Public Health in the Era of Genomics

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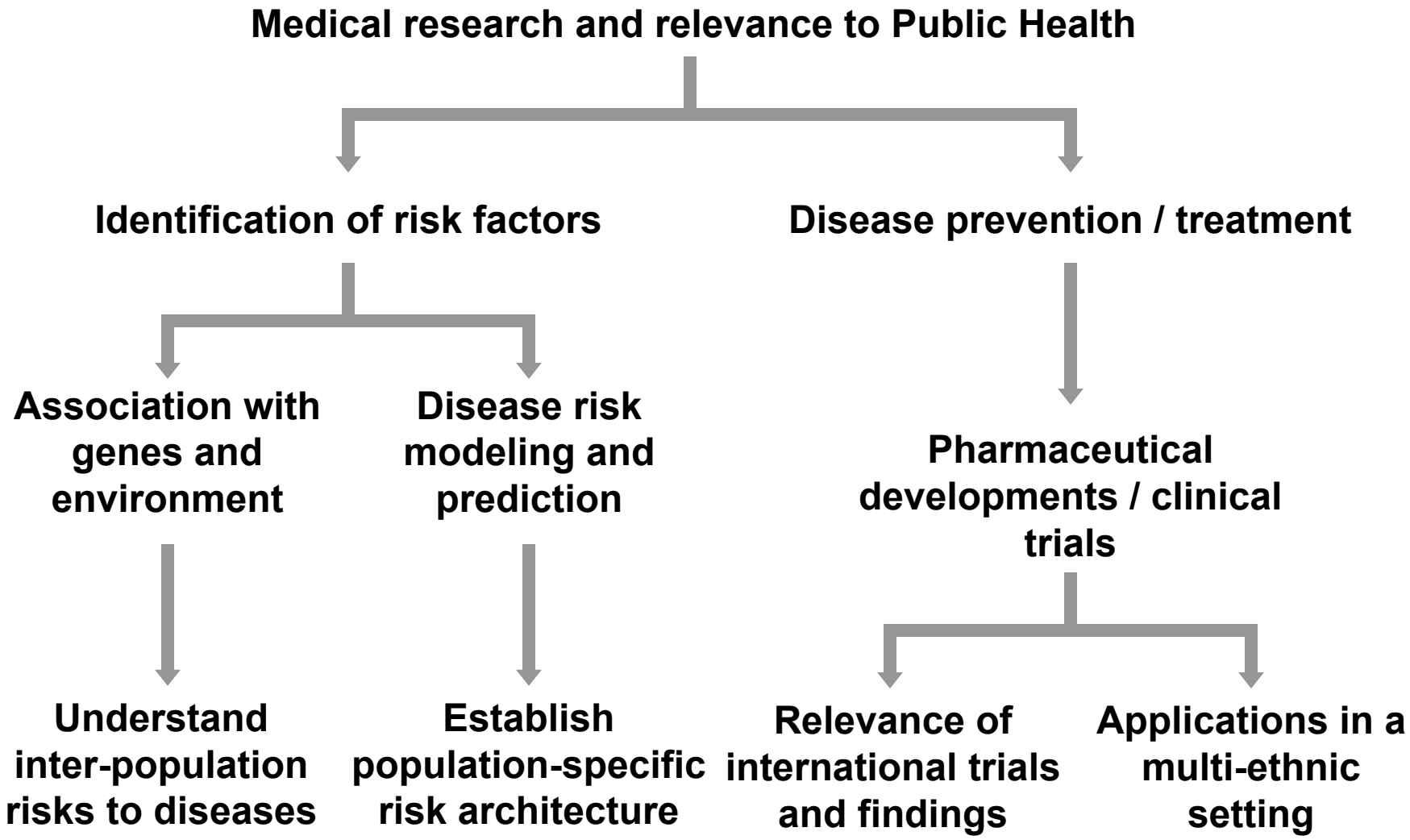
Genome Institute of Singapore, A*STAR

GEK

Medical research and Public Health



LEVELS OF "PREVENTION"

PRIMARY PREVENTION
Prevent disease onset, keep the population healthy. Health protection and health promotion.

SECONDARY PREVENTION
Early diagnosis and effective interventions to prevent or delay onset of clinical disease.

CLINICAL MEDICINE
Patient
Treatment
Institutional perspective

Public Health Genomics
Applicable in every aspects that we have showcased here

TERTIARY PREVENTION
Effective treatment to prevent or delay onset complications or death. Rehabilitation to improve quality of life.

PUBLIC HEALTH
Population
Health Protection and Promotion
National perspective

PH 1.0

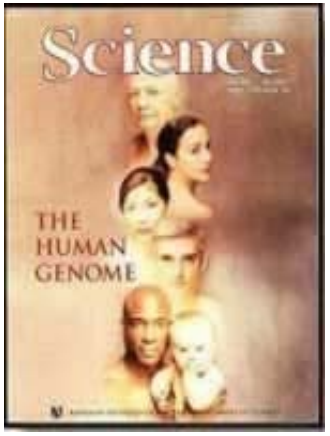
- Improvement of population health was primarily a by-product of economic and national development.
- Improvement in sanitation, housing, food and water supply.
- Little contribution from medical sciences.

Interesting Questions

- Can we identify from birth, who are the ones that are at risk for different health outcomes?
  - cystic fibrosis, G6PD deficiency, hemophilia
  - myopia, glaucoma, AMD, breast cancer, diabetes, malaria, Alzheimer's disease
  - eating disorders, risky behavior, violent tendencies
- What are the new modes of healthcare to prevent drug-resistance infectious diseases from emerging?
- Can we predict the risk of diabetes and cancer?
  - Using clinical biomarkers, genes, diet, exercise, alcohol intake, smoking, etc. other environmental factors?
- Does every drug treatment works the same for everyone?
  - If not, what are the new strategies for pharmaceutical developments and clinical medicine?

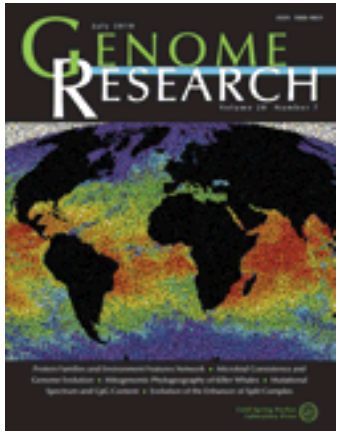
Progress of genomics in the past decade

2001



2001

2003, 2006, 2010



2009

2010

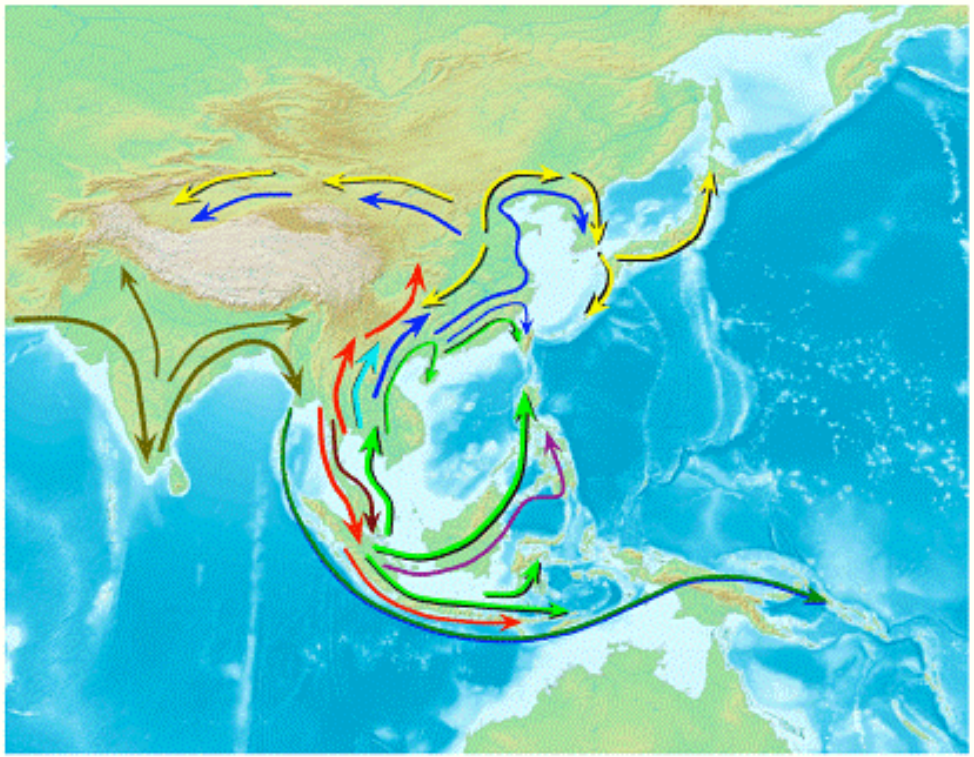
2010

Understanding the Genomic Diversity of Asian Populations

PAPGI

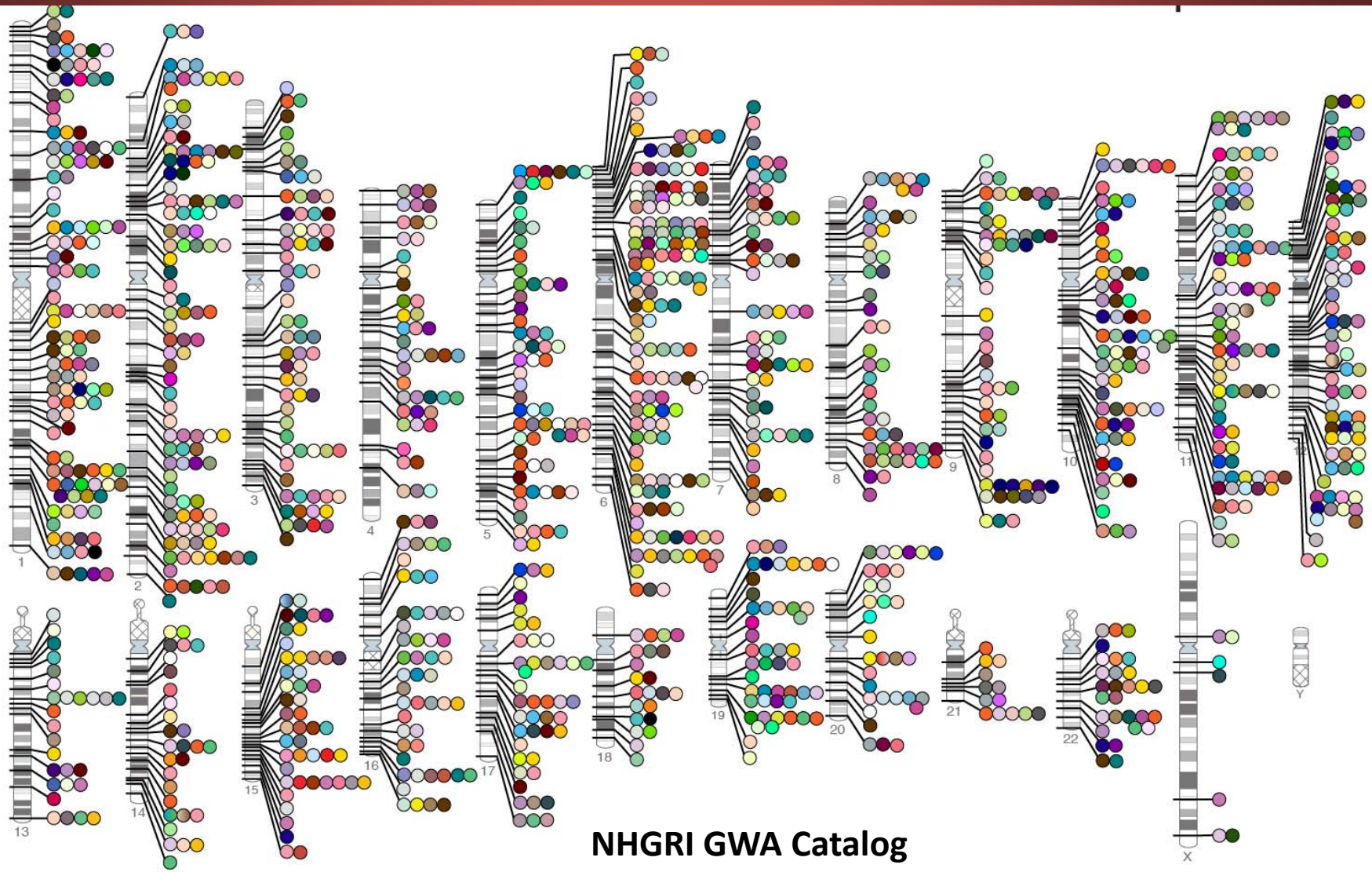
Pan Asian Population Genomics Initiative

Human Migration



- Aim to study the genetic diversity of at least 50 population groups in Asia
- Through whole-genome sequencing and high-density genotyping

Complex Traits and Common Diseases

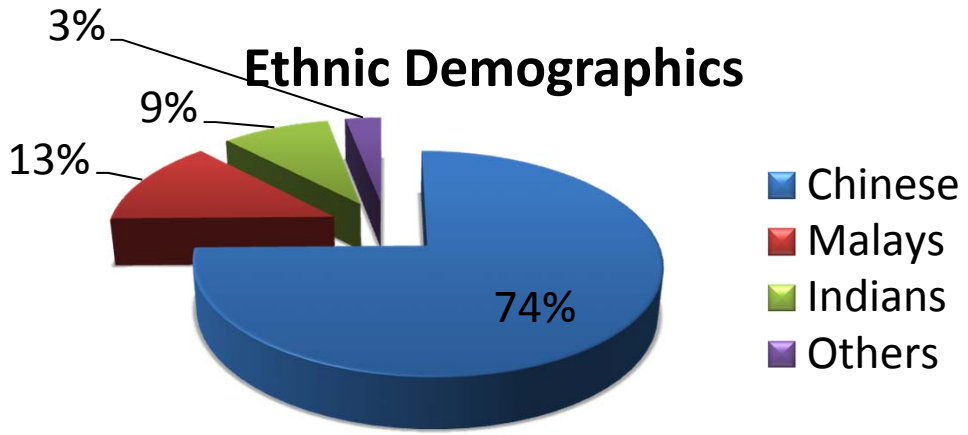


NHGRI GWA Catalog
www.genome.gov/GWAStudies

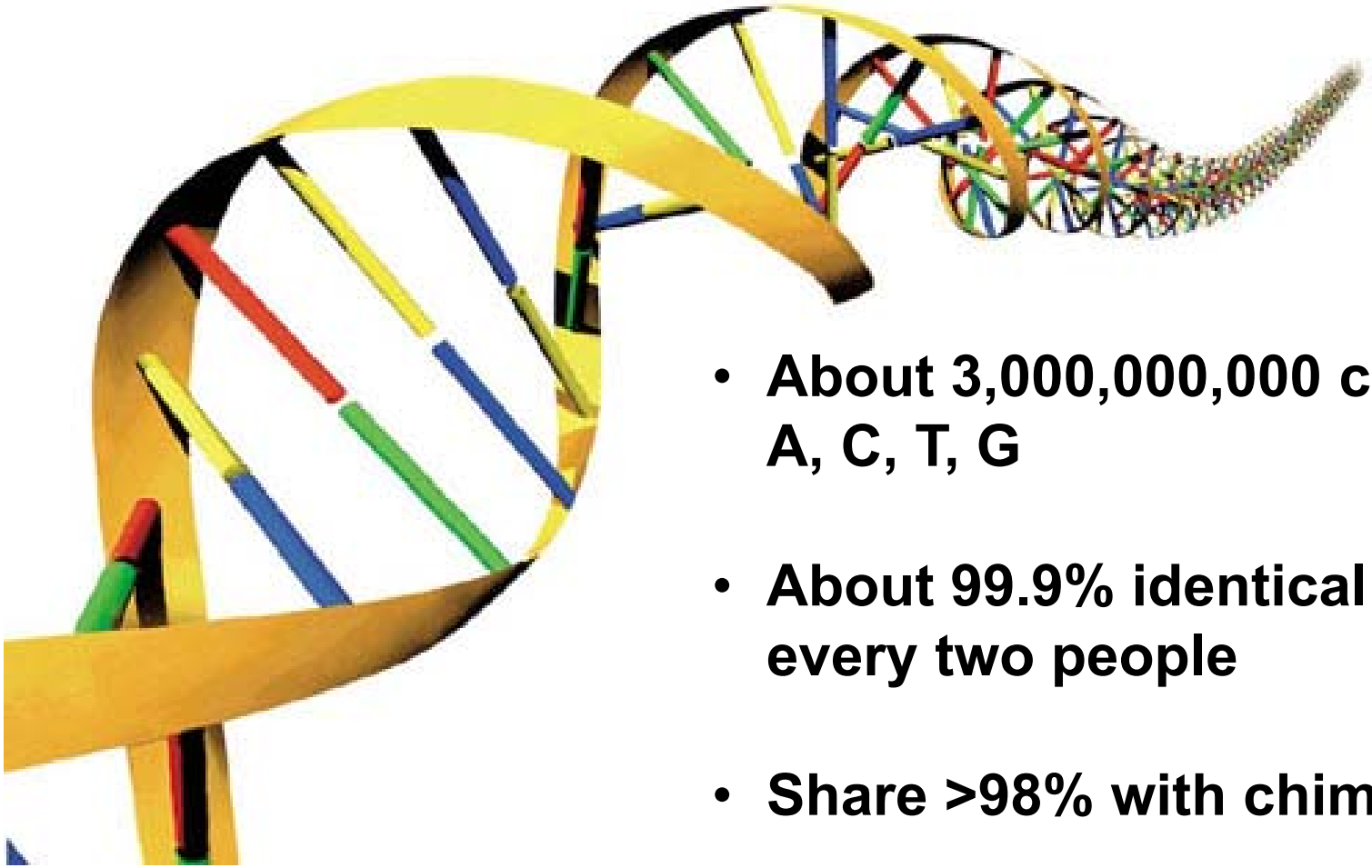
Genomics and Spectrum of Health Impact

What are the biological basis and consequences of differences between ethnic/population groups

- **To Discovering the Causes of Diseases and Complex Traits**
- **To Understanding the Clinical Implications to a Patient**
- **To Designing Healthcare Policies and Education Strategies for a Nation**



The Human Genome

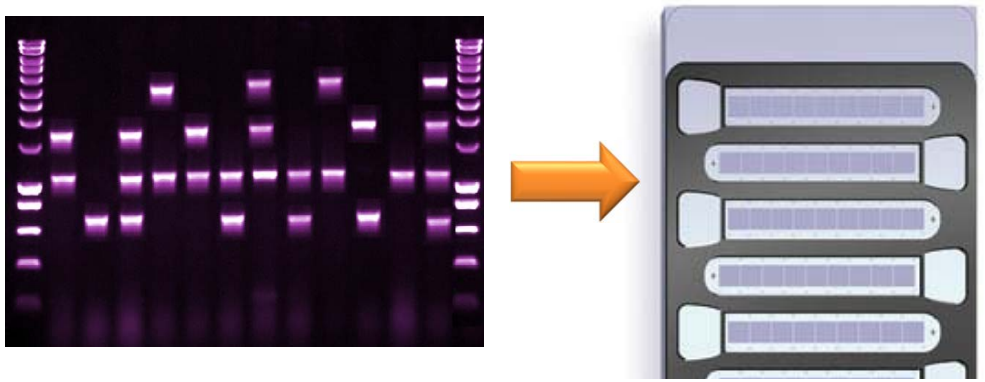


- **About 3,000,000,000 copies of A, C, T, G**
- **About 99.9% identical between every two people**
- **Share >98% with chimpanzees**
- **Greater degree of sharing within populations**

What are the genomics technologies available?

Genotyping

Looking at specific positions in the human genome, typically known sites.



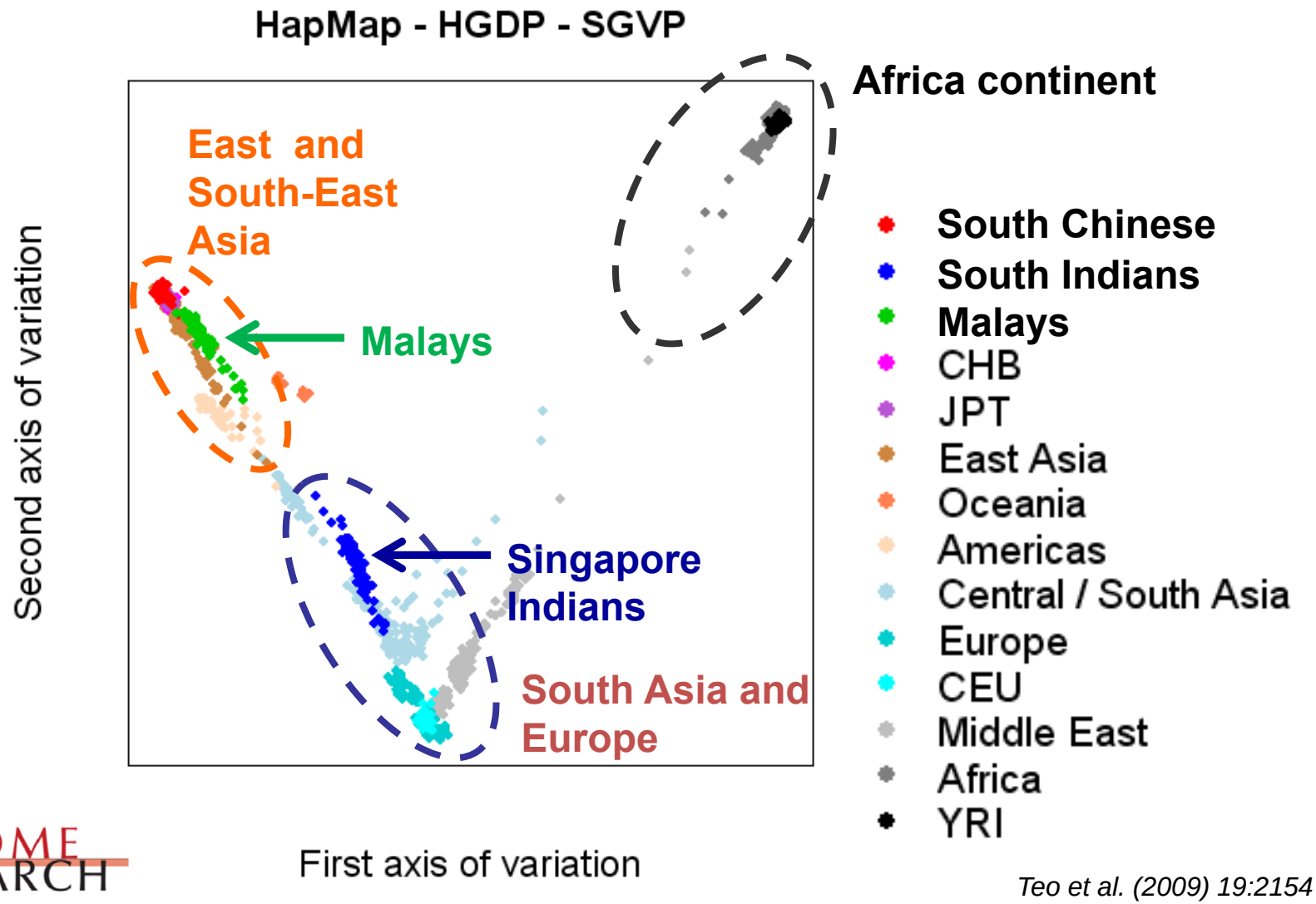
Sequencing

Agnostic investigation of the entire human genome across all 3×10^9 bases

Population Genetics

- Understanding differences between population groups, really is the very foundation to Public Health Genomics

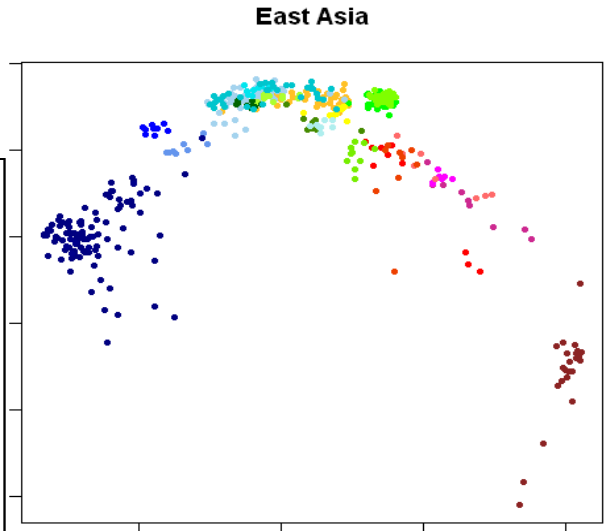
Genetic diversity across global populations



CSH PRESS GENOME RESEARCH

Teo et al. (2009) 19:2154

East and South-East Asia



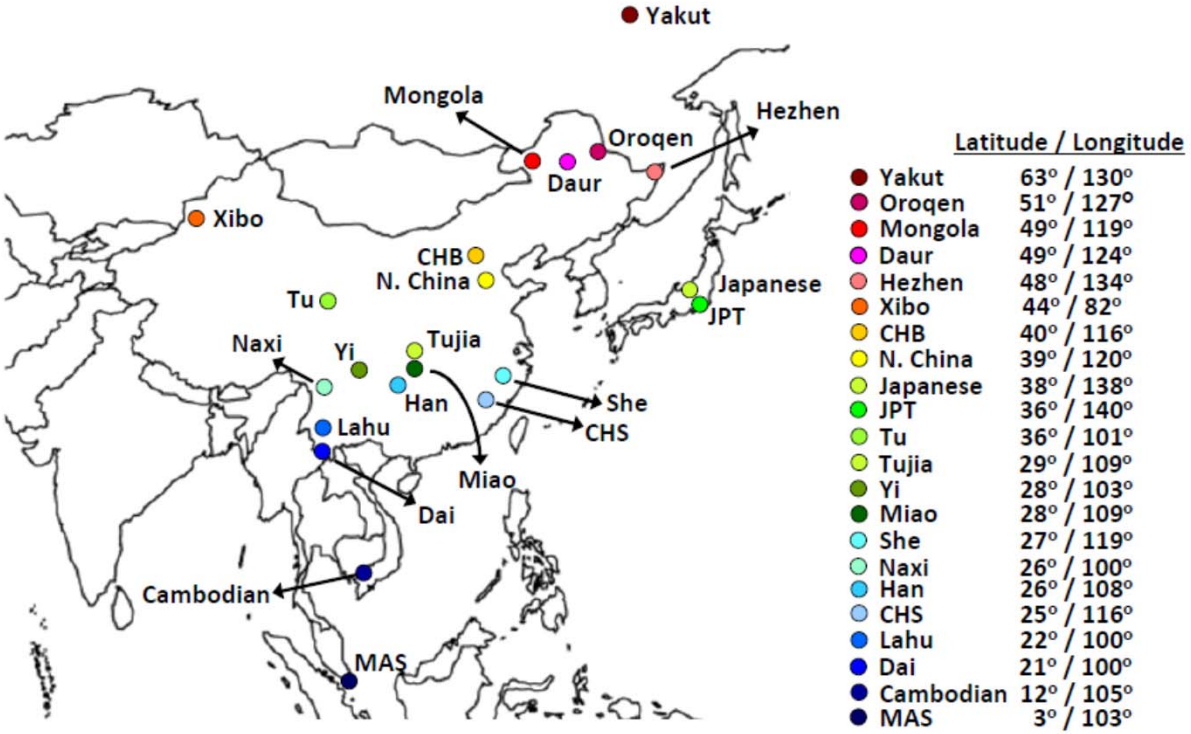
European Journal of Human Genetics (2012) 20, 102–110

www.nature.com/ejhg

ARTICLE

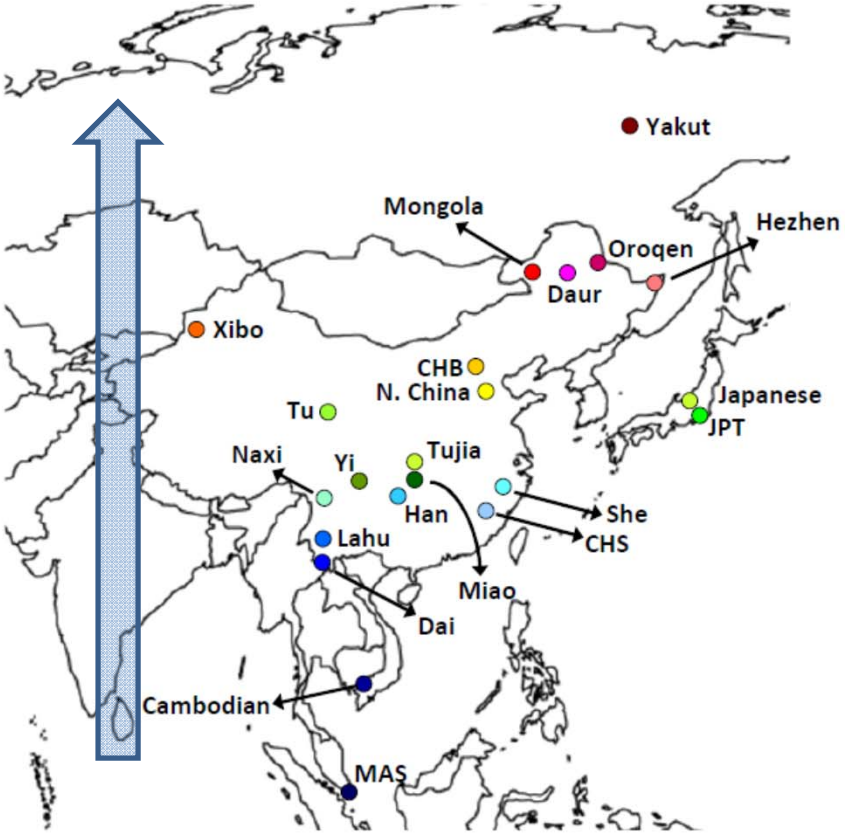
Natural positive selection and north–south genetic diversity in East Asia

Chen Suo[1,12], Haiyan Xu[1,12], Chiea-Chuen Khor[2], Rick TH Ong[1,2], Xueling Sim[1], Jieming Chen[2], Wan-Ting Tay[3], Kar-Seng Sim[2], Yi-Xin Zeng[4,5], Xuejun Zhang[6,7], Jianjun Liu[2], E-Shyong Tai[8,9], Tien-Yin Wong[3,9,10], Kee-Seng Chia[1,8] and Yik-Ying Teo*[,2,8,11]



	Latitude / Longitude
Yakut	63° / 130°
Oroqen	51° / 127°
Mongola	49° / 119°
Daur	49° / 124°
Hezhen	48° / 134°
Xibo	44° / 82°
CHB	40° / 116°
N. China	39° / 120°
Japanese	38° / 138°
JPT	36° / 140°
Tu	36° / 101°
Tujia	29° / 109°
Yi	28° / 103°
Miao	28° / 109°
She	27° / 119°
Naxi	26° / 100°
Han	26° / 108°
CHS	25° / 116°
Lahu	22° / 100°
Dai	21° / 100°
Cambodian	12° / 105°
MAS	3° / 103°

East and South-East Asia



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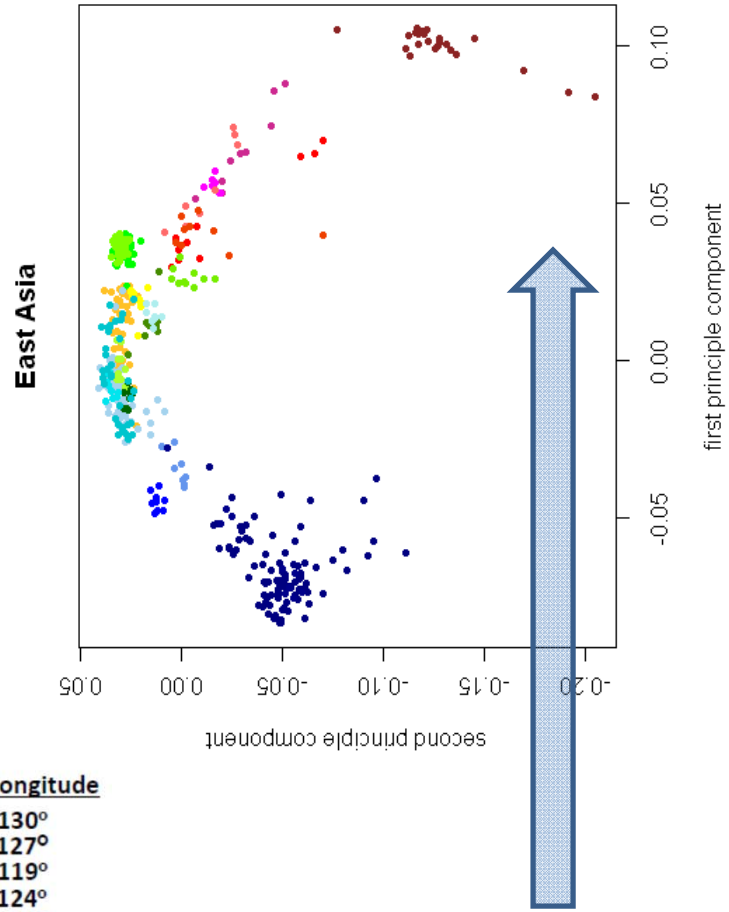
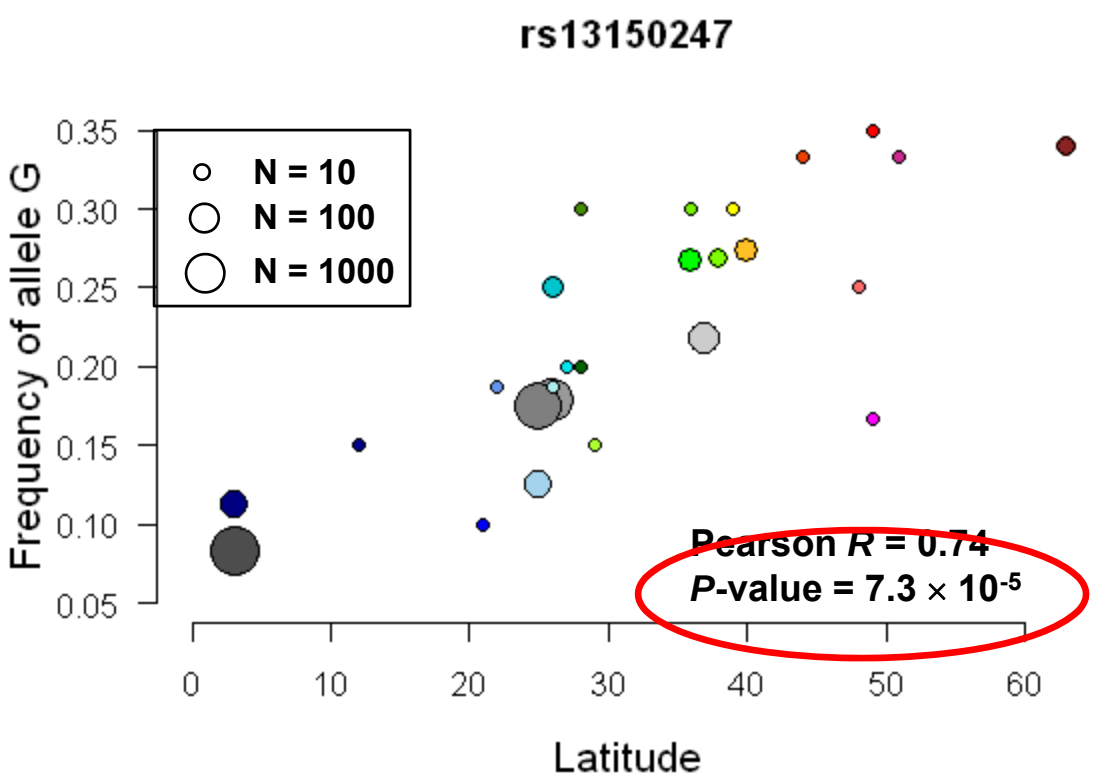
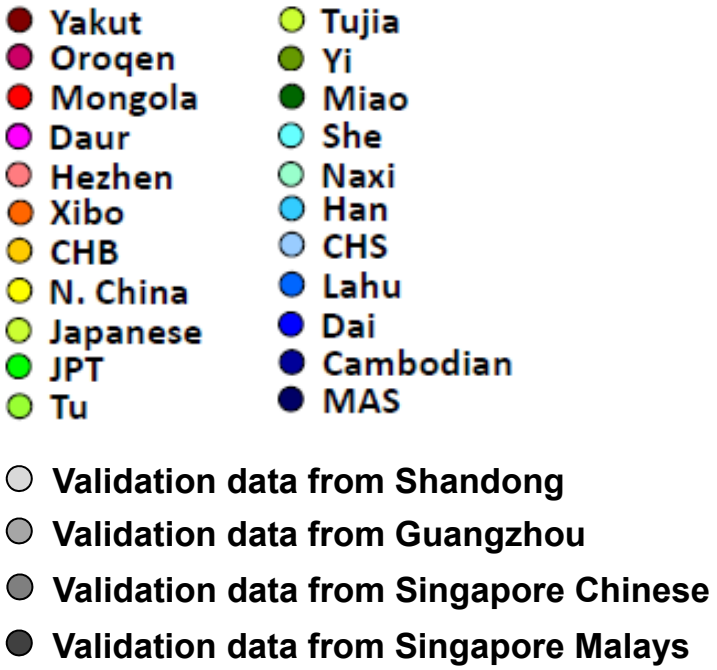


Suo et al. EJHG(2011) Jul 27

Metabolism of alcohol?





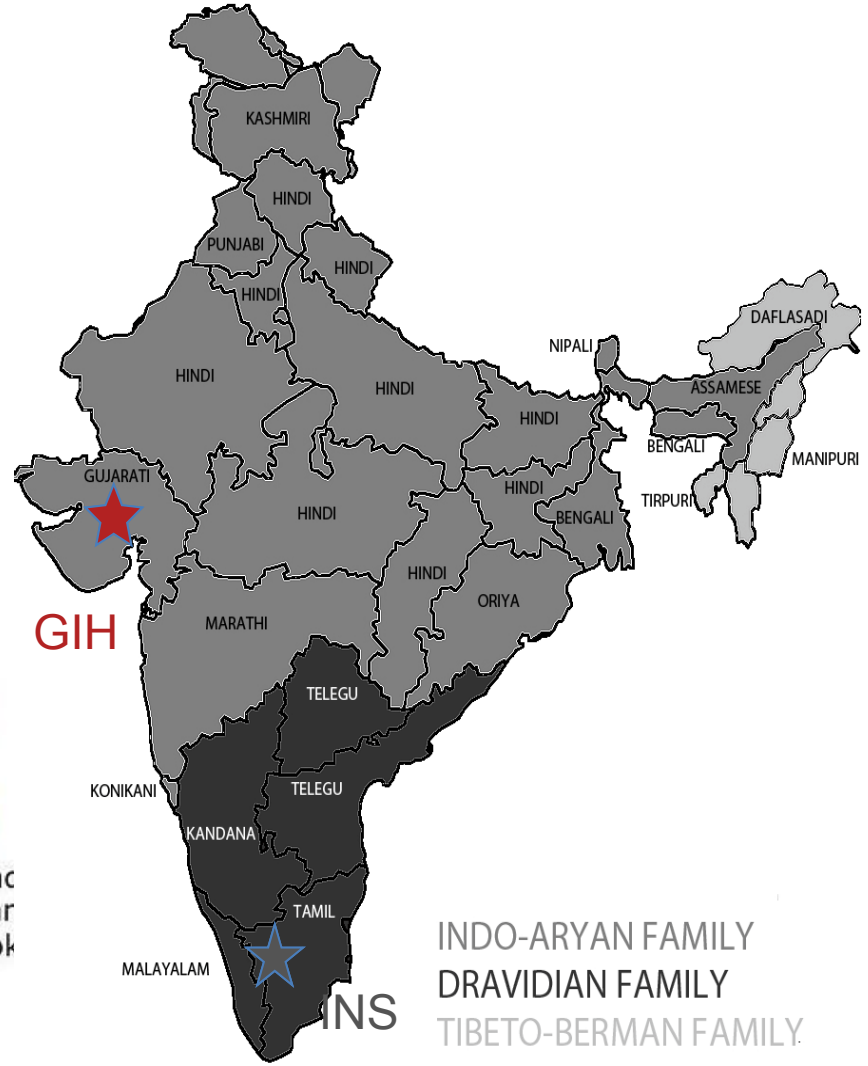
Suo et al. EJHG(2011) Jul 27

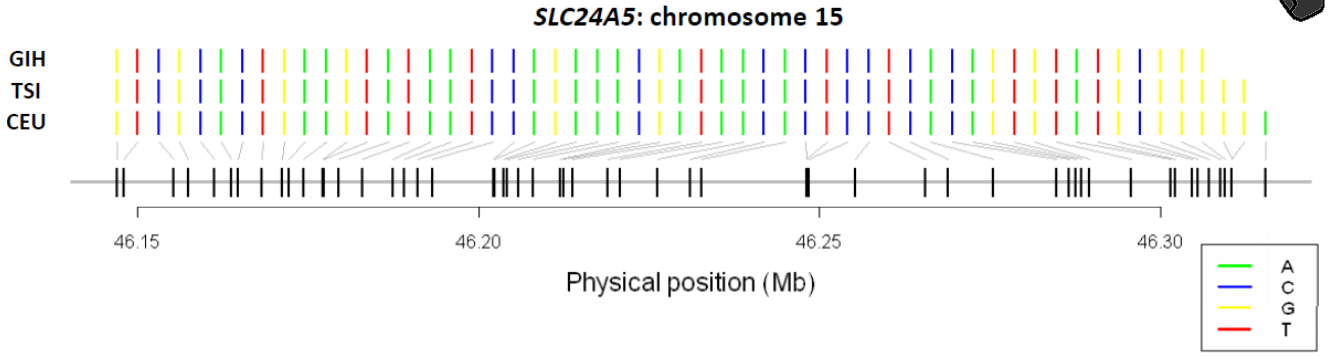
North-South Indian differences

North-West Indian Punjabi Sikh Women

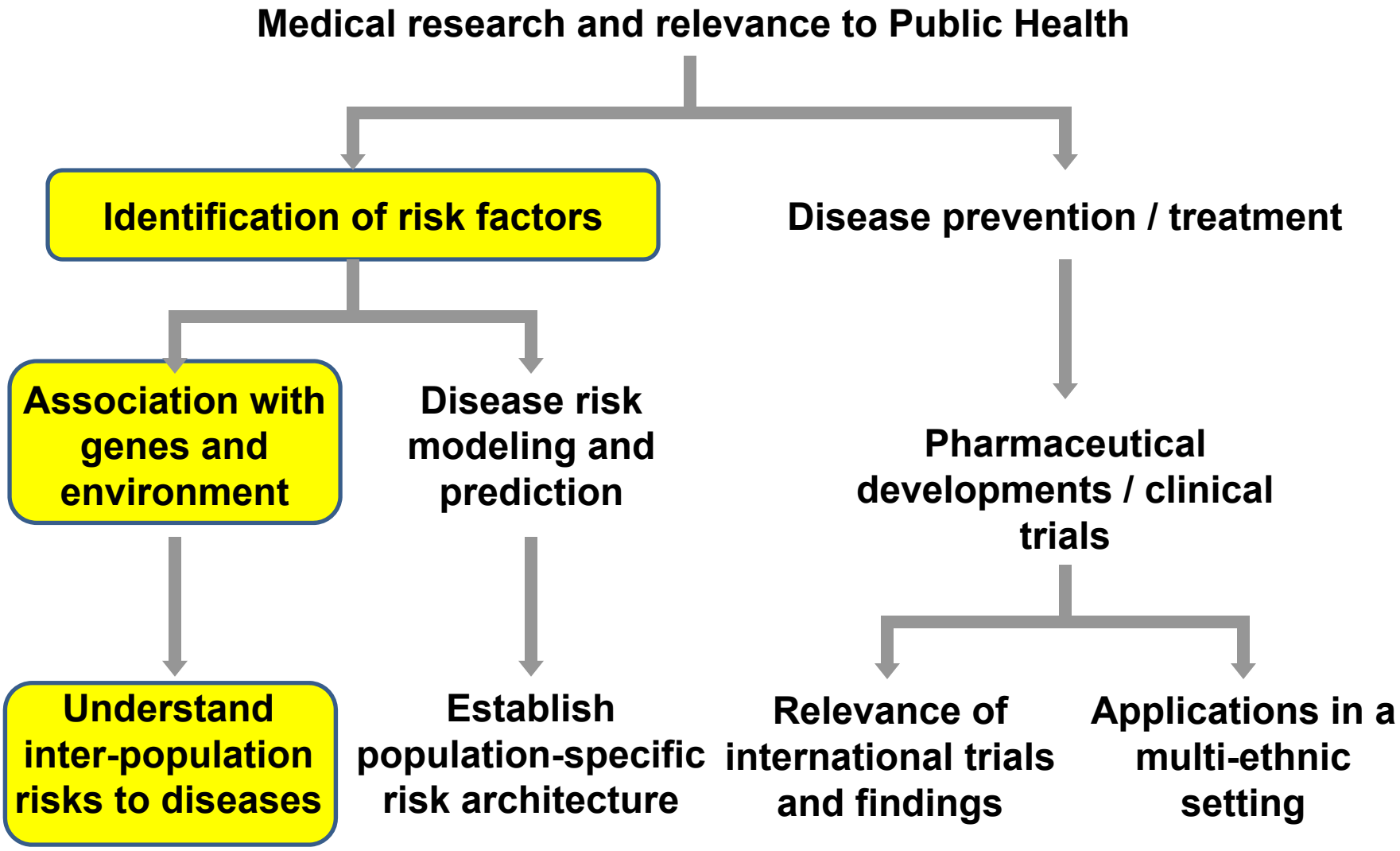
South Indian Tamil Hindu Women

* People of Southern India are much darker then people of Northern Inc
People of North India have narrower features, narrower noses, and ar
more Caucasoid then people of South India. People of North India look
similar to people of Afghanistan, or the Middle East, while people of
Southern India look similar to the Aboriginals of Austrailia.





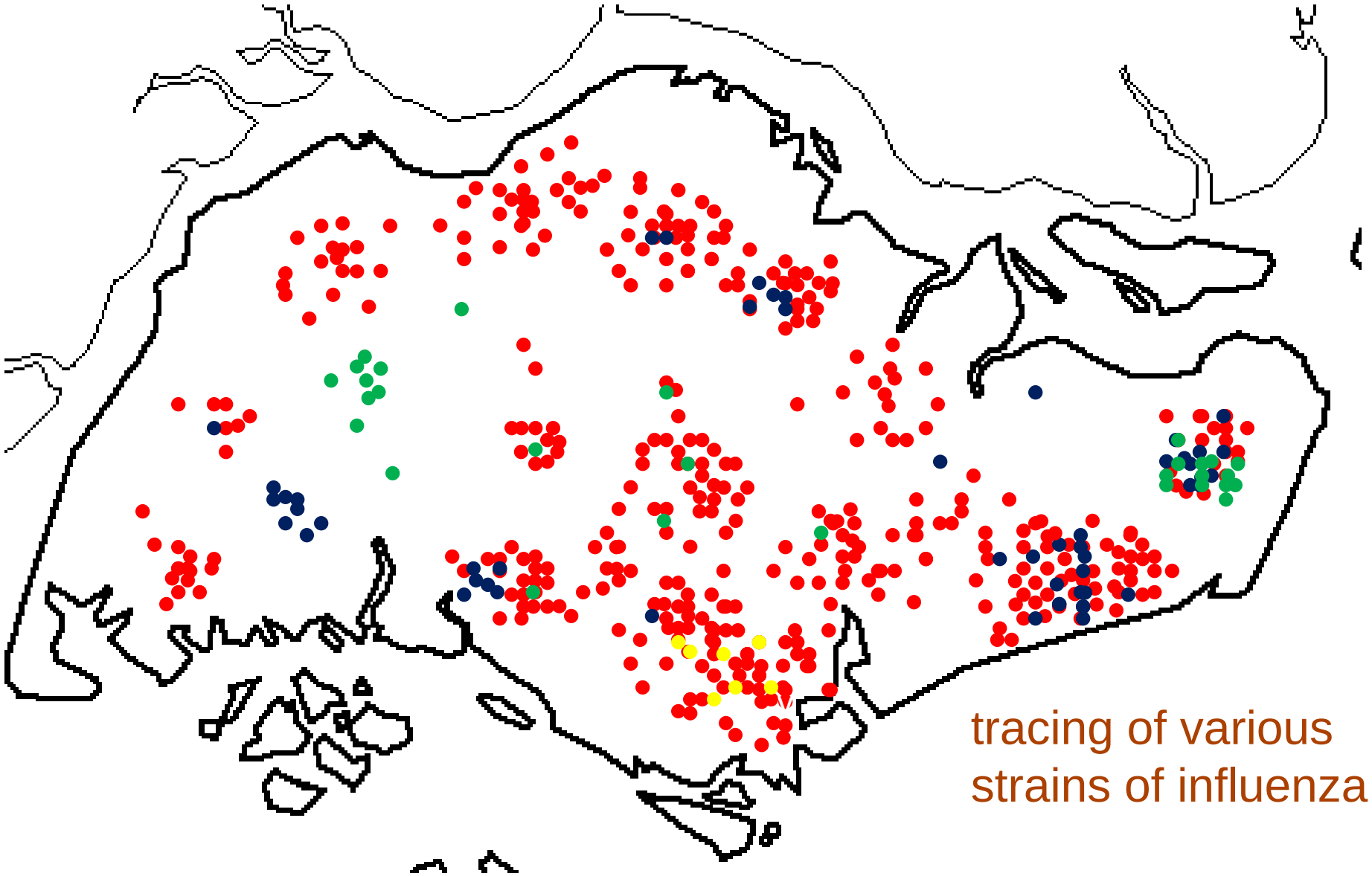
Medical research and Public Health



Genomic Medicine

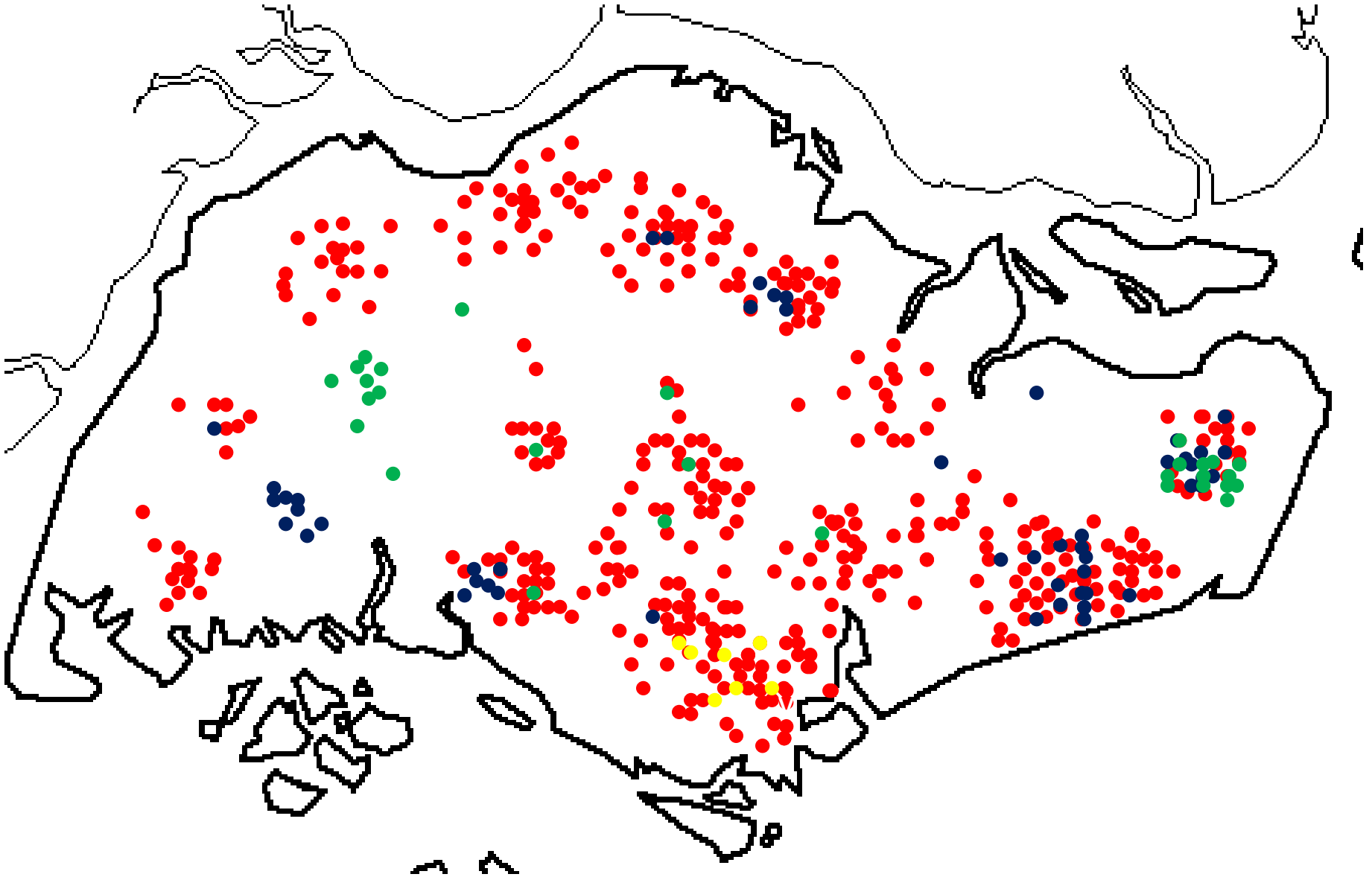
- Clinical medicine mainly reliant on observational evidence, with condition X + condition Y → disease onset.
- Already a reality in cancer medicine
  - Profile the tumours to identify the kind of cancer, and to recommend downstream therapeutic interventions
- Diabetes (complications include nephropathy, retinopathy, etc.)
- Early diagnosis of dengue versus normal flu (pathogen genomics)
- Use of genomics technology to track hospital-based or community-based spread of infectious diseases
  - Building a network or “infectivity tree” to track source/cause of the transmission, and to identify the introduction of new strains
  - Change in clinical practice and hospital operating procedures
  - Evaluate governmental policies to contain community infection

Transmission Epidemiology



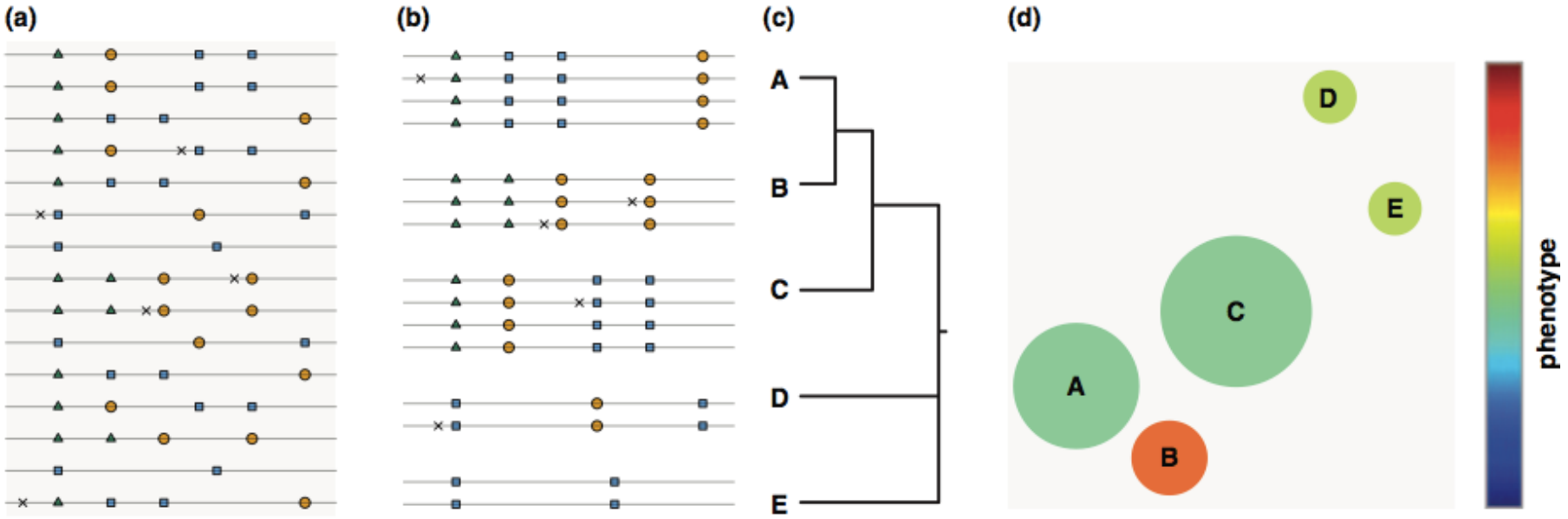
tracing of various strains of influenza

Transmission Epidemiology



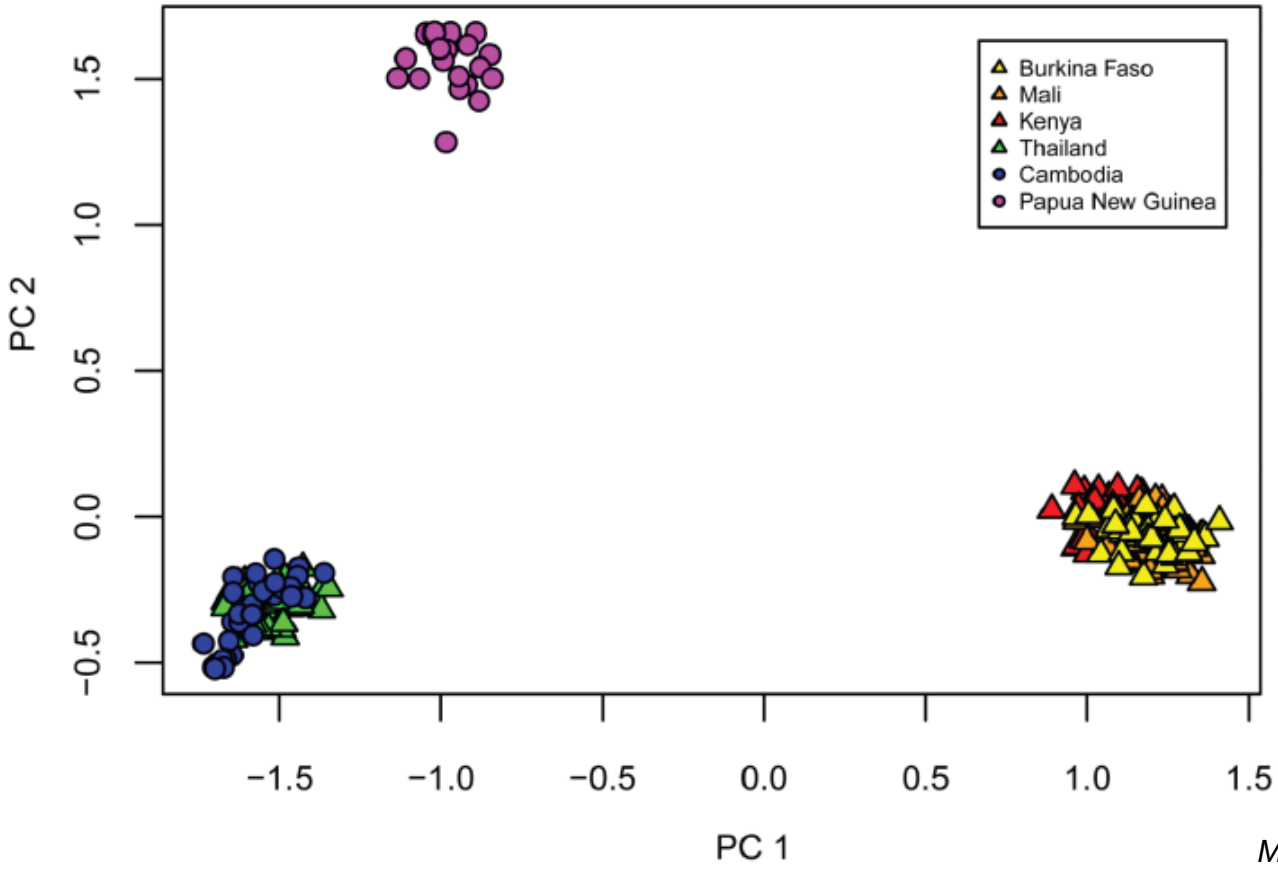
Case Study: Viral pathogen genomics

- Methodology development to identify and characterize intra-host dengue virus quasi-species
- Longitudinal pathogen sampling, and host genetic data
- Investigate host and viral genetic factors to DF/DHF progression



Malaria parasite genomics

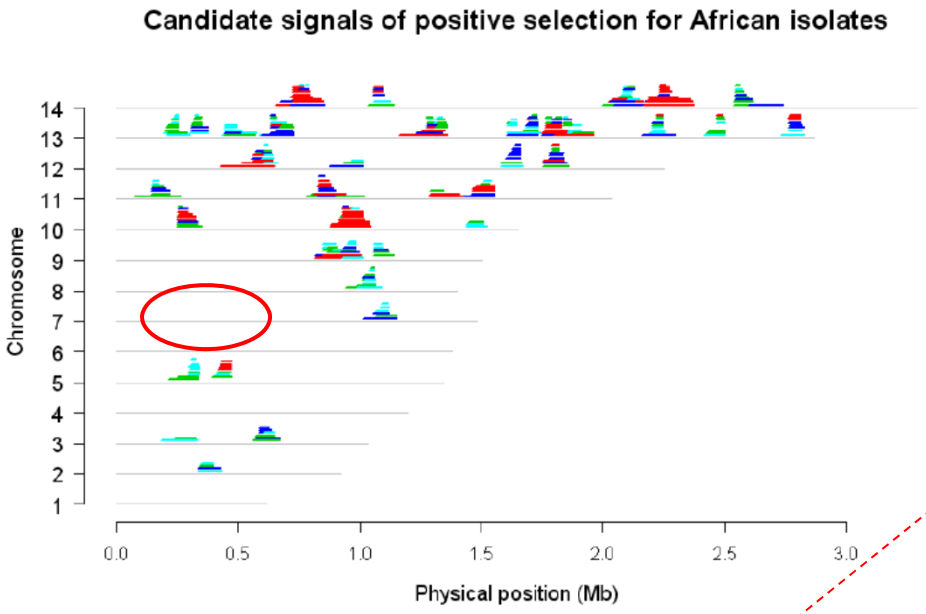
- Mapping genomic diversity of *P. falciparum*
- Genomics signatures of adaptation and drug-resistance (positive selection)

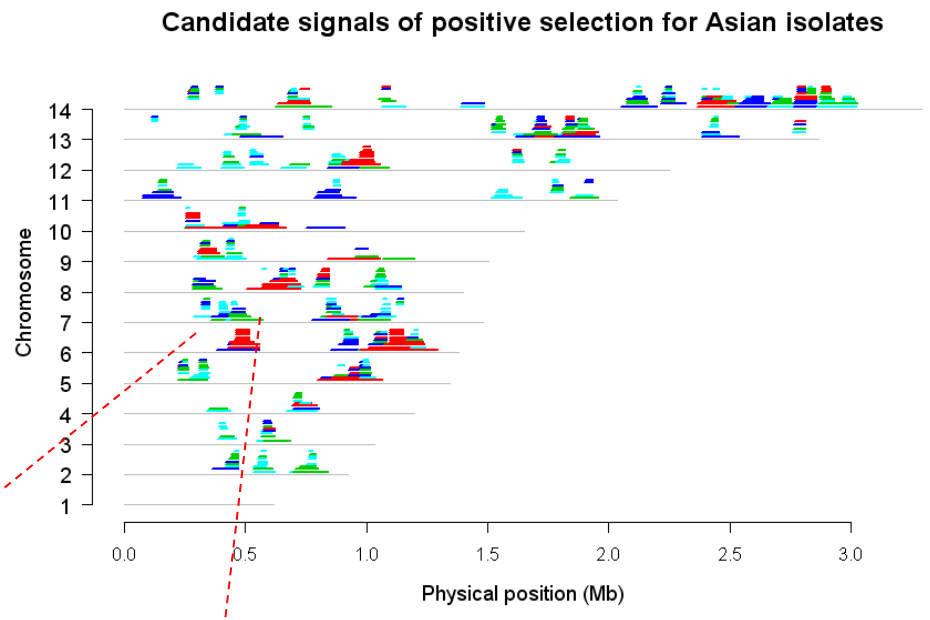


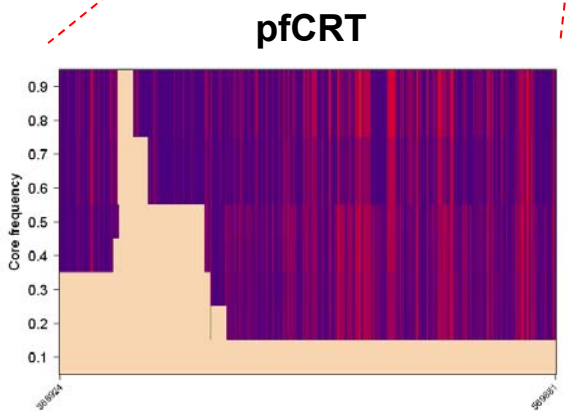
population differences that are linked to certain traits in humans

Manske et al. Nature(2012) 487:375-379

Malaria parasite genomics







Chloroquine resistance (emerged in Asia)

Surveillance and control of infectious diseases with genomic technology

- Vaccines, prophylaxis and treatment for infectious diseases have limited effective period
  - Think antibiotics resistance, antiretroviral resistance, antimalarial resistance

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7 April 2011 Last updated at 02:57 GMT

Share

Europe 'losing' superbugs battle

By Michelle Roberts
Health reporter, BBC News

Antibiotic-resistant infections have reached unprecedented levels and now outstrip our ability to fight them with existing drugs, European health experts are warning.

Each year in the EU over 25,000 people die of bacterial infections that are able to outsmart even the newest antibiotics.

The World Health Organization says the situation has reached a critical point.

A united push to make new drugs is urgently needed, it says.

Without a concerted effort, people could be dealing with the "nightmare scenario" of a worldwide spread of untreatable infections, says the WHO.

One example is the New Delhi or NDM-1 superbug recently found in UK

NDM-1 is carried by Gram-negative bacteria like Klebsiella

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5 April 2012 Last updated at 20:13 GMT

1.8K Share

Resistance spread 'compromising' fight against malaria

By Matt McGrath
Science reporter, BBC World Service

Scientists have found new evidence that resistance to the front-line treatments for malaria is increasing.

They have confirmed that resistant strains of the malaria parasite on the border between Thailand and Burma, 500 miles (800km) away from previous sites.

Researchers say that the rise of resistance means the effort to eliminate malaria is "seriously compromised".

The details have been **published in The Lancet** medical journal.

For many years now the most effective drugs against malaria have been derived from the Chinese plant, *Artemisia annua*. It is also known as sweet

Malaria is spread by mosquitoes

Related Stories

Malaria drugs may affect babies

infectious diseases have a very large burden

Surveillance and control of infectious

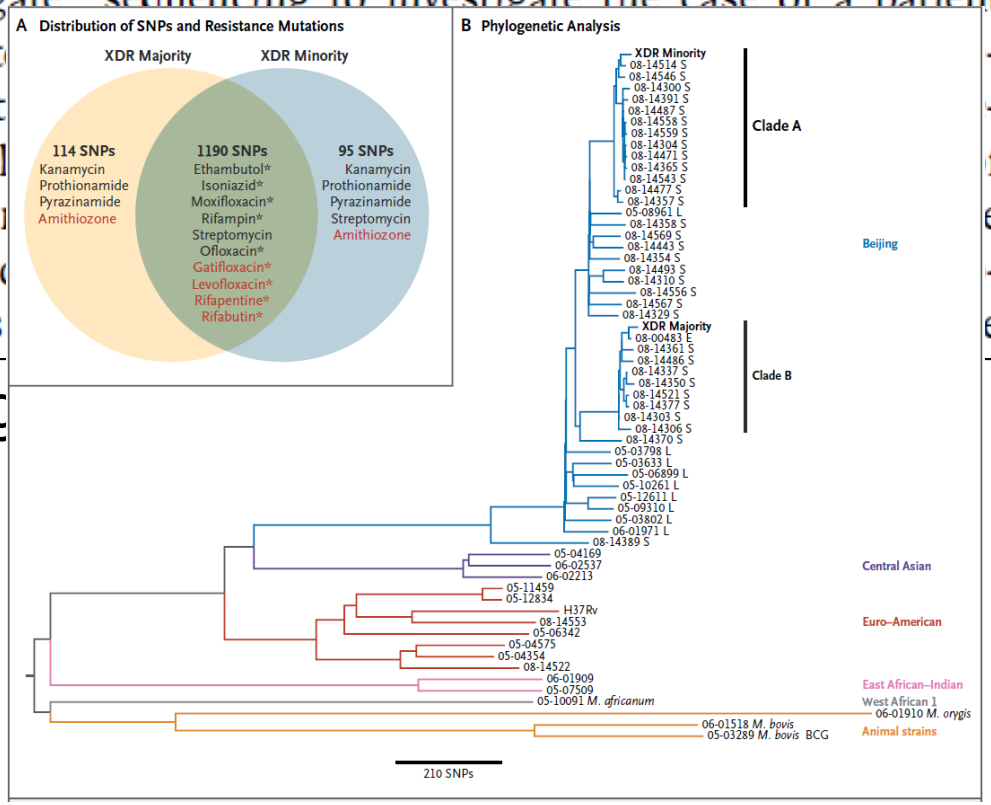
Whole-Genome Sequencing for Rapid Susceptibility Testing of *M. tuberculosis*

Sharon J. Peacock, Ph.D.
University of Cambridge

N ENGL J MED 369;3 NEJM.ORG JULY 18, 2013

TO THE EDITOR: Efforts to contain drug-resistant tuberculosis depend on the rapid detection and effective treatment of cases, together with public health interventions to prevent and investigate ongoing transmission. The necessary laborat support for these activities includes the ident cation of the *Mycobacterium tuberculosis* compl antimicrobial susceptibility testing, and bacte genotyping. However, even in well-resour countries, it typically takes 1 to 2 months *losis* complex for several weeks, until sufficient DNA can be extracted.[2,4]

Here we report the use of rapid whole-genome sequencing to investigate the case of a patient



- Does genomic technolog

Concept of Genomic Surveillance

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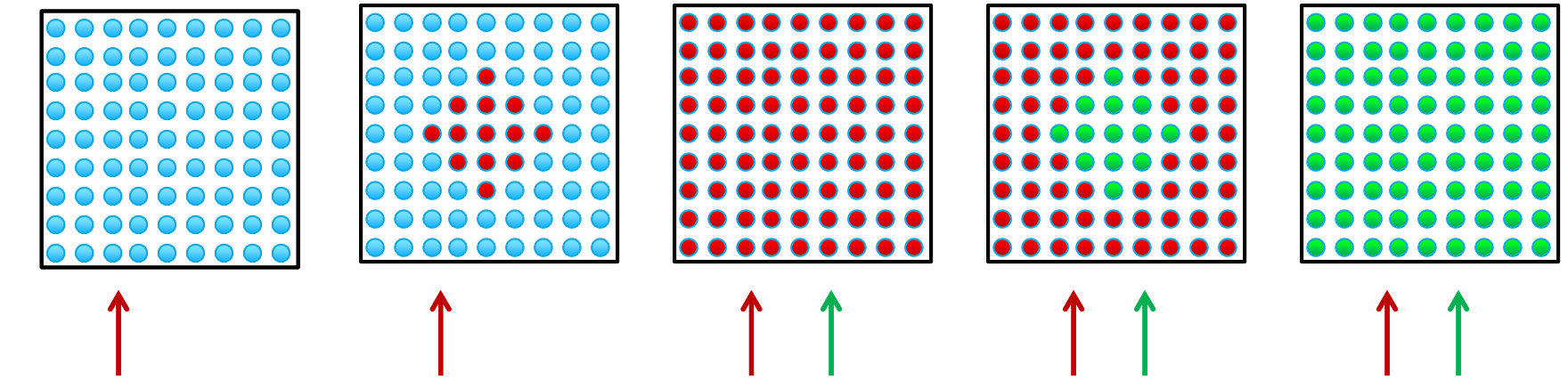
NO GENOMIC SURVEILLANCE



Treatment 1

Emergence of resistance

Fixation of resistant strain

Assignment of Treatment 2

Emergence of multi-drug resistance

Fixation of multi-drug resistant strain

- **Drug susceptible strain**
- **Treatment 1 resistant**
- **Treatment 1 and 2 resistant**

Concept of Genomic Surveillance

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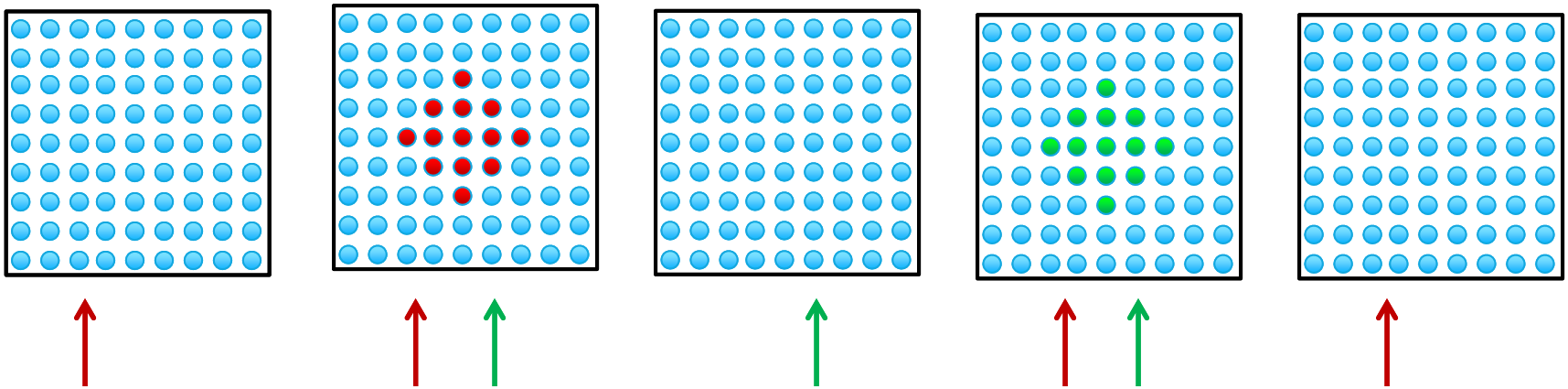
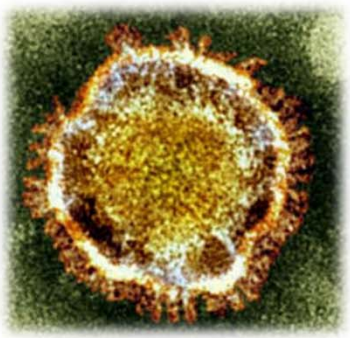
WITH ACTIVE GENOMIC SURVEILLANCE

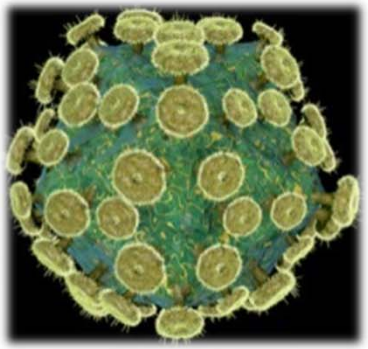


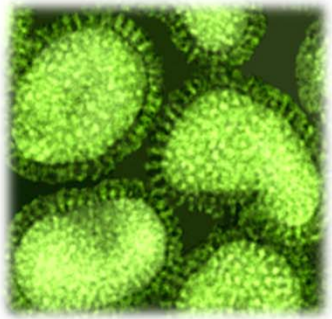
- Drug susceptible strain
- Treatment 1 resistant
- Treatment 2 resistant

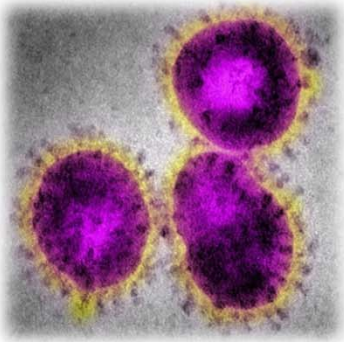
identification of mutated strains within individuals and target these people with a different treatment. considered as a genomic surveillance

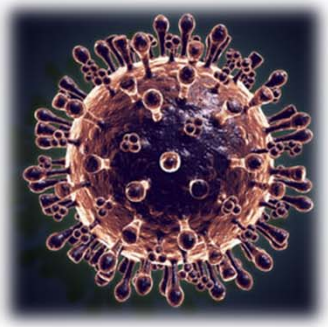

Ginsetin
Ginsetin





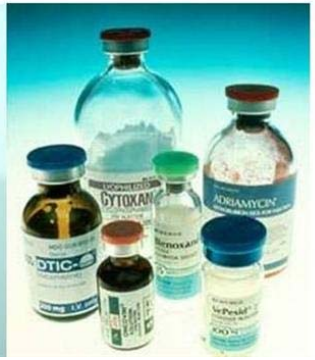


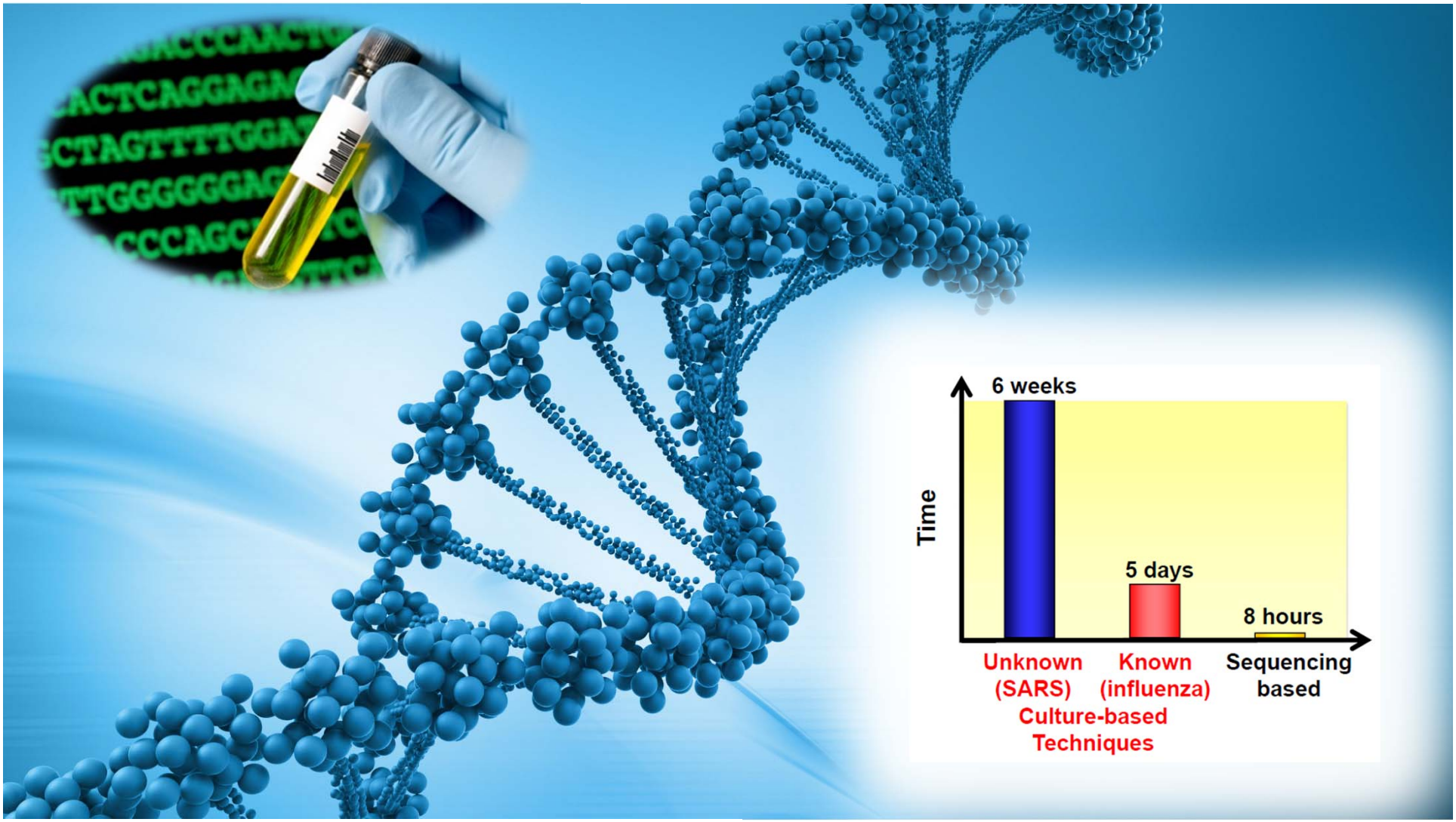


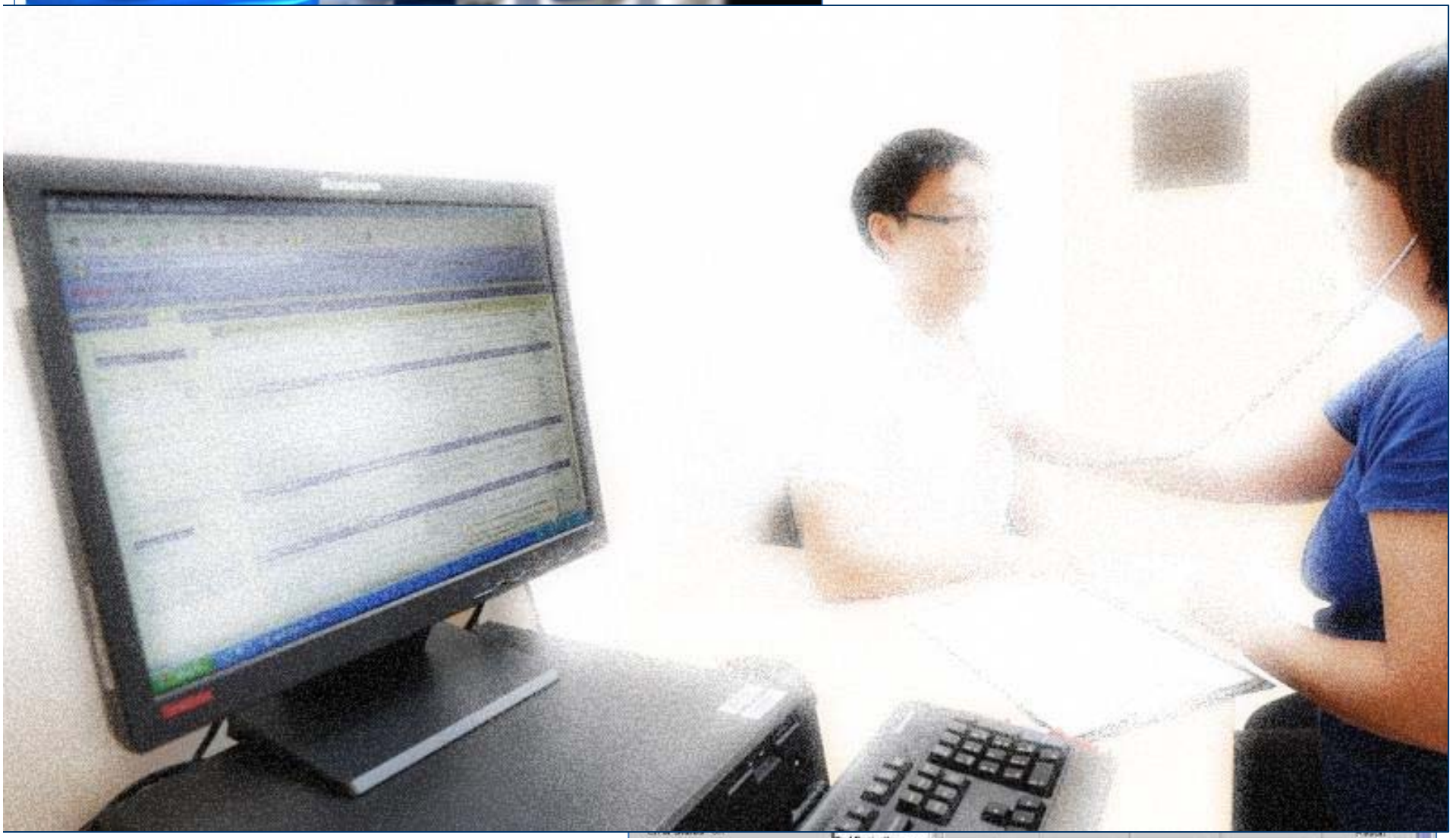



Rx
Rifampicin &
Isoniazid Tablets
IFAZEX-2
इफाजैक्स—2
10 x 10 Tablets
IFAZEX-2

QUINOLONES


CYTOXAN
ADRIAMYCIN


6 weeks
5 days
8 hours
Time
Unknown (SARS)
Known (influenza)
Sequencing based
Culture-based Techniques


User support
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Probe D 19.1 248.0 POS PASS
Probe C 17.7 278.0 POS PASS
Probe E 18.4 174.0 POS PASS
Probe B 18.8 214.0 POS PASS
Rg 27.4 248.0 NA PASS
Probe A 17.3 228.0 POS PASS

Concept of Genomic Surveillance

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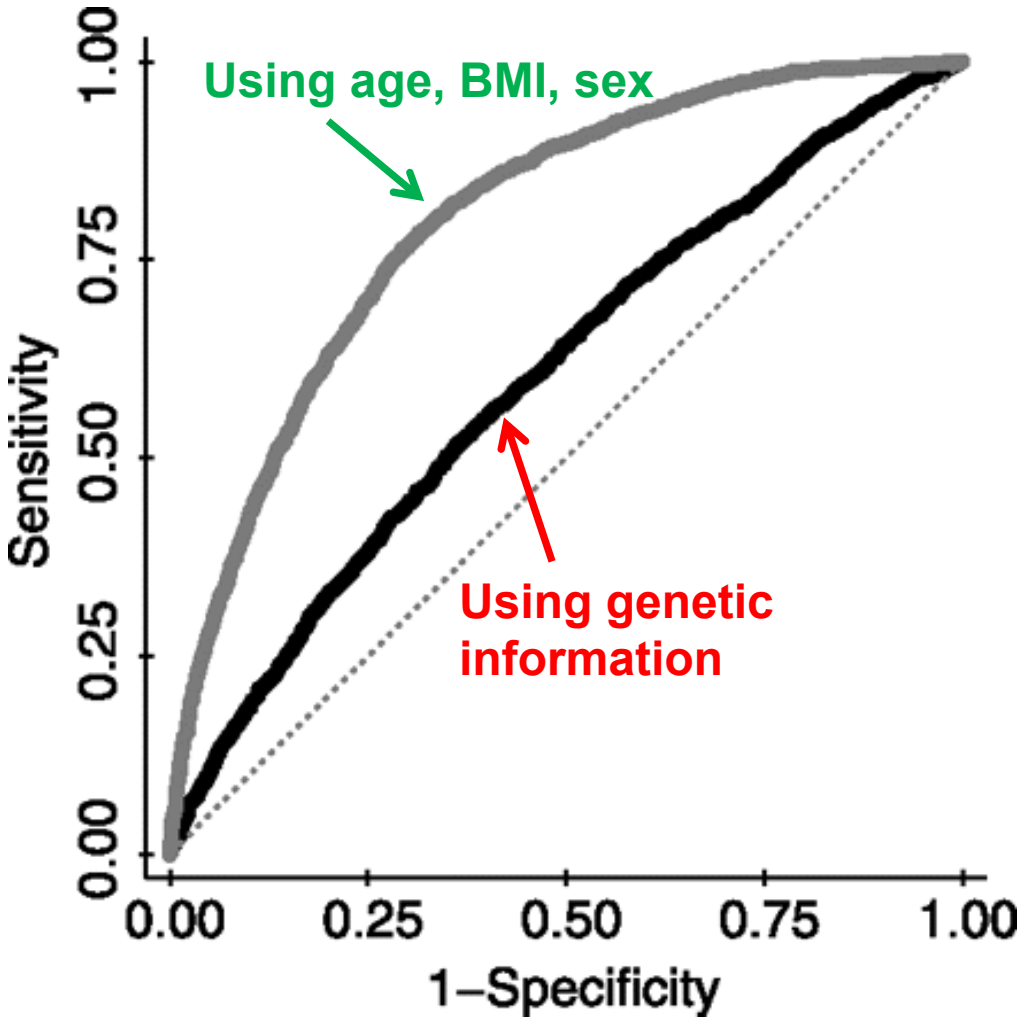
Three major gains

- Rapid molecular identification of **source and type** of infection, particular in zoonosis, by comparing against databases of known infections
- **Improve treatment efficacy** by recognising presence of drug-resistant pathogen strains, which together with GIS can **evaluate health systems** failure that encourage resistance
- Minimise **further progression to multi/extensive drug-resistance** to control against eventual total failure of existing treatment regimes

Questions

- Can we accurately define a medical condition (e.g. diabetes or cancer), and identify the most appropriate treatments?
- Can we predict the risk of diabetes and cancer?
  - Using clinical biomarkers, genes, diet, exercise, alcohol intake, smoking, etc. other environmental factors?
- Can we predict who is more susceptible to dengue?
  - Why are some people more protected against certain infectious diseases (dengue, malaria, HIV, etc.)?
- Does every drug treatment works the same for everyone?
  - If not, what are the new strategies for pharmaceutical developments?

Genetic risk prediction for Type 2 Diabetes



Sensitivity

Correct identification of diabetics

Specificity

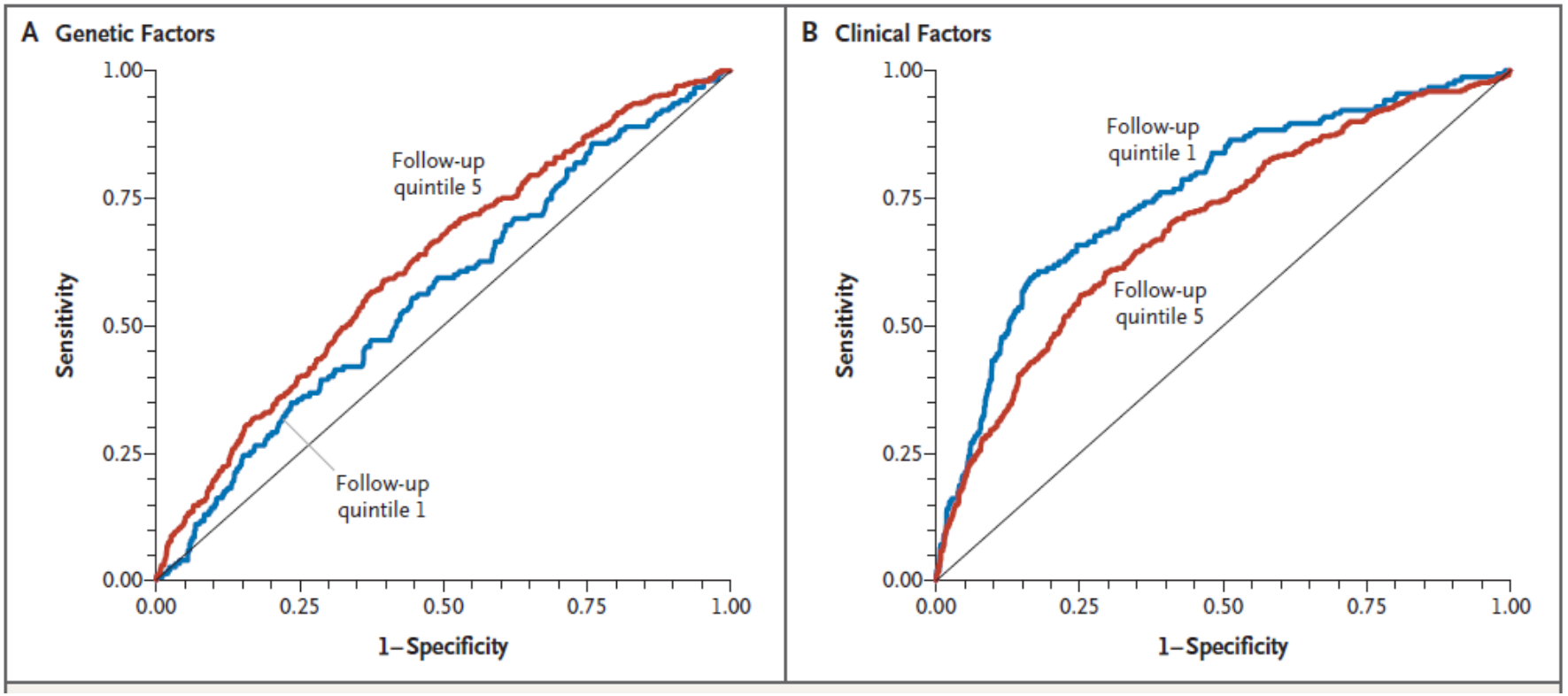
Correct identification of non-diabetics

Area under the curve

= Overall performance of the prediction

Diabetes. 2008 Nov;57(11):3129-35.

Impact of duration of follow-up on prediction using clinical vs. genetic factors



Lyssenko et al. N Engl J Med. 2008 Nov 20;359(21):2220-32

Genetic risk prediction

- Especially valuable to delay or prevent the onset of systemic diseases
  - individuals with high genetic risk can undertake lifestyle modifications and dietary interventions earlier in life
  - Relevance and informativeness of clinical biomarkers often vary significantly with age
  - Often, when clinical biomarkers are predictive, may already be too late for non-clinical lifestyle interventions, need clinical and therapeutic interventions.
  - But again, we all know about exercising and healthy eating… so again, does genetics really matter?

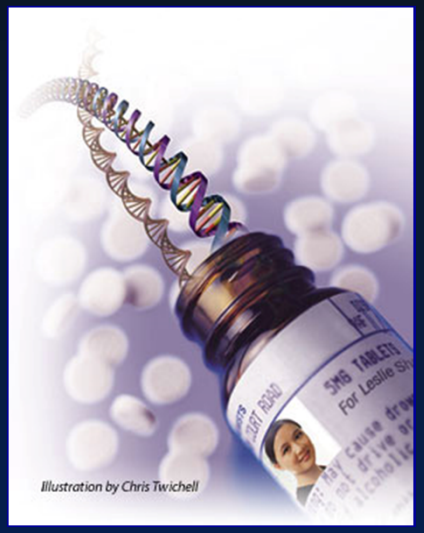
Empowerment and lifestyle modifications

- *BRCA1* mutations, 87% risk of breast cancer and 50% risk of ovarian cancer
- Mastectomy reduces risk from 87% to 5%

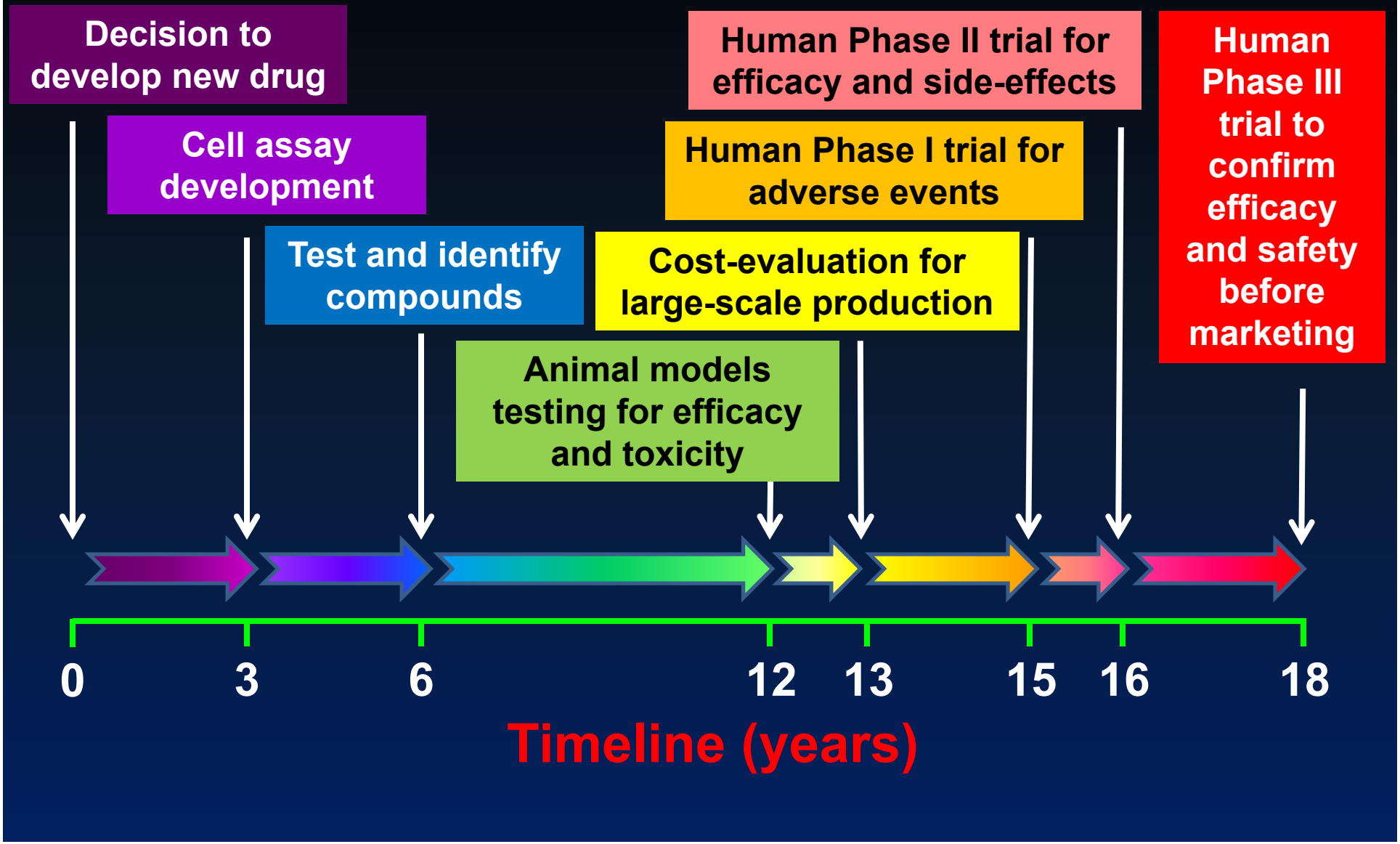
Questions

- Can we accurately define a medical condition (e.g. diabetes or cancer), and identify the most appropriate treatments?
- Can we predict the risk of diabetes and cancer?
  - Using clinical biomarkers, genes, diet, exercise, alcohol intake, smoking, etc. other environmental factors?
- Can we predict who is more susceptible to dengue?
  - Why are some people more protected against certain infectious diseases (dengue, malaria, HIV, etc.)?
- Does every drug treatment works the same for everyone?
  - If not, what are the new strategies for pharmaceutical developments?

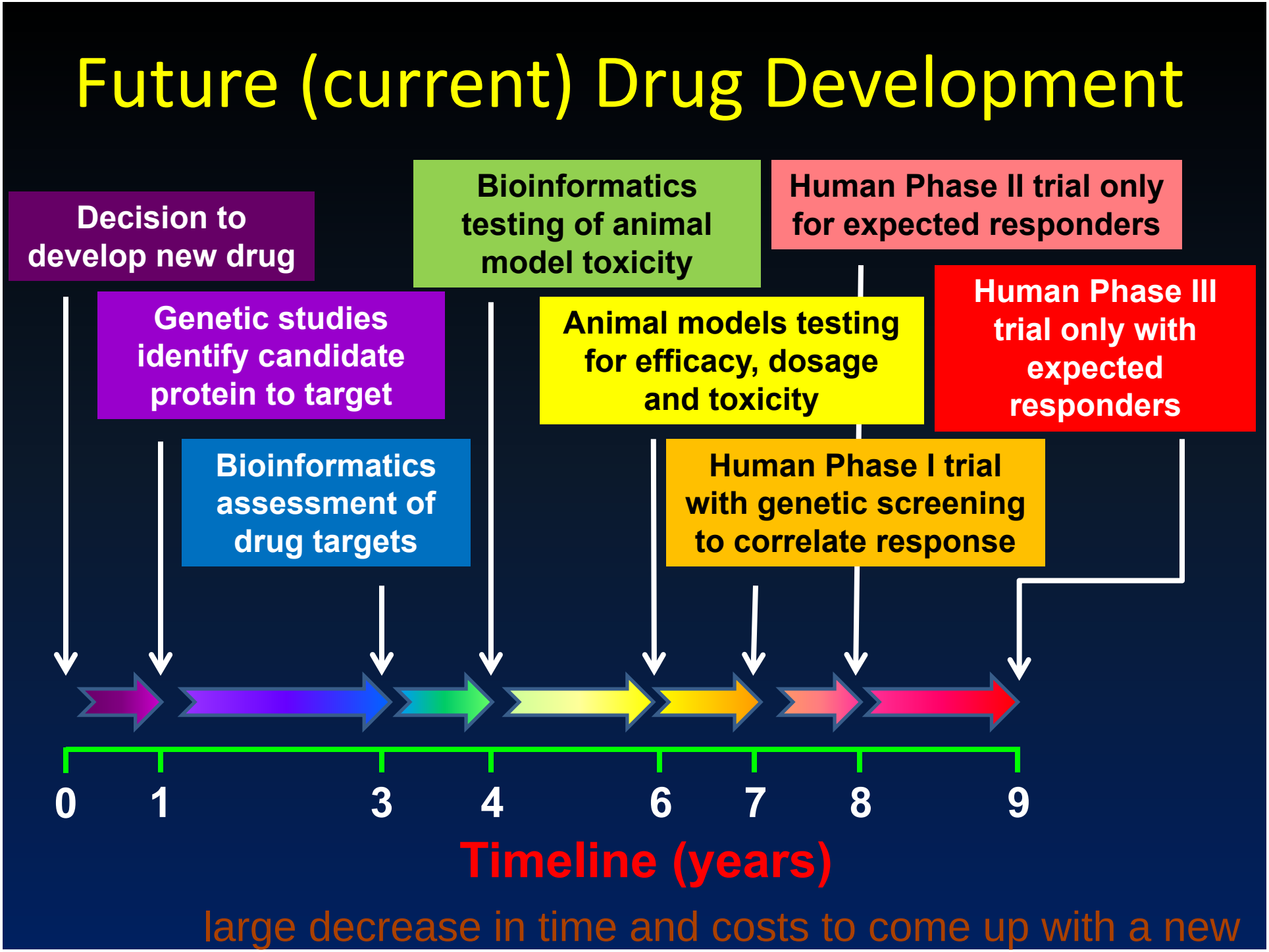
Public Health Pharmacogenomics



Drug discovery, design and trials

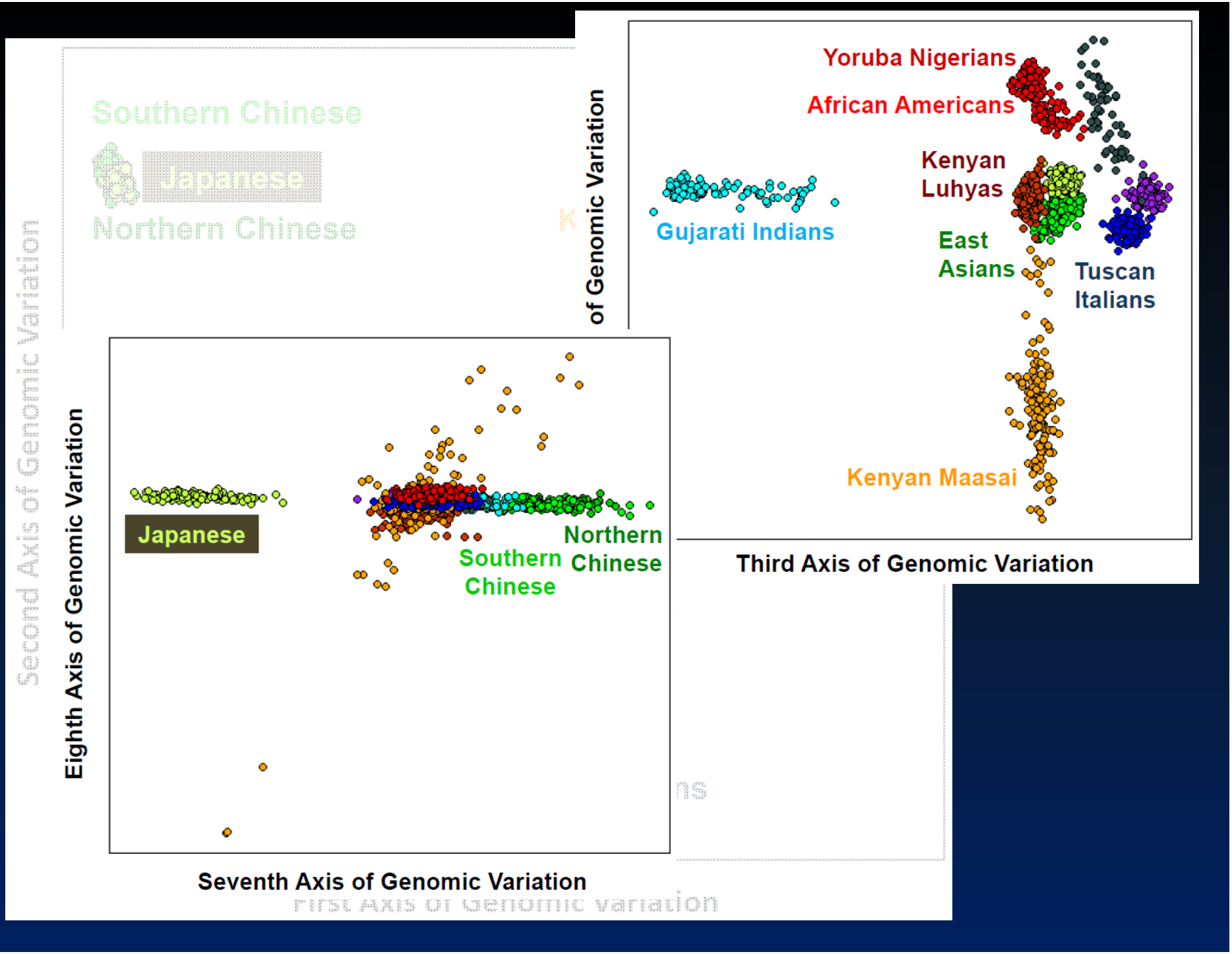


Future (current) Drug Development



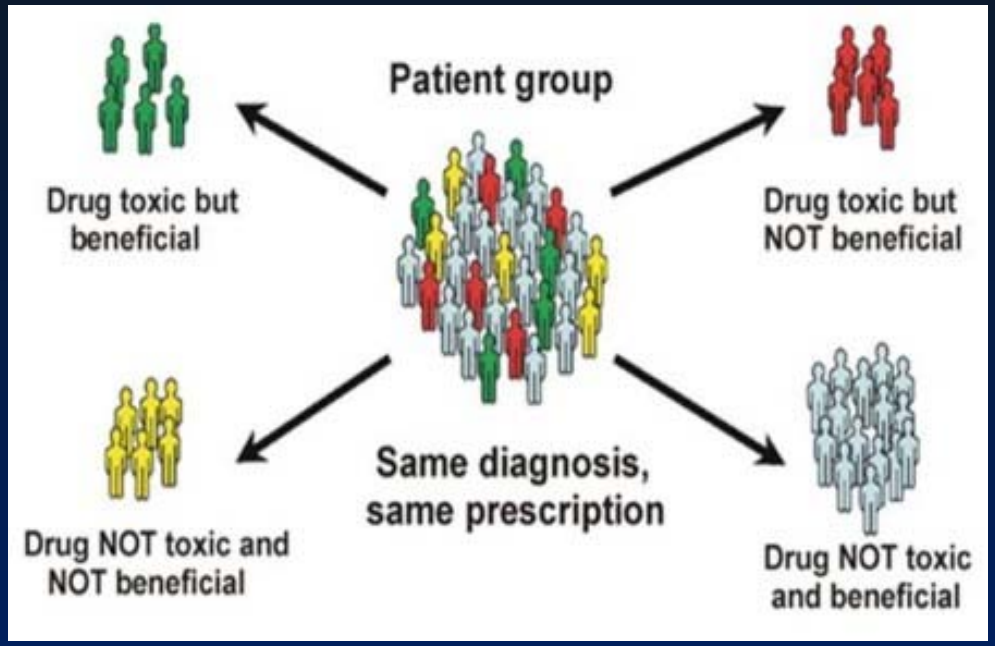
large decrease in time and costs to come up with a new drug

Genetics and Human Diversity


Yoruba Nigerians
African Americans
Kenyan Luhyas
Gujarati Indians
East Asians
Tuscan Italians
Kenyan Maasai
Third Axis of Genomic Variation
Japanese
Northern Chinese
Southern Chinese
Eighth Axis of Genomic Variation
Seventh Axis of Genomic Variation

What's the difference

- Cheaper and faster to design a new drug therapy
- Better knowledge of the efficacy and target population
- **Practice of clinical medicine to rely on genomic information (due to the way drugs are designed)**



Examples of Current PGx

Drug	EMA/US FDA	Indication
Tamoxifen	None/None	Poor response to postmenopausal breast cancer treatment
Statins	None/None	Define maximum statin dosage
Clopidogrel	None/**Props**	Poor response to postmyocardial infarction treatment
Warfarin	None/**Recm**	Initial warfarin dosing
Abacavir	**Mand**/**Mand**	Hypersensitivity in HIV treatment

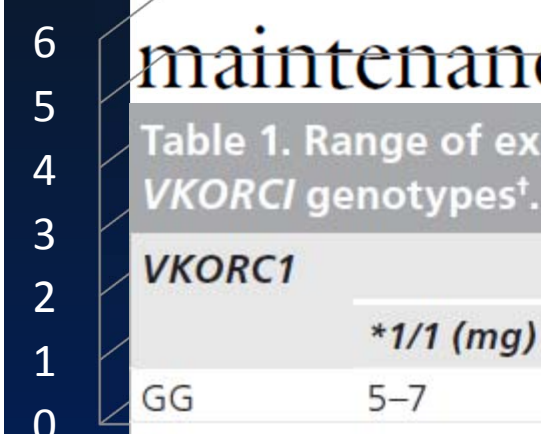
EMA: European Medicines Agency; US FDA: Food and Drug Administration in USA
PGx: Pharmacogenomics

Adapted from *Pharmacogenomics* (2011) **12**: 113-124

Warfarin

- Anticoagulant, accurate dosaging is important
- Dosaging appears to vary with populations
- Genetic basis to the variation
- USFDA recommended genetic screening to

Interethnic variability of warfarin maintenance requirement is explained by



3% Singapore Ethnic Demographics

Table 1. Range of expected therapeutic warfarin doses based on *CYP2C9* and *VKORCI* genotypes†.

VKORC1	*CYP2C9*					
	**1/1 (mg)*	**1/*2 (mg)*	**1/*3 (mg)*	**2/*2 (mg)*	**2/*3 (mg)*	**3/*3 (mg)*
GG	5–7	5–7	3–4	3–4	3–4	0.5–2
GA	5–7	3–4	3–4	3–4	0.5–2	0.5–2
AA	3–4	3–4	0.5–2	0.5–2	0.5–2	0.5–2

Pharmacogenomics (2011) **12**(1), 113–124

Abacavir

- Anti-retroviral used for HIV treatment
- ~5-10% of Caucasian patients experienced hypersensitivity side-effects, some with fatal outcomes
- Withdrawal of abacavir
- Hypersensitivity strongly associated with a particular genetic variant, HLA-B*5701
- Abacavir use with legislation for compulsory genetic screening before prescription (in Europe and US)

it works but it makes a small fraction of people ill, thus is a waste. impacting clinical medicine

Genetic Screening and Society

- Already a routine procedure, and accepted in most instances
- Newborn screening of treatable diseases, early interventions can be recommended
- Four crucial questions of:
  - Who to screen
  - What to screen for
  - Who has access to the data
  - Who pays for the screening

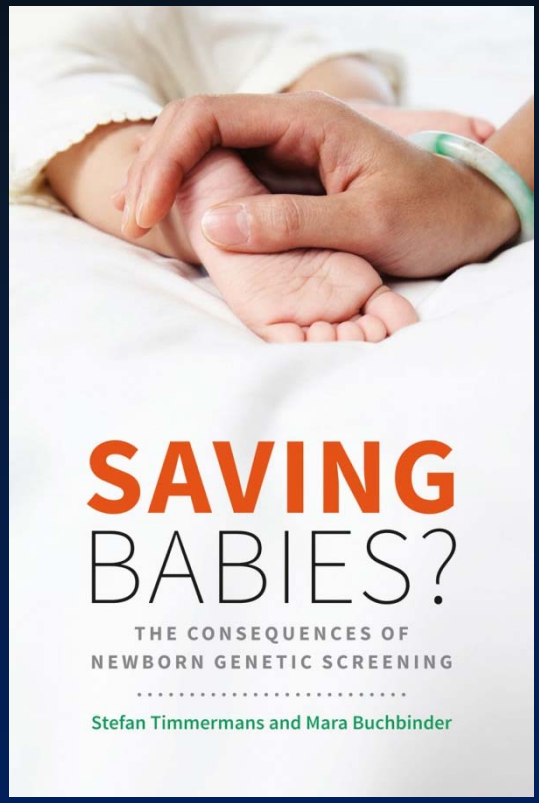
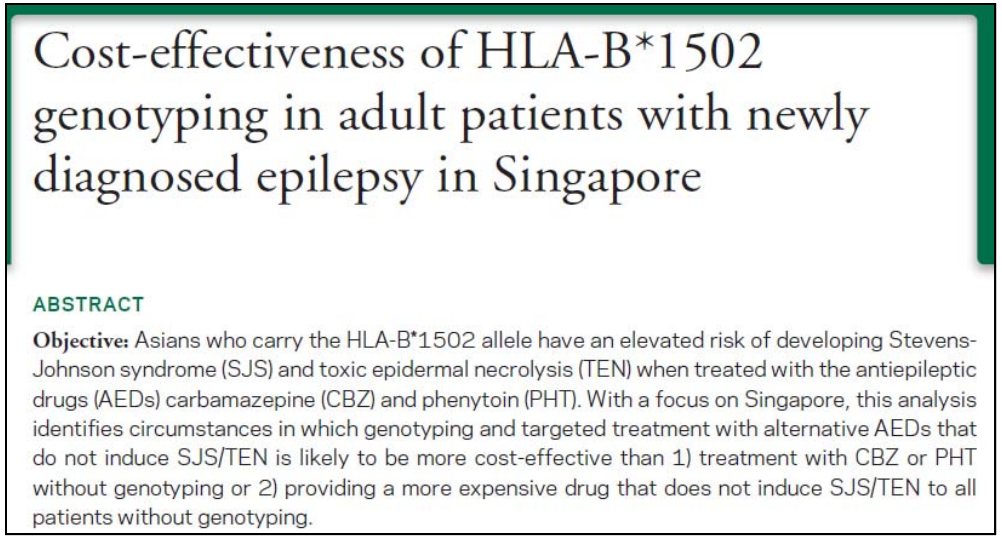


Photo credit: University of Chicago Press

Is genomics screening even cost-effective?

NUS National University of Singapore | Saw Swee Hock School of Public Health

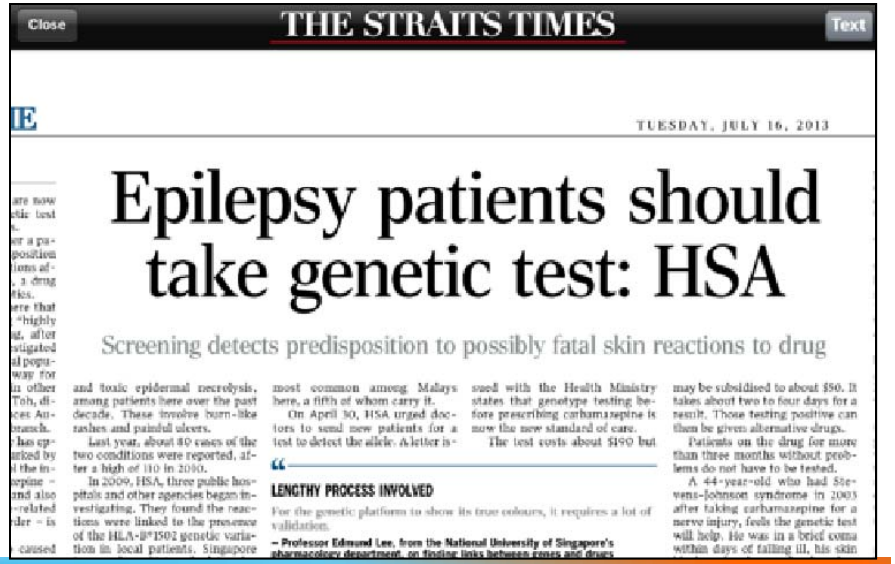
- **Health Technology and Cost-Effectiveness Assessments**
  - New technologies for screening, diagnostics and prognostics
  - **Clinically relevant, but is it cost-effective**?
  - Background information on hospitalization costs, to work closely with hospital administrators, in addition to clinicians and having population level information
  - Economic evaluator, and assess burden to healthcare system



Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore

ABSTRACT

Objective: Asians who carry the HLA-B*1502 allele have an elevated risk of developing Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) when treated with the antiepileptic drugs (AEDs) carbamazepine (CBZ) and phenytoin (PHT). With a focus on Singapore, this analysis identifies circumstances in which genotyping and targeted treatment with alternative AEDs that do not induce SJS/TEN is likely to be more cost-effective than 1) treatment with CBZ or PHT without genotyping or 2) providing a more expensive drug that does not induce SJS/TEN to all patients without genotyping.



Close THE STRAITS TIMES Text

TUESDAY, JULY 16, 2013

Epilepsy patients should take genetic test: HSA

Screening detects predisposition to possibly fatal skin reactions to drug

LENGTHY PROCESS INVOLVED

OECD Science, Technology and Industry Policy Papers No. 8

OECD (2013), "Public Health in an Age of Genomics", *OECD Science, Technology and Industry Policy Papers*, No. 8, OECD Publishing.
http://dx.doi.org/10.1787/5k424rdzj3bx-en

Public Health in an Age of Genomics

OECD

EXECUTIVE SUMMARY

- While the application of genomics for the development of stratified medicine remains predominantly a research field, with relatively few actual examples of successful implementation to show to date, the use of genomics more broadly for infectious disease control is already yielding significant public health benefits, both in terms of the ability to diagnose and track the movement of infectious disease outbreaks and in terms of the ability to enhance and accelerate the production of effective vaccines.

- It is generally agreed that international collaboration in both research and implementation is essential if the full potential of genomics for infectious disease control both nationally and globally is to be realised. By contrast the development of stratified medicine tends to be seen as primarily a national issue, with international initiatives in this area directed towards fostering an appropriate regulatory and economic environment supportive of national innovation.

- There appear to be significant differences of priority between higher income countries, which have already completed the epidemiological transition, and which are motivated primarily by the promise of stratified medicine as a means of addressing their growing burden of chronic disease, and lower and middle income countries, which tend to concentrate more heavily on efforts to control the infectious diseases that still beset them.

Challenges of Big Data in health and healthcare

- How do we **interpret** the data
  - Computing costs
  - Computing skills
  - Public health impact of rare variants
- Do the clinicians, healthcare workers and policy makers even understand the importance and relevance of Big Data information?

[1] Manolio, *Nature* 461, 747-753 (8 October 2009), [2] Makowsky PLOS Genetics, Beyond Missing Heritability: Prediction of Complex Traits

Challenges of Big Data in health and healthcare

- How do we **manage** the data – Ethical Challenges

  - ESLI (Ethical, Social & Legal Issues Research)
    - About 3-5% of the budget
    - Current operating budget – 30 M USD

Challenges of Big Data in health and healthcare

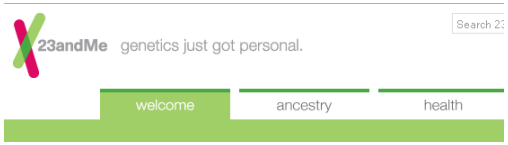
How do we **manage** the data – Ethical Challenges

Confidentiality

ELSI

Discrimination
-Insurance
-Employment
-Loans
-GINA (US Congress, 2008)

Genetic testing
- Marketed as
  - -Empowering
  - - Recreational
-Unclear risk
- Psychological impact
- Burden on medical system



Kaye et al, 2008, Sharp, R. (2007), http://hstalks.com.libproxy1.nus.edu.sg/bio

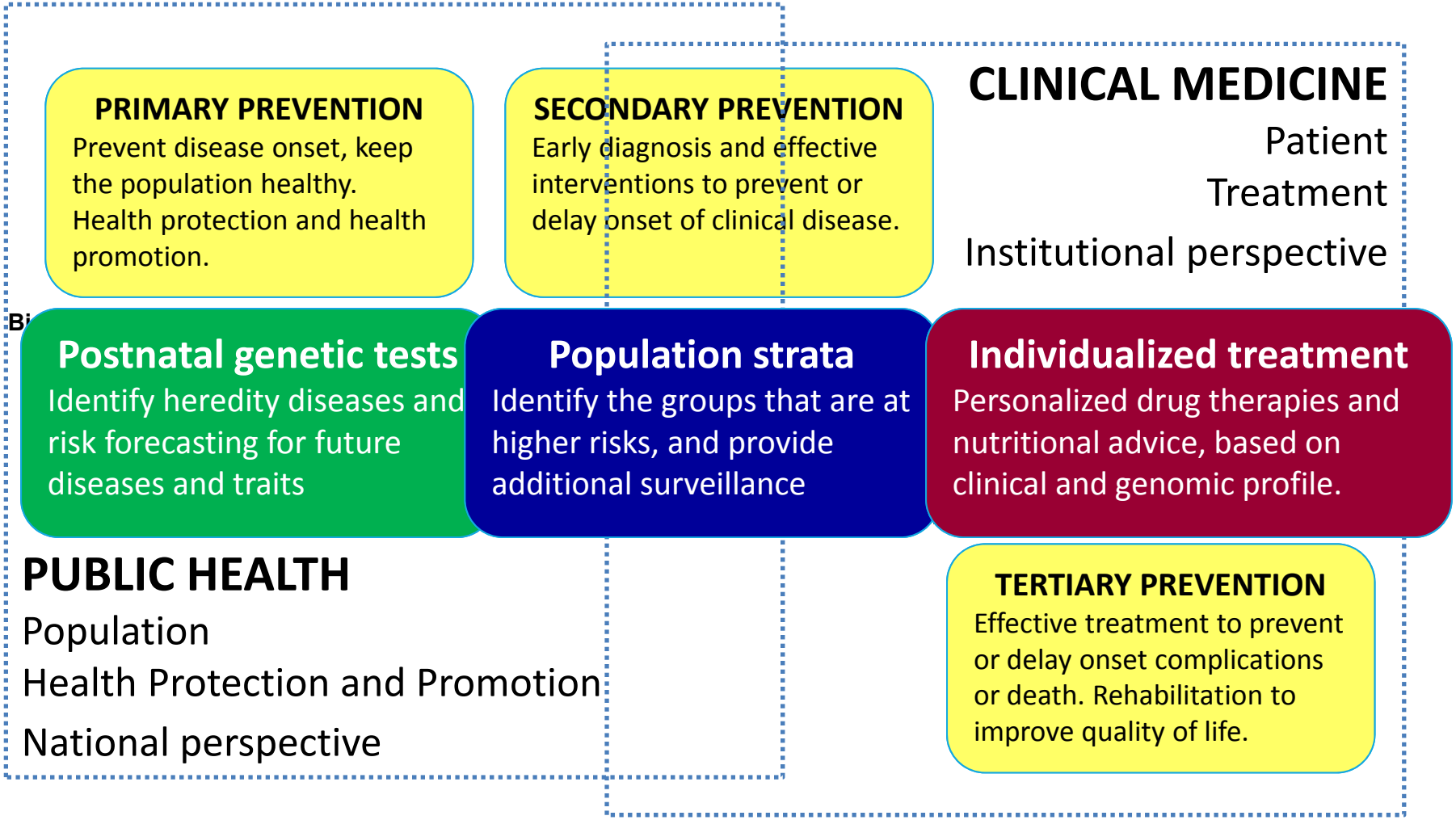
Era of “Big Data” in health research

- So overwhelmingly large that standard computational tools are not able to cope (think Excel, Access, even SPSS, R!)
- Typically in order of gigabytes onwards…
  - Bytes (enough for coding numbers)
  - Kilobytes (think early generation computer games in ‘90s)
  - Megabytes (one VCD movie ~ 700Mb)
  - Gigabytes (one HD movie ~ 4Gb)
  - Terabytes (one human genome sequence ~ 1Tb)
  - Petabytes (expected storage for health research by 2014 – 5Pb)
  - Exabytes (expected storage before end 2020)
- Very common in omics: genomics, nutriomics, lipidomics, enviromics,

Challenges of Big Data

- Storage
  - Costs, space, infrastructure, power
- Access and search
  - Tools to access and search?
  - Linux-based, versus Windows-based
  - Time taken to access and search, in order of days
- Sharing and transfers
  - FTP (geekspeak for “file transfer protocol”)
  - Time taken to transfer, in order of months (bandwidth issues)
  - Fed-Ex hard-disks around
- Analysis (multiple hypotheses, data dredging, too much data!)
- Visualization (how to condense the information in a figure?)

LEVELS OF "PREVENTION"



Precision Health and Healthcare

- Personalized nutrition and dietary advice?
- Personalized medicine?
- Personalized lifestyle management?