant by Digital Single Nucleotide Polymorphism Analysis[1]

Hsueh-Wei Chang, Syed Z. Ali, Sarah K. R. Cho, Robert J. Kurman, and Ie-Ming Shih[2]

Departments of Pathology [H-W. C., S. Z. A., S. K. R. C., R. J. K., I-M. S.] and Gynecology and Obstetrics [R. J. K.], The Johns Hopkins University School of Medicine, Baltimore, Maryland 21231

Tumor

Case No.	Diagnosis	Age	DNA conc.	SNP markers						
				8118	486	273	2952	331	852	1085
T1	OVCA	45	1388							
T2	OVCA	55	127							
T3	OVCA	71	240							
T4	OVCA	73	606							
T5	OVCA	44	31							
T6	OVCA	60	405							
T7	OVCA	53	42							
T8	OVCA	36	1430							
T9	OVCA	45	550							
T10	Colon CA	69	2711							
T11	OVCA	48	180							
T12	OVCA	51	58							
T13	Pancrease CA	53	37							
T14	OVCA	53	399							
T15	Colon CA	46	289							
T16	OVCA	53	880							
T17	OVCA	74	5774							
T18	OVCA	59	40							
T19	Pancrease CA	63	1195							
T20	Pancrease CA	56	26							

Normal

Case No.	Diagnosis	Age	DNA conc.	SNP markers						
				8118	486	273	2952	331	852	1085
N1	NFT	49	10							
N2	NFT	48	168							
N3	NFT	58	2							
N4	NFT	73	8							
N5	NFT	55	22							
N6	NFT	41	2							
N7	NFT	62	15							
N8	NFT	44	9							
N9	NFT	62	16							
N10	NFT	41	25							
N11	NFT	75	19							
N12	NFT	38	293							
N13	NFT	53	7							
N14	NFT	44	4							
N15	NFT	34	1141							
N16	Ovarian cyst	45	10							
N17	Ovarian cyst	65	6							
N18	NFT	63	208							
N19	NFT	32	49							
N20	NFT	37	16							

OVCA: ovarian carcinoma; CA: carcinoma; NFT: negative for tumor; Conc: concentration; NI: not informative;

Allelic balance

Allelic imbalance

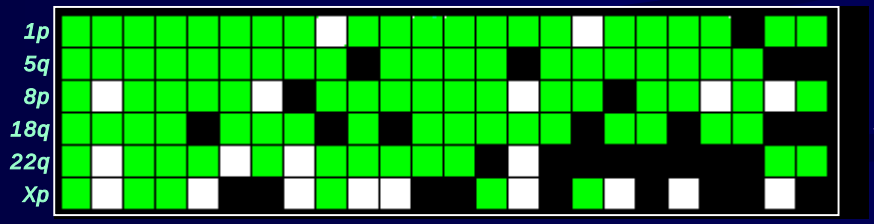
Undetermined

Homozygous (non-informative)

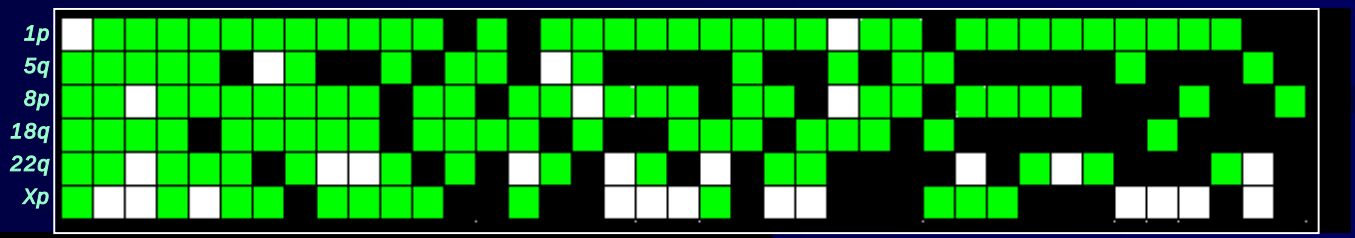
Diverse Tumorigenic Pathways in Ovarian Serous Carcinoma

Am J Pathol 2002, 160:1223–1228

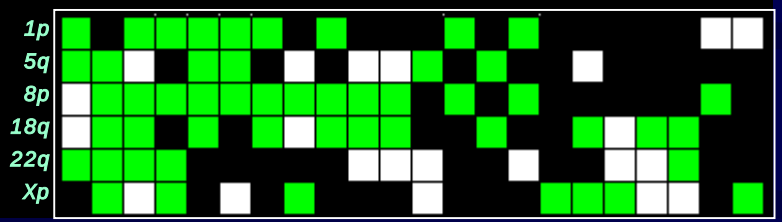
Gad Singer*, Robert J. Kurman,*†
Hsueh-Wei Chang,* Sarah K.R. Cho,* and
Ie-Ming Shih*



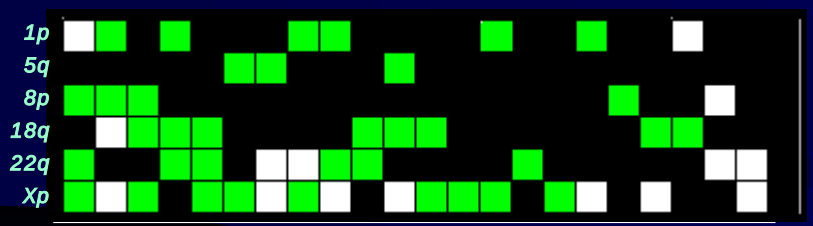
S B T (Serous borderline tumor)



Noninvasive MPSC



Invasive MPSC



Conventional serous carcinoma

Paraffin tissue DNA

Allelic balance

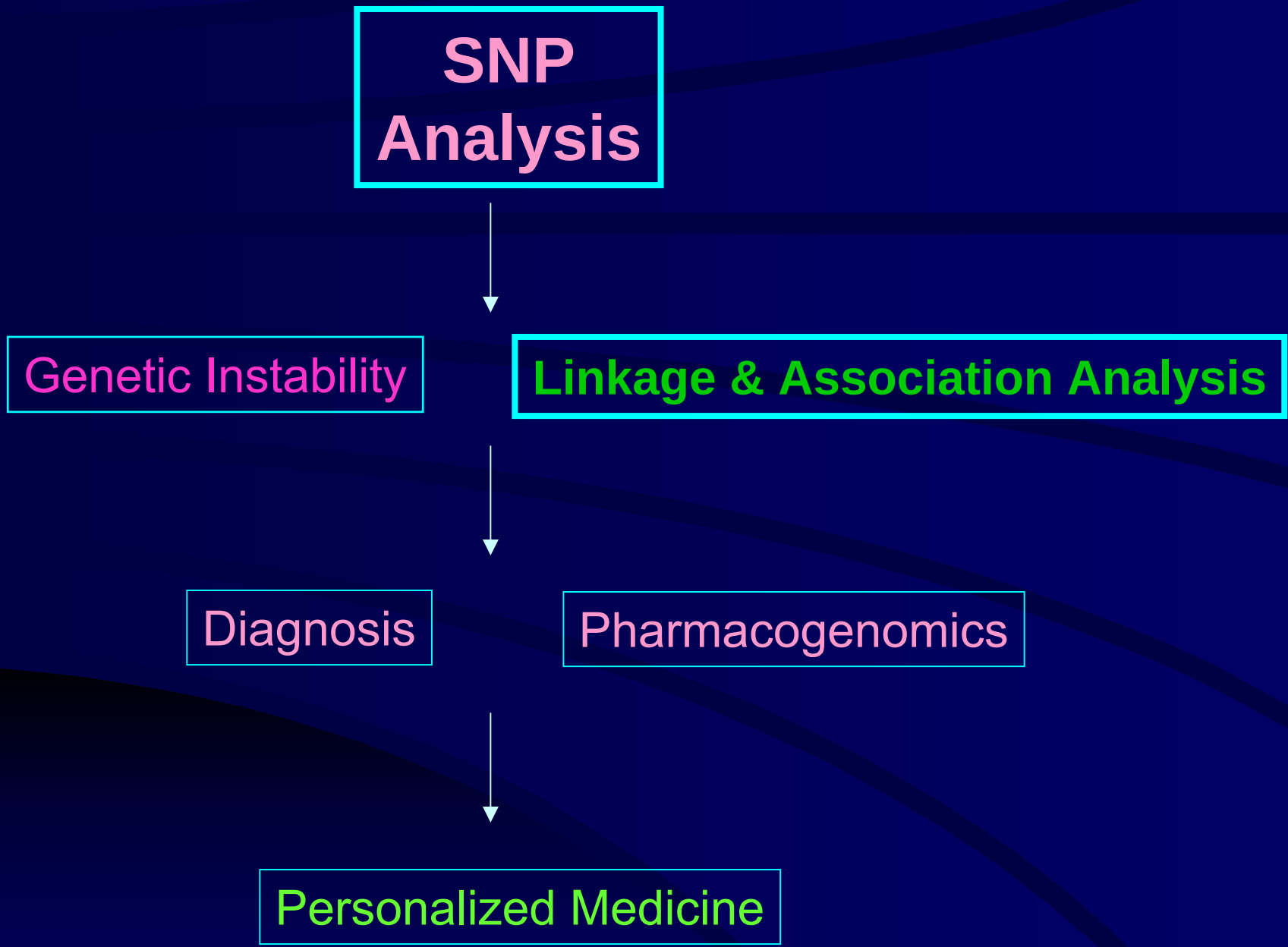
Allelic imbalance

Homozygous (non-informative)

Gad Singer et al. 2002

Conclusion I

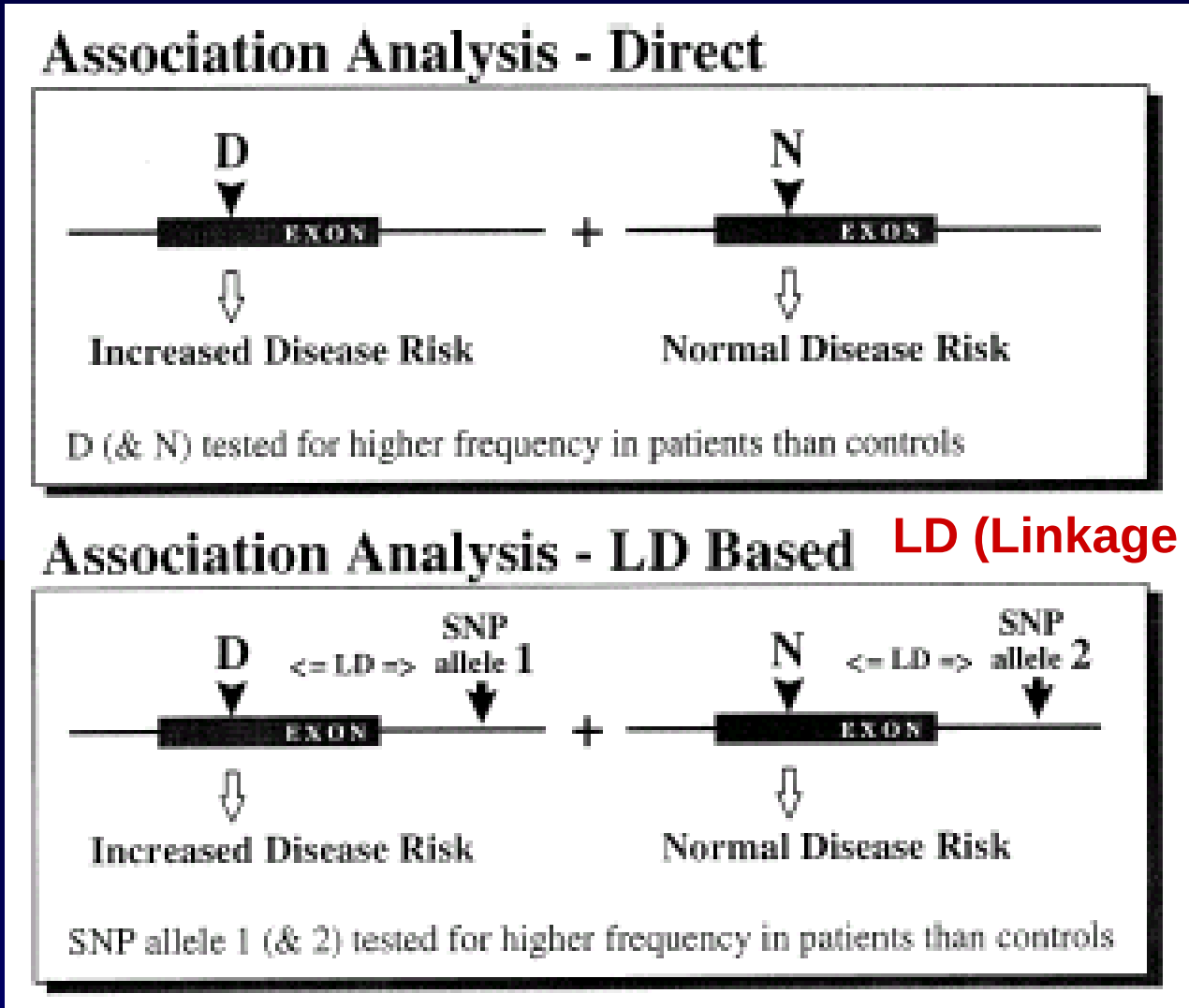
Digital SNP analysis can count the allelic imbalance in samples from plasma, ascites, paraffin …etc. in the presence of background (normal) DNA.


SNP Analysis
Genetic Instability
Linkage & Association Analysis
Diagnosis
Pharmacogenomics
Personalized Medicine

SNP-based marker discovery

Strategies for association analysis

Gene 234 (1999) 177–186



LD (Linkage disequilibrium)

Some Diseases Involve Many Genes

- There are a number of classic “genetic diseases” caused by mutations of a single gene
  - Huntington’s, Cystic Fibrosis, PKU, etc.
- There are also many diseases that are the result of the interactions of many genes:
  - asthma, heart disease, cancer
- Each of these genes may be considered to be a **risk factor** for the disease.
- Groups of SNP markers may be associated with a disease without determining mechanism

People React Differently to Drugs

- Side effects
- Effectiveness
- There are genes that control these reactions
- SNP markers can be used to identify these genes

Pharmacogenetics/Pharmacogenomics

"Medicine tailored to the individual"

Nature Reviews Genetics **4**, 937-947 (2003); doi:10.1038/nrg1229

printable PDF

[873K]

PHARMACOGENETICS GOES GENOMIC

David B. Goldstein[1], **Sarah K. Tate**[1] & **Sanjay M. Sisodiya**[2] about the authors

[1] Department of Biology (Galton Laboratory), University College London, The Darwin Building, Gower Street, London WC1E 6BT, UK.
[2] Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, London WC1N 3BG, UK.

Pharmacogenetics is an old discipline, with antecedents that stretch back to the beginning of the twentieth century[1]. Like many other branches of the biomedical sciences it has been invigorated by recent advances in genomics, which have led to expectations that the safety and efficacy of medicines will soon be notably improved by genetic personalization. The excitement has also generated yet another compound name: pharmacogenomics. Although often used interchangeably, pharmacogenetics and pharmacogenomics have different connotations and a range of alternative definitions have been offered. Some have suggested that the difference is just in scale and that pharmacogenetics implies the study of a single gene whereas pharmacogenomics implies the study of many genes or entire genomes. Others have suggested that pharmacogenomics covers levels above that of DNA, such as mRNA or proteins, or that it relates more to drug development than does pharmacogenetics. These distinctions are variable and fuzzy, and are probably not worth formalizing. Here, we use the term pharmacogenetics, which has historical priority, according to its broadest meaning — relating heritable variation to inter-individual variation in drug response.

Pharmacogenetics

The study of how people respond differently to medicines due to their genetic inheritance.

Pharmacogenomics

Goal is to use a *genome-wide approach* to define the contributions of genetic differences in drug disposition or drug targets to drug response, in order to improve the safety and efficacy of drug therapy through use of genetically guided, individualized treatment.

pharmacogenomics

Pharmacogenomics is the study of the inherited basis of differences in response to drugs.

These interindividual differences are often more than tenfold.

A ‘slow metabolizer’ or ‘low-responsive’ individual might therefore require ten times less than the recommended dose of a drug than a ‘rapid metabolizer’ or ‘high-responsive’ person.

The slow metabolizer is often more likely to experience drug toxicity than a rapid metabolizer.

Our knowledge is developing rapidly to the point that the physician will soon use DNA-based tests to aid in decision-making with respect to the most appropriate drug and dosage given to each patient.

Various SNP effects on gene expression

• 'Silent' polymorphisms in coding sequences, no amino acid change, hence no change in properties.
• Formation of a variant protein, which might have altered properties as a consequence of change in structure.

• Polymorphic sequences within *both exon and intron regions*, which can also result in differential splicing, protein truncation and additional functional anomalies.
• Polymorphisms in *regulatory regions* that can alter gene expression, RNA levels and stability, and consequently protein expression levels.

SNPs and their significance

Presence of SNP can alter drugs interaction with receptors, transporters, metabolizers and disease causing genes. Thus change in a single nucleotide can have vast effect in many aspect of drug metabolism.

Expression of P-glycoprotein and Genotype (MDR1 3435)

P-gp Genotype	P-gp Expression
T T	Reduced
C T	Normal
C C	Increased

Pharmacogenomics and Asthma

Drug Category	Effector Variability
β-agonists	Receptor at codons 16, 27
Corticosteroids	IL-4 polymorphisms
Leukotriene inhibitors	ALOX5 core promoter expression

Hypertension: The α-Adducin Gene Variant and the Rate of MI or CVA

Genotype	Odds Ratio of Clinical Events
Wild Type (n=653)	1.09 (0.78-1.52)
Variant Allele (n=385)	0.49 (0.32-0.77)

Psaty, JAMA, 2002

Warfarin Toxicity and CYP2C9 Variability: Clinical Correlates

Warfarin maintenance dose (mg)

Wild type: *1*1	**5.63**
Variant: *1*2	**4.88**
Variant: *1*3	**3.32**

Higashi, JAMA, 2002

Functional SNPs in the lymphotoxin-α gene that are associated with susceptibility to myocardial infarction

Kouichi Ozaki[1], Yozo Ohnishi[1], Aritoshi Iida[2], Akihiko Sekine[2], Ryo Yamada[3], Tatsuhiko Tsunoda[4], Hiroshi Sato[5], Hideyuki Sato[5], Masatsugu Hori[5], Yusuke Nakamura[2,6] & Toshihiro Tanaka[1]

Nat Genet. 2002 Dec;32(4):650-4.

European Heart Journal (2001) **22**, 845–848
doi:10.1053/euhj.2000.2400, available online at http://www.idealibrary.com on IDEAL®

The human G-protein β3 subunit C825T polymorphism is associated with coronary artery vasoconstriction

A. Meirhaeghe[1], C. Bauters[1,2], N. Helbecque[1], M. Hamon[3], E. McFadden[2], J.-M. Lablanche[2], M. Bertrand[2] and P. Amouyel[1,4]

J Mol Med (2001) 79:732–737
DOI 10.1007/s001090100265

ORIGINAL ARTICLE

Laura Viitanen · Jussi Pihlajamäki · Raija Miettinen
Päivi Kärkkäinen · Ilkka Vauhkonen · Pirjo Halonen
Anu Kareinen · Seppo Lehto · Markku Laakso

Apolipoprotein E gene promoter (–219G/T) polymorphism is associated with premature coronary heart disease

[CANCER RESEARCH 62, 4992–4995, September 1, 2002]

A Novel Polymorphism in Human Cytosine DNA-Methyltransferase-3B Promoter Is Associated with an Increased Risk of Lung Cancer[1]

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[CANCER RESEARCH 62, 152–155, January 1, 2002]

The *XRCC1* Arg399Gln Polymorphism, Sunburn, and Non-melanoma Skin Cancer: Evidence of Gene-Environment Interaction[1]

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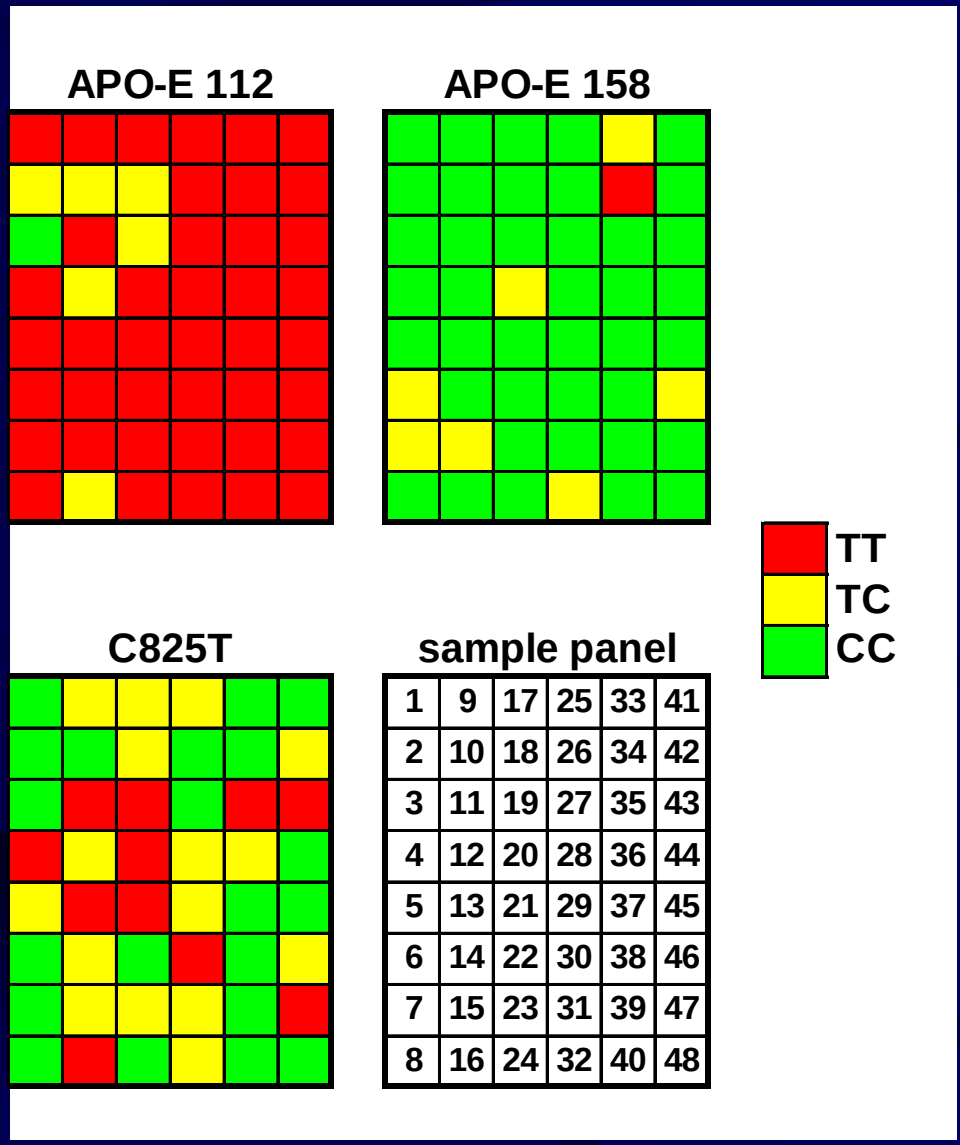
Genotype Analysis Using Human Hair Shaft

Cancer Epidemiology, Biomarkers & Prevention *11: 925–929, 2002*

Hsueh-Wei Chang, Ching-Yu Yen, Shyun-Yui Liu, Gad Singer, and Ie-Ming Shih*

SNP Genotyping



Genotype and allele frequency of APO-E

		APO-E								
Populations	n	Genotype (%)						Allele (%)		
		E2/E2	E2/E3	E3/E3	E2/E4	E3/E4	E4/E4	ε2	ε3	ε4
Taiwanese	48	2.1	14.6	68.8	0.0	12.5	2.1	9.4	82.3	8.3^{ns}
Chinese[22]	141	1.4	12.1	70.9	0.0	14.9	0.7	7.4	84.4	8.2^{ns}
European[19]	590	0.8	9.3	57.3	1.9	27.3	3.4	6.4	75.6	18.0*

ns = not significant; * $p < 0.03$

Genotyping of C825T

		C825T		
Populations	n	Genotype (%)		
		TT	TC	CC
Taiwanese	48	23.0^{ns}	41.0	36.0
Chinese[12]	960	22.4^{ns}	50.6	27.0
European[12]	277	10.0*	43.7	46.2

ns = not significant; *$p < 0.001$

Phylogenomics

The application to genomics of principles and techniques from evolutionary biology, to achieve a better understanding of gene function.

Pharmacophylogenomics

‘Pharmacophylogenomics’is the use of phylogenomics in aid of drug discovery, through improved target selection and validation.

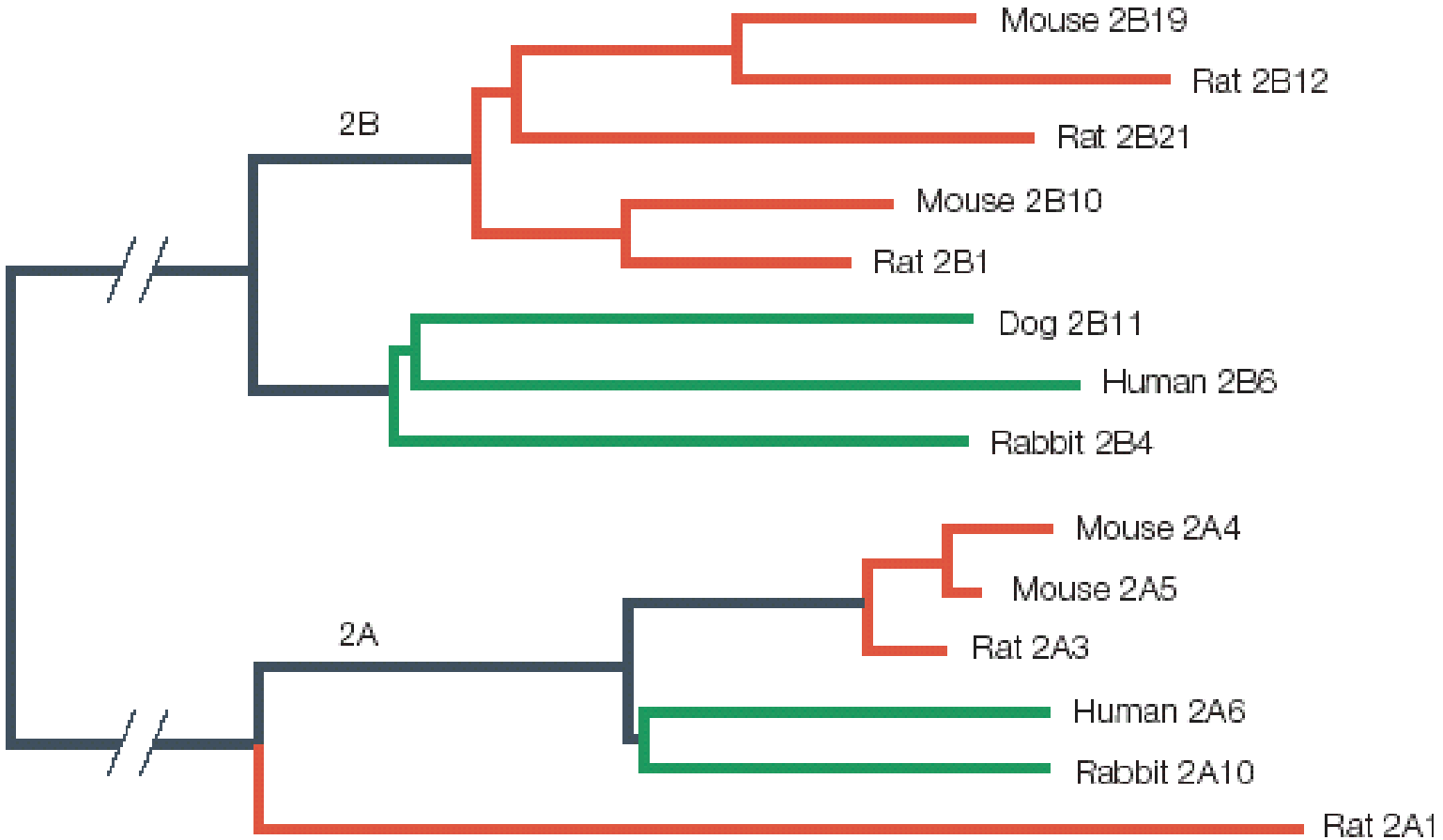


Figure 2 | **Phylogenetic reconstruction of the CYP2 family of cytochrome P450s.** The tree was constructed from selected CYP2A and B isoforms by a simple neighbour-joining procedure. The CYP2B subfamily shows a characteristic clustering of rodent orthologues and paralogues, well separated from other mammals. The CYP2A subfamily, however, isolates the rat 2A1 isoform on its own long branch, which accords well with a known functional shift in the metabolism by 2A1 of the substrate coumarin (see text).

mRNA-based marker discovery

Gene Expression (phenotype) Profiling

- Sequence bulk cDNAs from different tissues
  - SAGE
  - Microarrays

Toxicogenomics

Toxicogenomics is the study of the response of the genome to toxic agent exposure.

The term ‘toxicogenomics’ in its broadest meaning encompasses profiling of *gene expression*, protein composition *(proteomics)* and the metabolic constituents *(metabonomics)* of a cell.

A key toxicogenomic technique:

is to profile (using a DNA microarray or ‘gene chip’) the cell-wide changes in gene expression following exposure to toxins.

This approach creates the potential to provide a molecular ‘fingerprint’ of exposure or toxicological response to specific classes of toxic substances.

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Toxicogenomic approach for assessing toxicant-related disease

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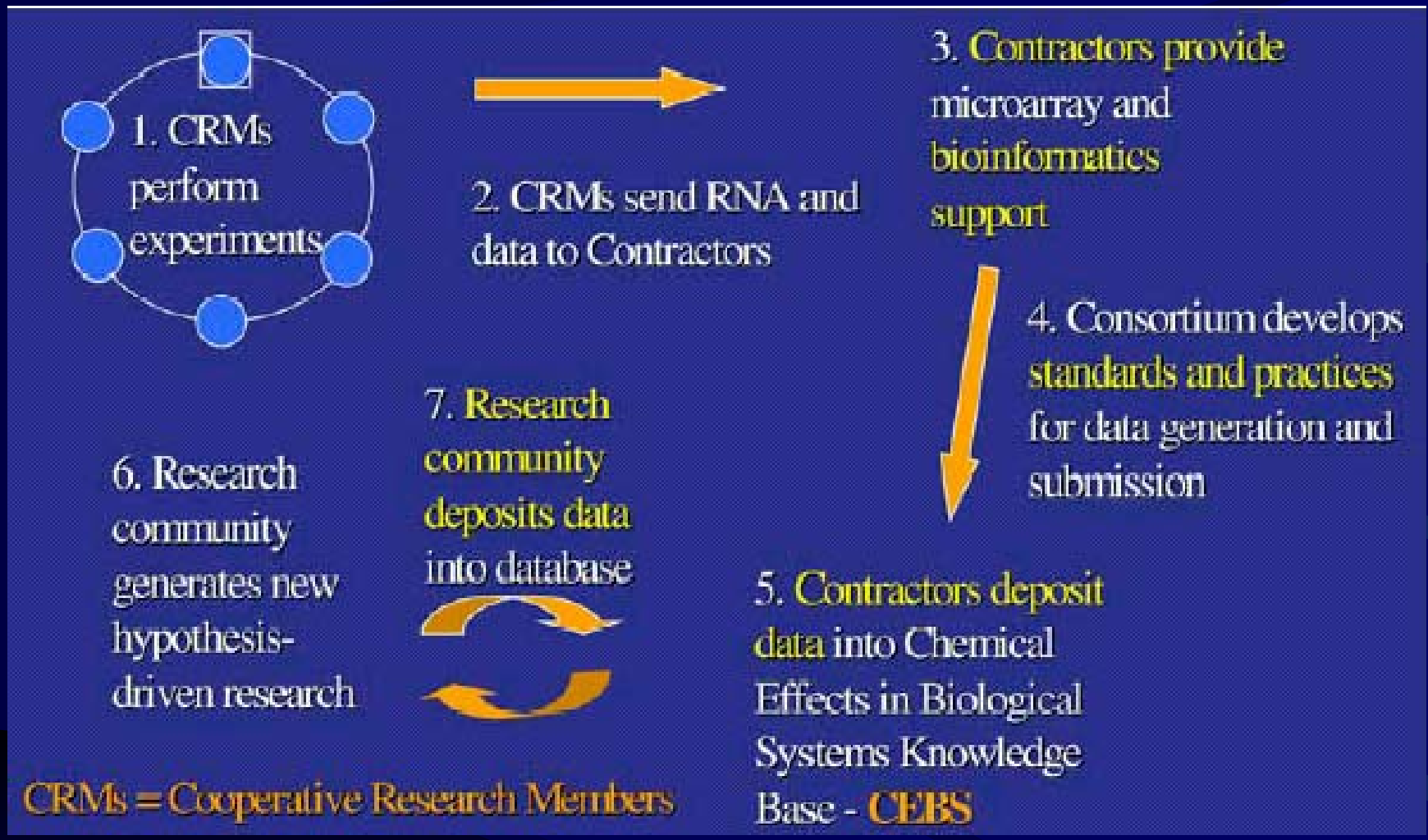

Fig. 1. The NIEHS Toxicogenomics Research Consortium and resource contracts for microarray, bioinformatics and database support.

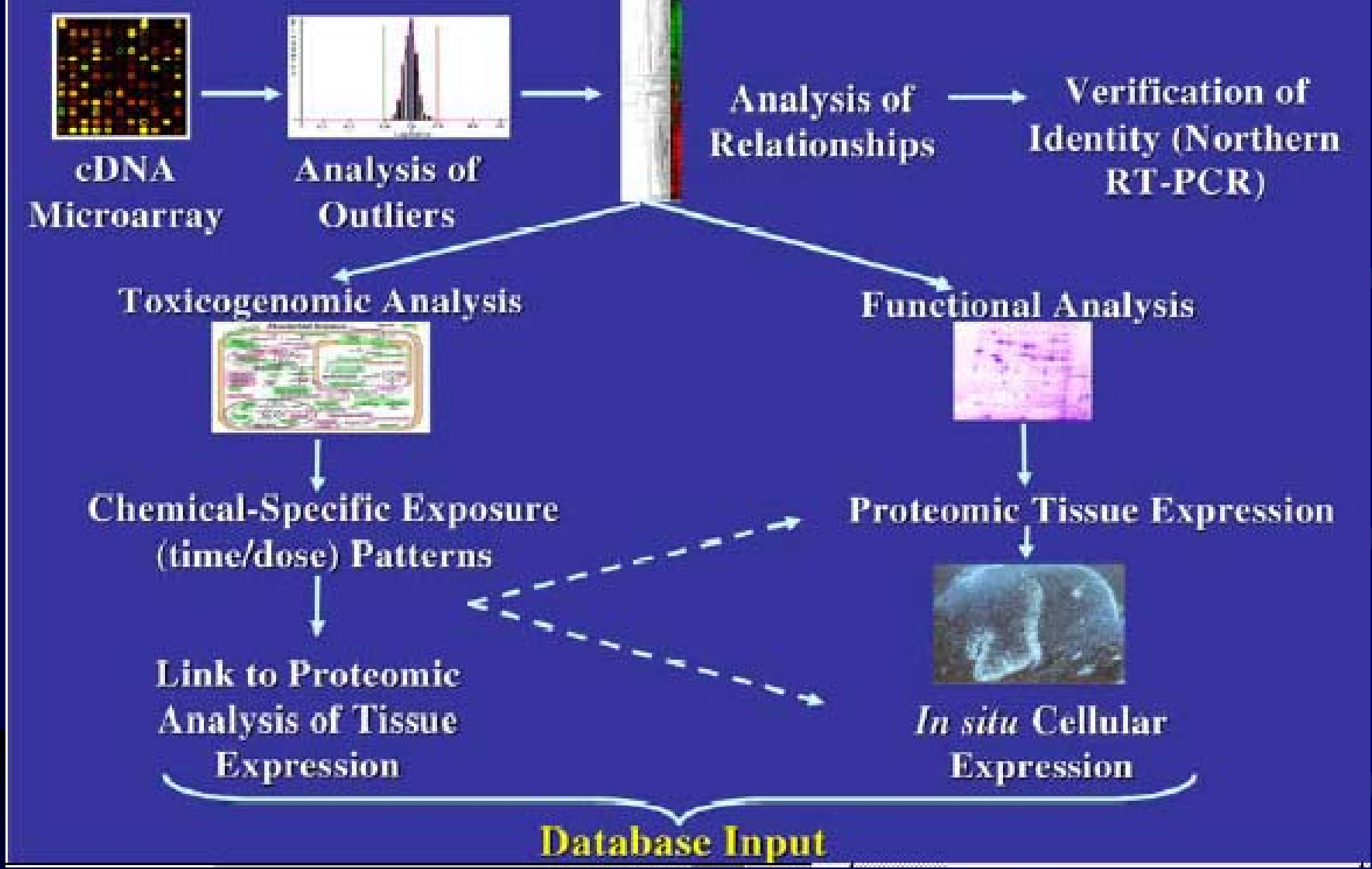

Fig. 2. Integration of microarray and proteomics data for database input.

Chemical genomics in the global study of protein functions

X.F. Steven Zheng and Ting-Fung Chan

Small, cell-permeable and target-specific chemical ligands offer great therapeutic value. They can also be used to dissect diverse biological processes, such as cellular metabolism, signal transduction and intracellular protein trafficking. With cutting-edge technologies in synthetic chemistry and ligand screening and identification, chemical ligands have become more readily available for research. Chemical ligands are used increasingly in genomics approaches to understand the global functions of proteins, an emerging frontier called 'chemical genomics'. Chemical genomics should greatly accelerate discovery in biology and medicine in the near future.

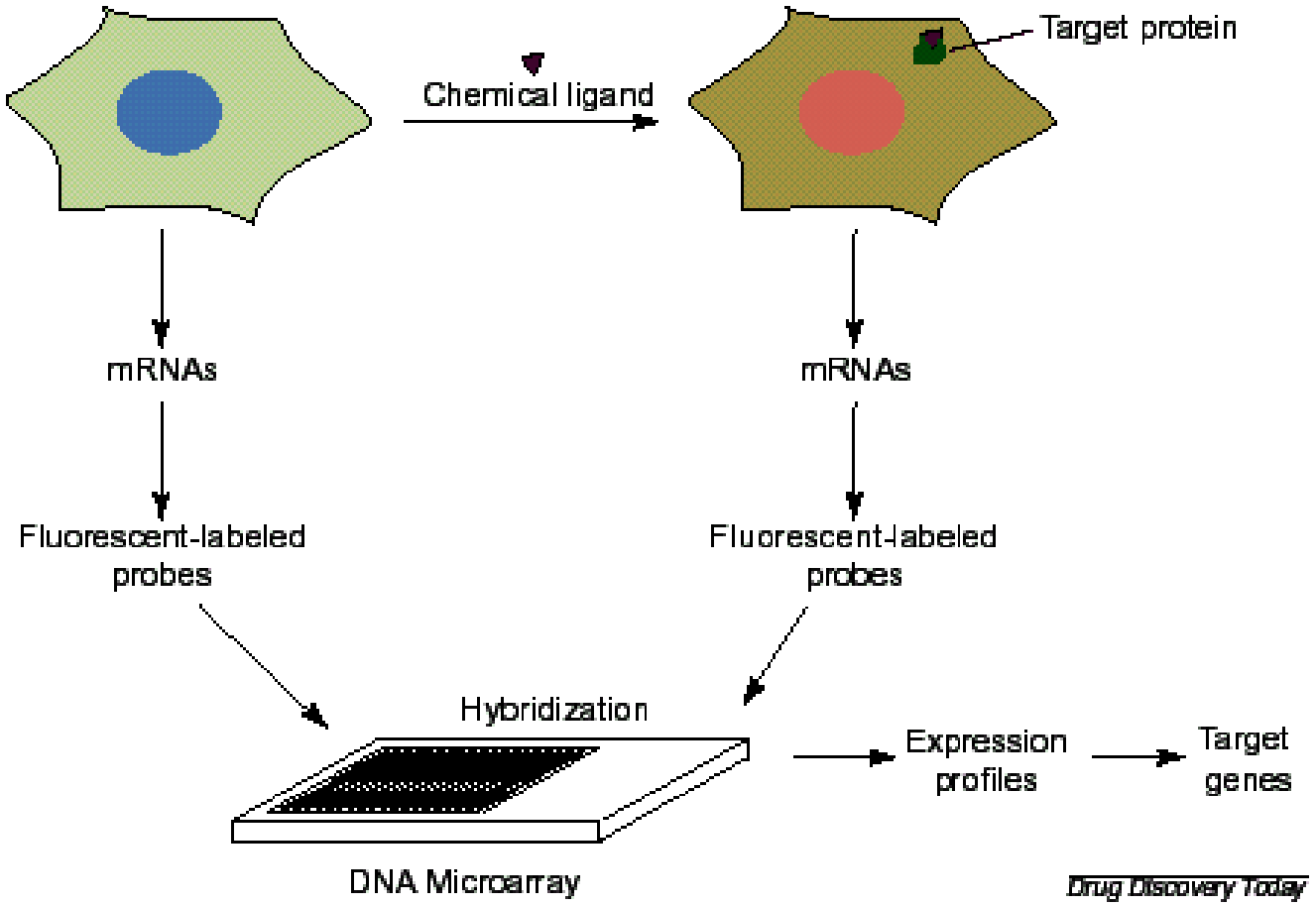

Figure 2. Chemical ligands and global gene-expression profiling. To study the role of a protein in global gene transcriptional control, a target-specific chemical ligand is used to modulate its activity. Total cellular mRNAs are extracted from the cells before and after treatment with the chemical ligand. Fluorescence-labeled cDNA are generated and used to hybridize a high-density DNA microarray. Comparing the expression profiles of the samples reveals the genes under the control of the drug target protein.

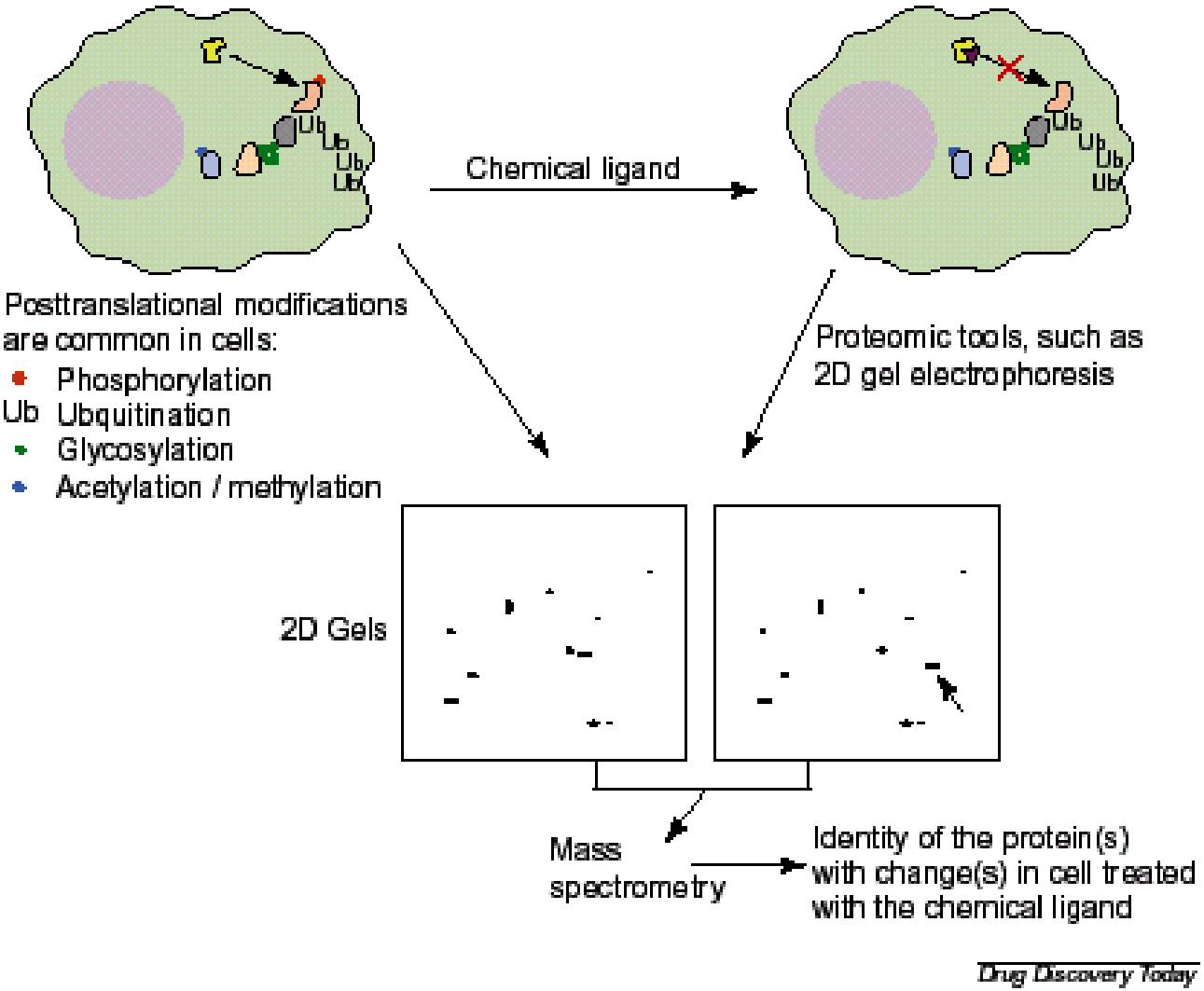

Figure 3. Chemical ligands and protein profiling. A cell-permeable, target-specific chemical ligand that perturbs posttranslational modification of a downstream target protein can be studied by protein profiling technologies, such as two-dimensional (2D) gel electrophoresis. A change in modification of a protein (as shown by an arrow) could be detected by comparison of the protein migration patterns before and after treatment with the chemical ligand. The identity of the protein can then be revealed by MS.

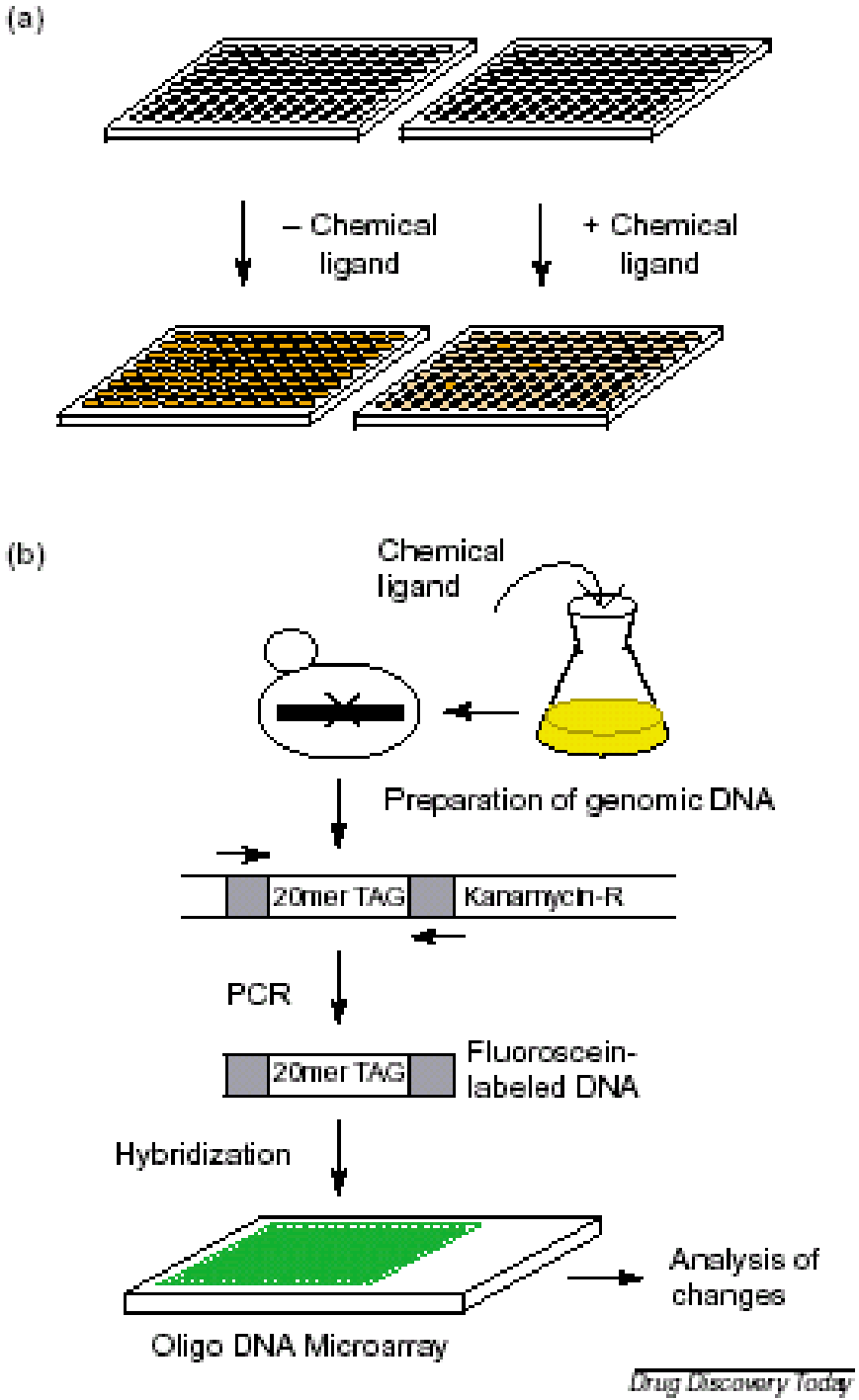

Figure 4. Chemical ligands and the global study of genetic interactions. In a typical global study of genetic interactions, the sensitivity of individual deletion mutants to a drug is systematically measured in a 96-well plate-based assay **(a)** or a bar-code oligonucleotide microarray-based assay **(b)**. Mutants that are hypersensitive or resistant to the drug can be determined by comparison of samples in the absence and presence of the drug. The genetic interaction network can be assembled by pooling genes in the same genetic or biological pathways.

Research, intervention and personalized medicine opportunities at stages of a hypothetical disease.

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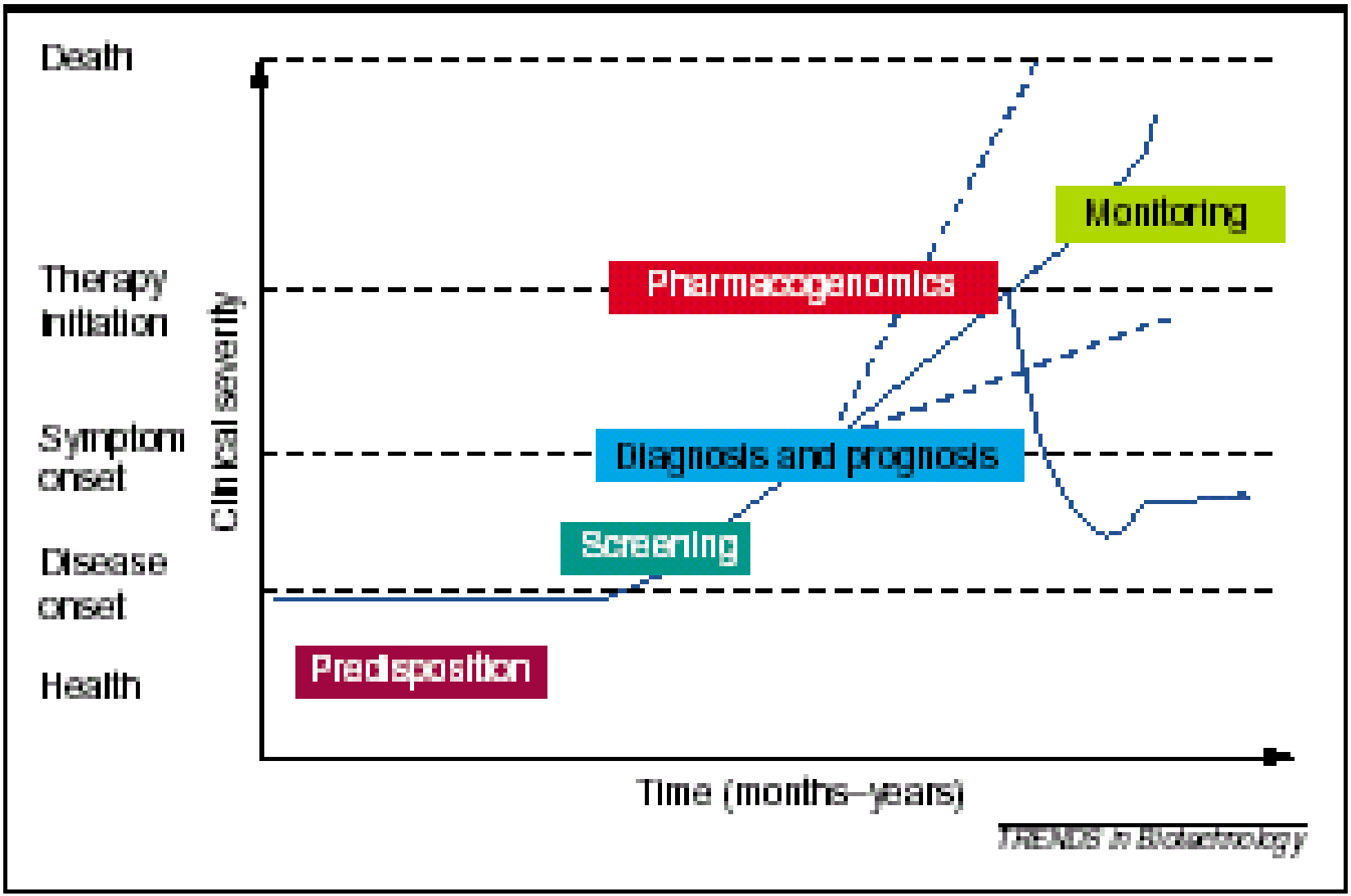

from "One Drug Fits All" to personalized therapy