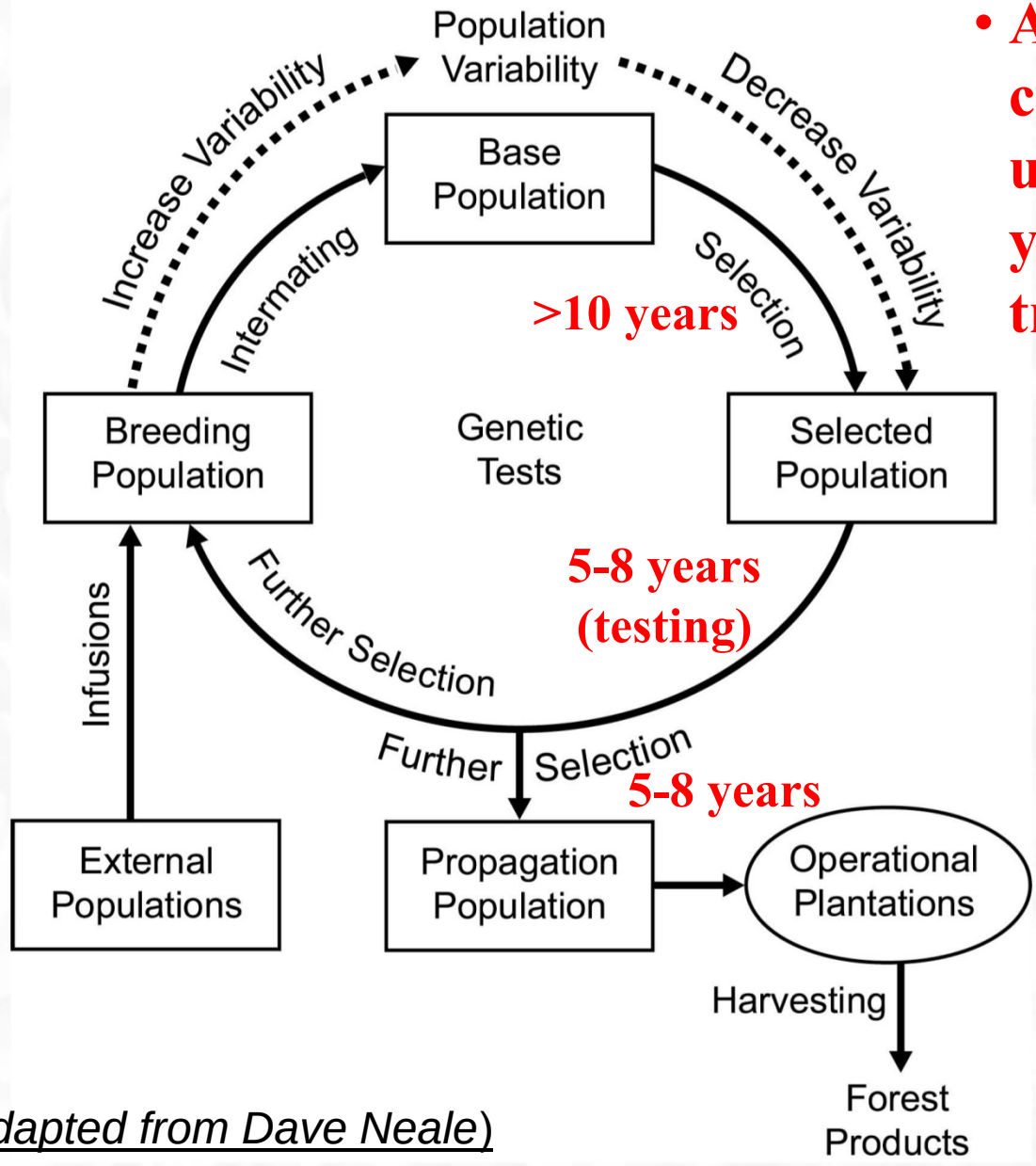
Приложения в геномике

- Genomic selection
- Medical genomics
- Paleogenomics
- Metagenomics
- Nutrigenomics
- Gerontogenomics
- Phylogenomics

Traditional forest tree breeding



- **A full breeding cycle may take up to 20-25 years in forest trees!**

(*Adapted from Dave Neale*)

Traditional forest tree breeding

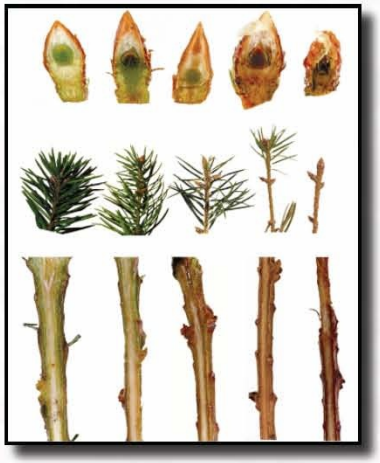
What we have learned from traditional forest tree breeding:

- Most breeding and adaptive traits are complex quantitative traits controlled by environment and multiple genes of small effect

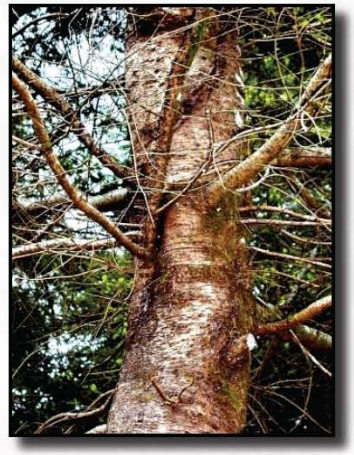
Traditional molecular breeding and Marker-Aided Selection (MAS)

Growth

Adaptability



Straightness



Disease resistance

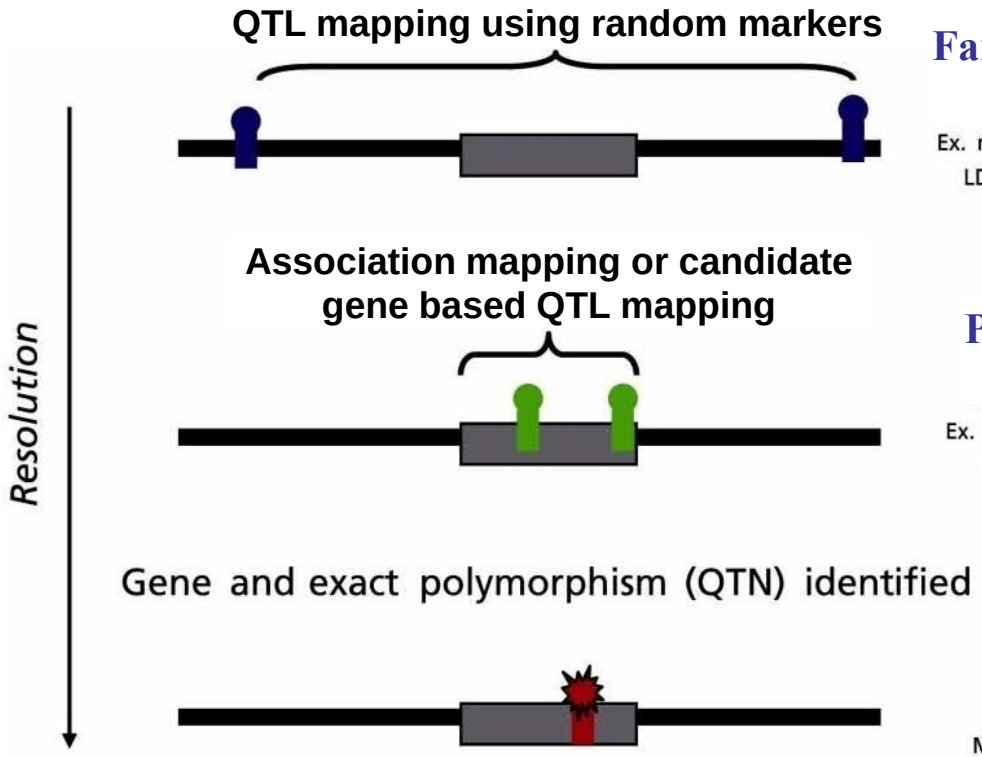
Insect resistance

Wood quality

(*Adapted from Dave Neale*)

Traditional molecular breeding and Marker-Aided Selection (MAS)

Classification of three different types and resolutions of marker-trait associations:



Family-based Linkage Disequilibrium (LD) MAS (LD markers)

Ex. microsatellite markers flanking a QTL mapped in a high LD pedigree - Centimorgan resolution ~ 10^5 a 10^7 bp

Population-based LD MAS (LD and direct markers)

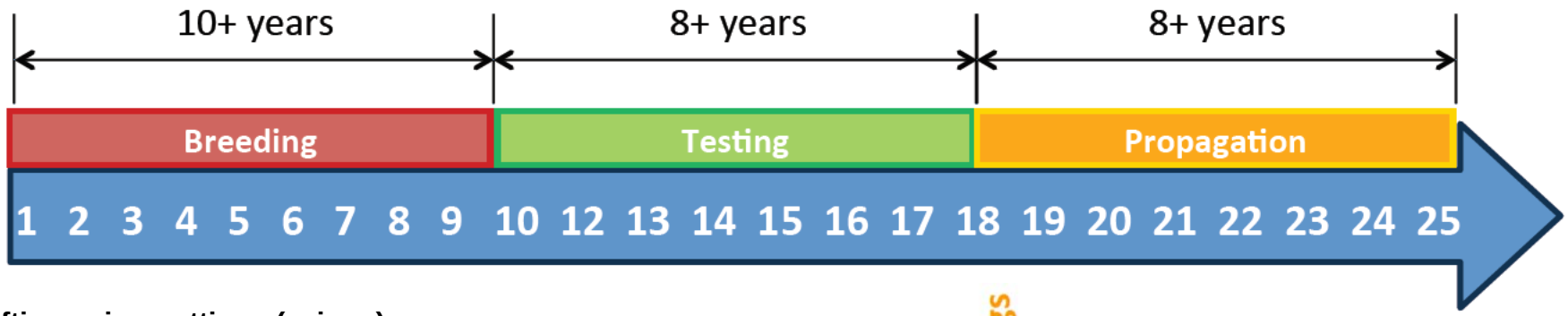
Ex. SNPs strongly associated with the QTL or candidate gene - Subcentimorgan resolution ~ 10^2 a 10^4 bp

Gene-based LD MAS (direct markers)

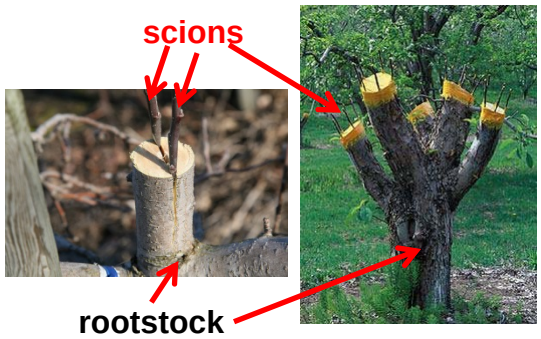
Ex. causal SNPs (QTNs) of quantitative variation
Maximum resolution and identification of exact allele

Modified from Grattapaglia (2007)

Traditional pine breeding

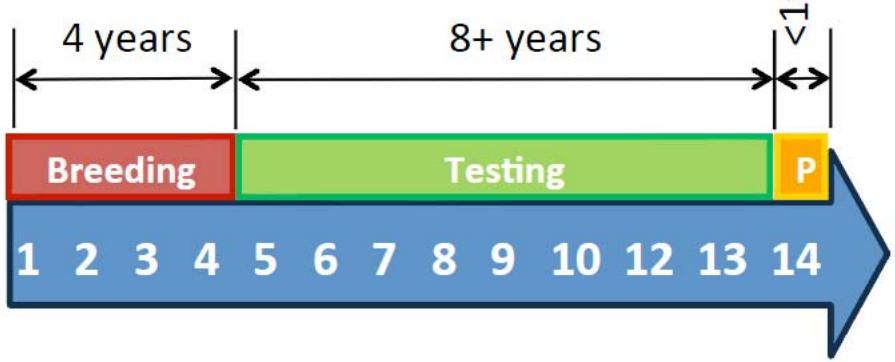


Top grafting using cuttings (scions) from improved or plus trees



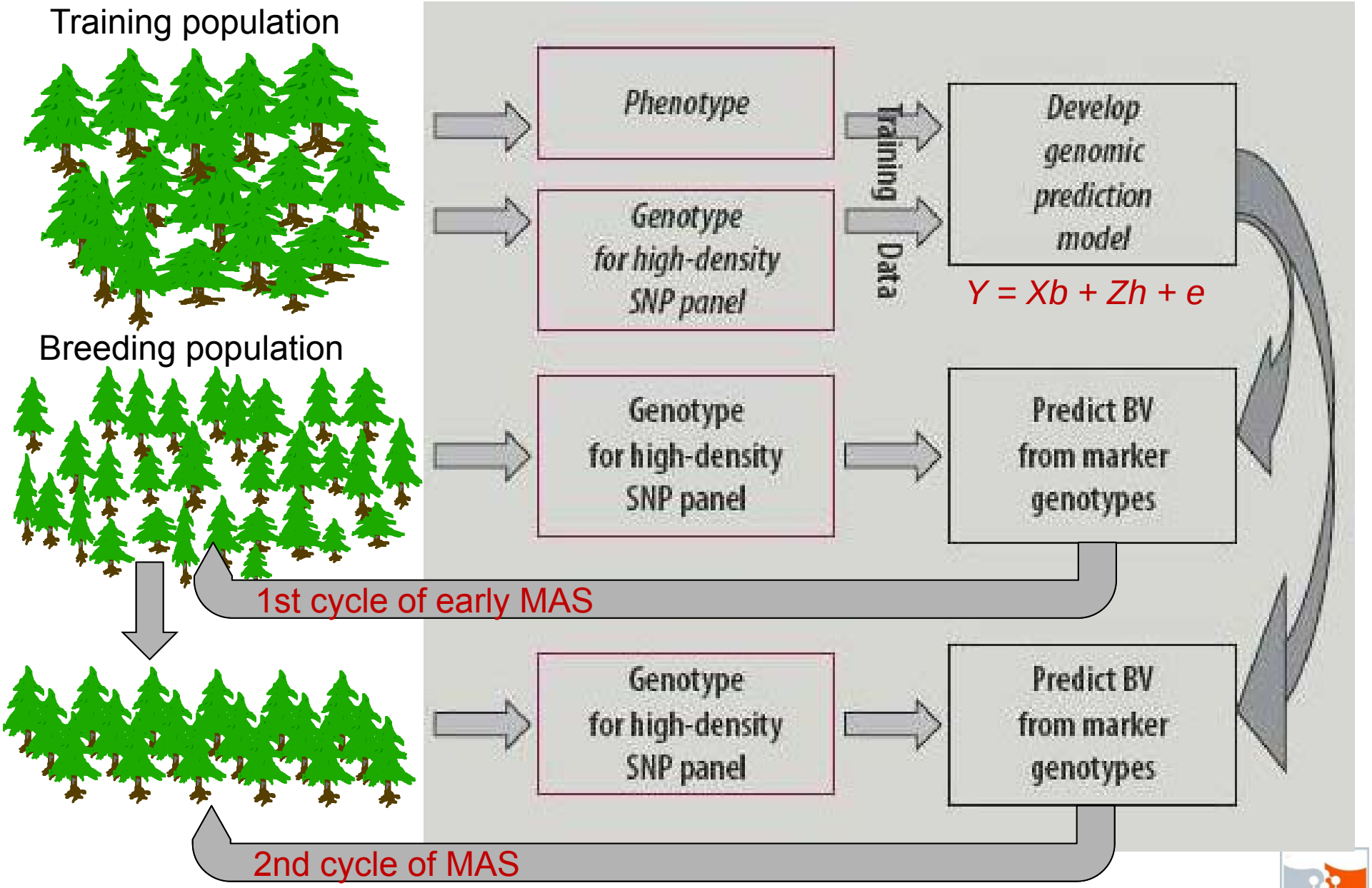
Top-grafting

SE/Rooted cuttings



(*Adapted from Matias Kirst*)

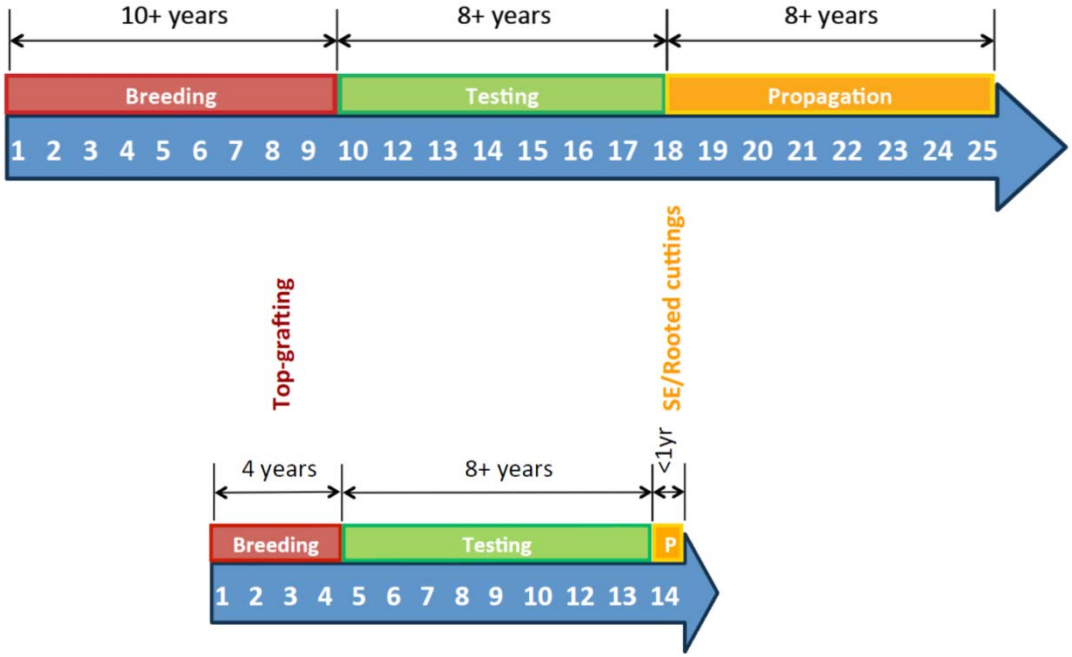
Genomic selection



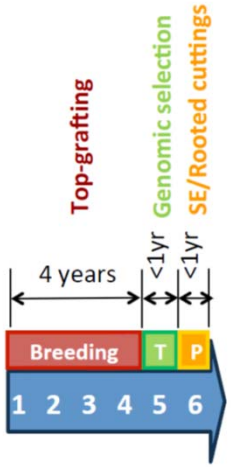
New type of Marker-Aided Selection (MAS):
Genome-wide based selection or
Genomic selection

- needs genome-wide comprehensive number of markers
- needs efficient high-throughput genotyping
- needs complex regression models to predict phenotypes and breeding values (e.g., GBLUP, Bayes A/B)
- needs high-quality phenotyping
- depends on Linkage Disequilibrium (LD) (ideally – genotyping-by-sequencing – GBS):
  - low LD – more markers are needed;
  - high LD – less number of markers needed

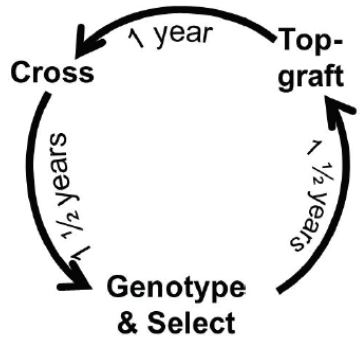
Traditional pine breeding:



Genomic selection:



Genomic Selection Guided Crosses

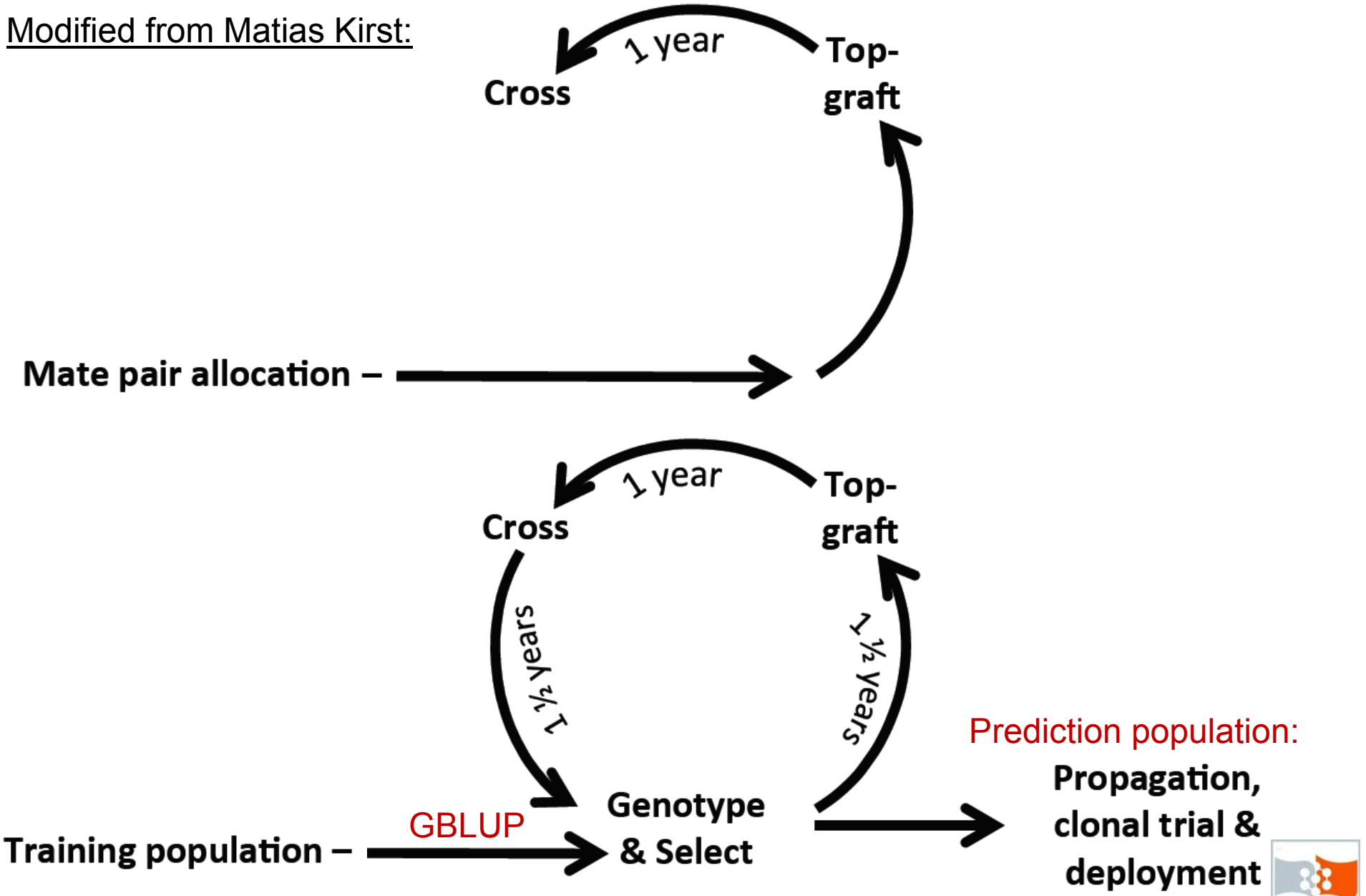


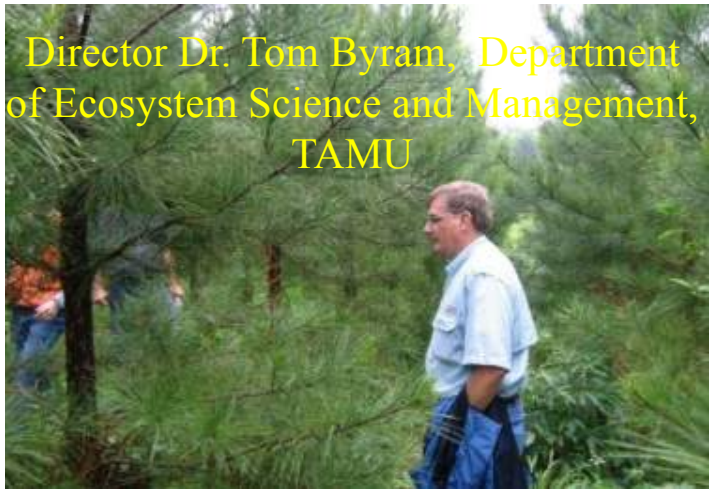
"Surgical" breeding

(*Adapted from Matias Kirst*)

Genomic selection incorporated into pine breeding

Modified from Matias Kirst:





Western Gulf Forest Tree Improvement Program

Texas Forest Service Gene Conservation Program

Forest Science Laboratory, Texas A&M University, College Station, TX, USA

http://www.ars-grin.gov/misc/wgftip/about.html

- The WGFTIP is a cooperative tree breeding project founded in 1969 with the objective of providing the best genetic quality seed for use in forest regeneration programs in the Western Gulf Region of the United States.
- Base Population: 3300 loblolly & 1000 slash pines.
- Progeny Tests: > 1500, 3 mln trees, 4,000 ac
- Current members include 5 states and 8 industrial members collectively responsible for planting 300,000,000 seedlings per year.
- The cooperative is preserving and improving populations of five southern pine species and several hardwood species

Genomic selection – Conclusions

- Accuracy of prediction will increase with:
  - more markers
  - more individuals
  - higher heritability
  - higher LD
- It can be done, but most likely in the family based breeding

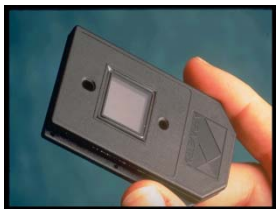
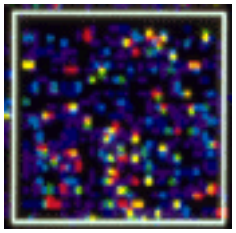
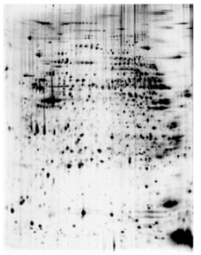
Medical genomics

- can discover disease associated genes
- can discover disease causing genes.
- provides understanding of disease
- provides basis for novel drug development
- provides basis for novel genetic and stem cell therapies
- provides the basis for preventive medicine

Use of genomic information

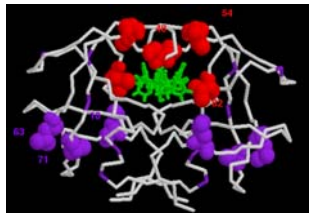
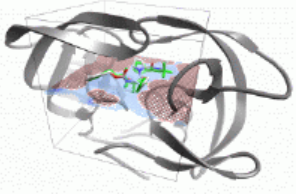
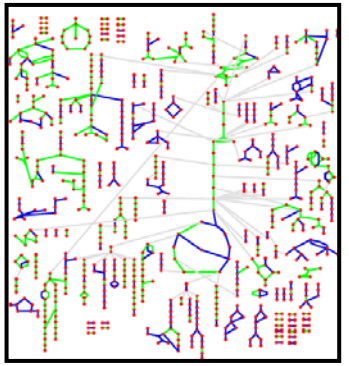
Novel Diagnostics

- Microchips & Microarrays - DNA
- Gene Expression - RNA
- Proteomics - Protein

Novel Therapeutics

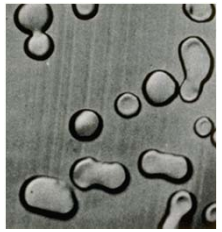
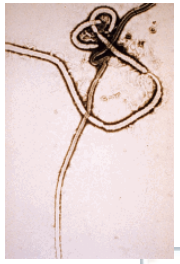
- Drug Target Discovery
- Rational Drug Design
- Molecular Docking
- Gene Therapy
- Stem Cell Therapy

Understanding Metabolism

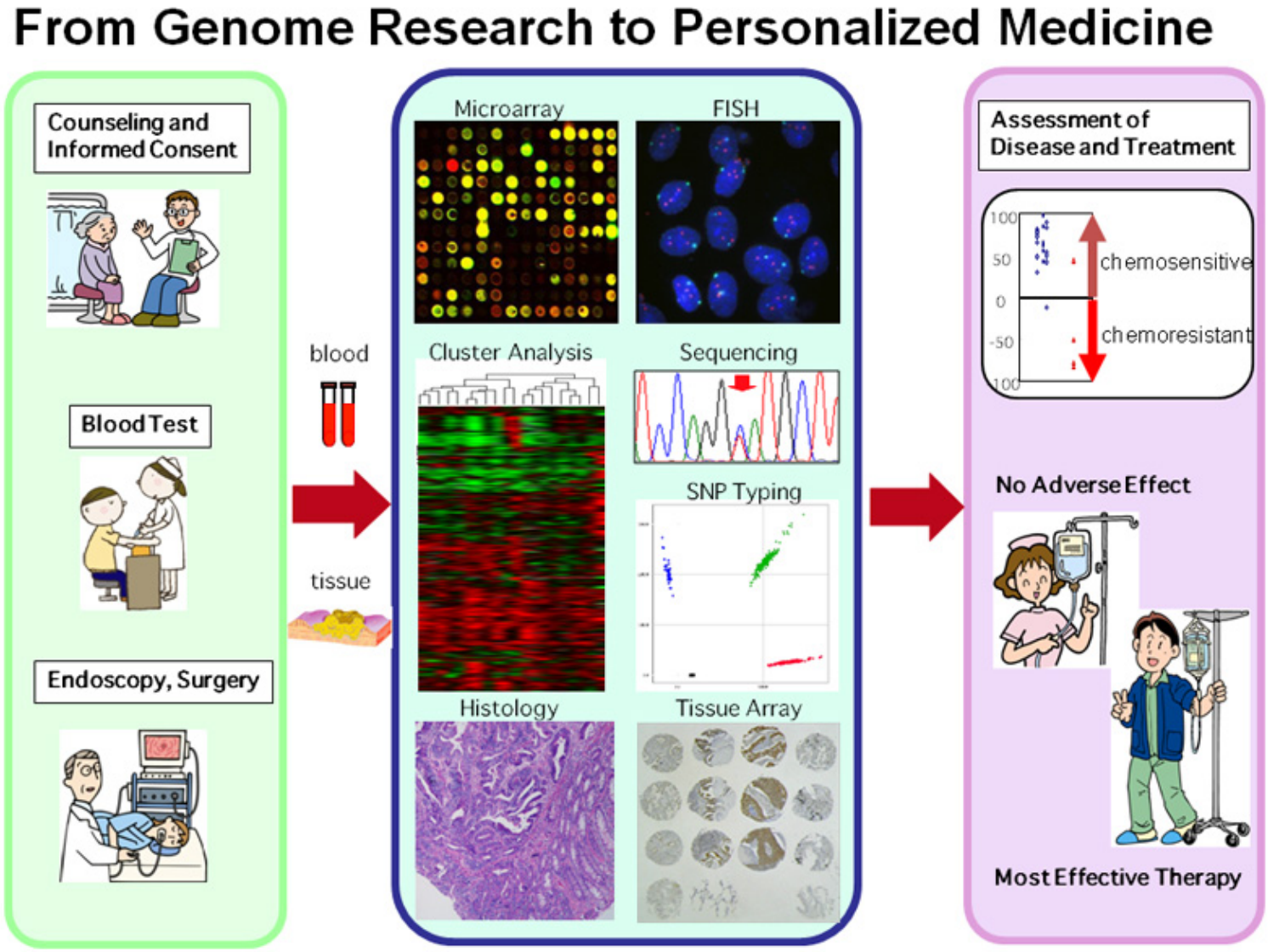
Understanding Disease

- Inherited Diseases - OMIM
- Infectious Diseases
- Pathogenic Bacteria
- Viruses

Personalized genomic medicine

The right treatment, for the right patient, at the right



Examples for complex polygenic diseases & responses

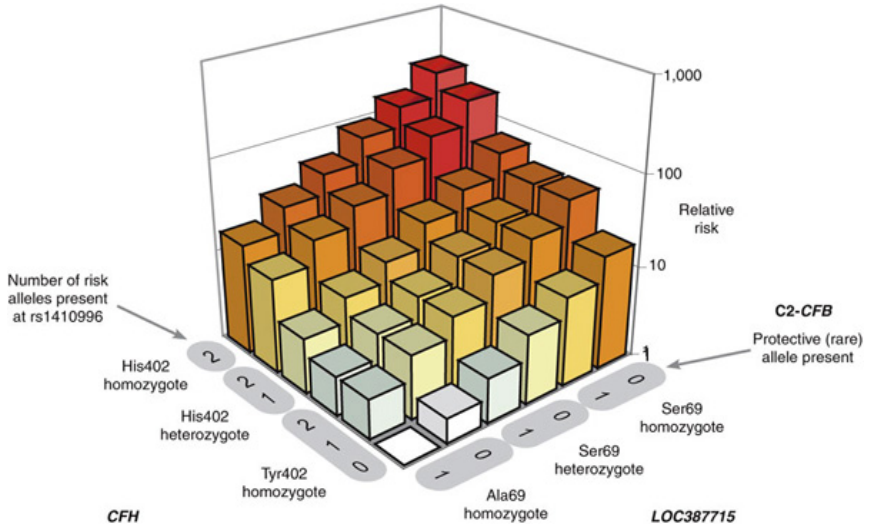
Medullary thyroid cancer & *RET* mutation testing: Multiple Endocrine Neoplasia 2 (MEN2) (If RET +, prophylactic thyroidectomy is offerred)

Predicting toxicity from chemotherapy based on retrospective analysis of clinical trial data. Toxicity and sensitivity depend on thiopurine methyltransferase (TPMT) activity. There is individual genetic polymorphisms that affect this enzymatic activity.

Multiple contributors to **asthma**: *Genetics (*beta-adrenergic receptor, GSTM1, GSTT1, IL-4, IL-4RA, IL-13, TNF-alpha, and 30-50 other genes) + *Environment* (mites, cockroaches, pollens, animal danders, cigarette smoke, diesel fuel)

Estimate of lifetime diabetes risk based on presence/absence of disease-associated mutations

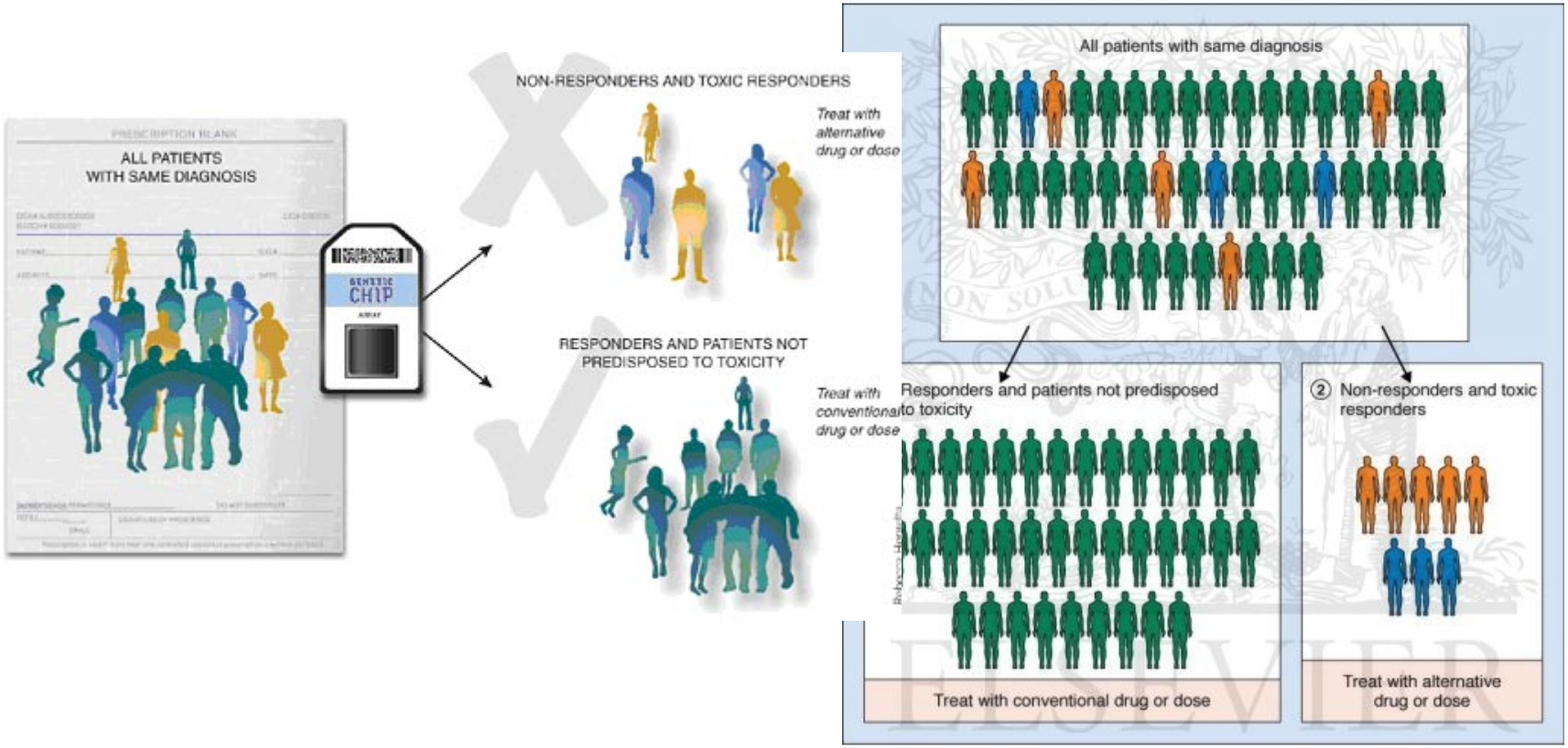
Risk of age-related macular degeneration (AMD) depends on variation in 3 genes



1% have > 50% risk of AMD most have risk close to average (Nat Genet 2006; 38:1055-9)

Personalized genomic medicine

The right treatment, for the right patient, at the right time



Personalized genomic medicine


In a First, Test of DNA Finds Root of Illness - NYTimes.com - Mozilla Firefox

The New York Times

HEALTH

152 COMMENTS

In a First, Test of DNA Finds Root of Illness

By CARL ZIMMER JUNE 4, 2014

Joshua Osborn, 14, lay in a coma at American Family Children's Hospital in Madison, Wis. For weeks his brain had been swelling with fluid, and a battery of tests had failed to reveal the cause.

The doctors told his parents, Clark and Julie, that they wanted to run one more test with an experimental new technology. Scientists would search

Joshua Osborn outside his home in Cottage Grove, Wis., with his father, Clark Osborn. Joshua suffered from swelling in the brain, but tests, a spinal tap


The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Actionable Diagnosis of Neuroleptospirosis by Next-Generation Sequencing

Michael R. Wilson, M.D., Samia N. Naccache, Ph.D., Erik Samayoa, B.S., C.L.S., Mark Biagtan, M.D., Hiba Bashir, M.D., Guixia Yu, B.S., Shahriar M. Salamat, M.D., Ph.D., Sneha Somasekar, B.S., Scot Federman, B.A., Steve Miller, M.D., Ph.D., Robert Sokolic, M.D., Elizabeth Garabedian, R.N., M.S.L.S., Fabio Candotti, M.D., Rebecca H. Buckley, M.D., Kurt D. Reed, M.D., Teresa L. Meyer, R.N., M.S., Christine M. Seroogy, M.D., Renee Galloway, M.P.H., Sheryl L. Henderson, M.D., Ph.D., James E. Gern, M.D., Joseph L. DeRisi, Ph.D., and Charles Y. Chiu, M.D., Ph.D.

SUMMARY

A 14-year-old boy with severe combined immunodeficiency presented three times to a medical facility over a period of 4 months with fever and headache that progressed to hydrocephalus and status epilepticus necessitating a medically induced coma. Diagnostic workup including brain biopsy was unrevealing. Unbiased next-generation sequencing of the cerebrospinal fluid identified 475 of 3,063,784 sequence reads (0.016%) corresponding to leptospira infection. Clinical assays for leptospirosis were negative. Targeted antimicrobial agents were administered, and the patient was discharged home 32 days later with a status close to his premorbid condition. Polymerase-chain-reaction (PCR) and serologic testing at the Centers for Disease Control and Prevention (CDC) subsequently confirmed evidence of *Leptospira santarosai* infection.

MORE THAN HALF THE CASES OF MENINGOENCEPHALITIS REMAIN UNdiagnosed, despite extensive clinical laboratory testing.[1-4] Because more than 100 different infectious agents can cause encephalitis, establishing a diagnosis with the use of cultures, serologic tests, and pathogen-specific PCR assays can be difficult. Unbiased next-generation sequencing has the potential to revolutionize our ability to discover emerging pathogens, especially newly identified viruses.[5-8] However, the usefulness of next-generation sequencing for the diagnosis of infectious diseases in a clinically relevant timeframe is largely unexplored.[9] We used unbiased next-generation sequencing to identify a treatable, albeit rare, bacterial cause of meningoencephalitis. In this case, the results of next-generation sequencing contributed directly to a dramatic effect on the patient's care, resulting ultimately in a favorable outcome.

CASE REPORT

A 14-year-old boy with severe combined immunodeficiency (SCID) caused by adenosine deaminase deficiency and partial immune reconstitution after he had undergone two haploidentical bone marrow transplantations initially presented to the emergency department in early April 2013 after having had headache and fevers,

From the Departments of Biochemistry and Biophysics (M.R.W., J.L.D.), Neurology (M.R.W.), and Laboratory Medicine (S.N.N., E.S., G.Y., S.S., S.F., S.M., C.Y.C.), and the Department of Medicine, Division of Infectious Diseases (C.Y.C.), University of California, San Francisco (UCSF), and UCSF–Abbott Viral Diagnostics and Discovery Center (S.N.N., E.S., G.Y., S.S., S.F., S.M., C.Y.C.) — both in San Francisco; the Department of Medicine, Division of Allergy and Immunology (M.B., H.B., J.E.G.), and the Departments of Pathology and Laboratory Medicine (S.M.S., K.D.R.) and Pediatrics (T.L.M., C.M.S., S.L.H., J.E.G.), University of Wisconsin, Madison; the Experimental Transplantation and Immunology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD (R.S., F.C.); the Departments of Pediatrics and Immunology, Division of Allergy and Immunology, Duke University, Durham, NC (R.H.B.); and the Centers for Disease Control and Prevention, Atlanta (R.G.). Address reprint requests to Dr. Chiu at the Department of Laboratory Medicine, University of California, San Francisco, 185 Berry St., Box 134, San Francisco, CA 94107, or at charles.chiu@ucsf.edu.

This article was published on June 4, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1401268

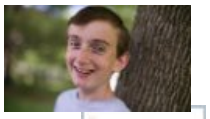
Copyright © 2014 Massachusetts Medical Society.

N ENGL J MED NEJM.ORG 1

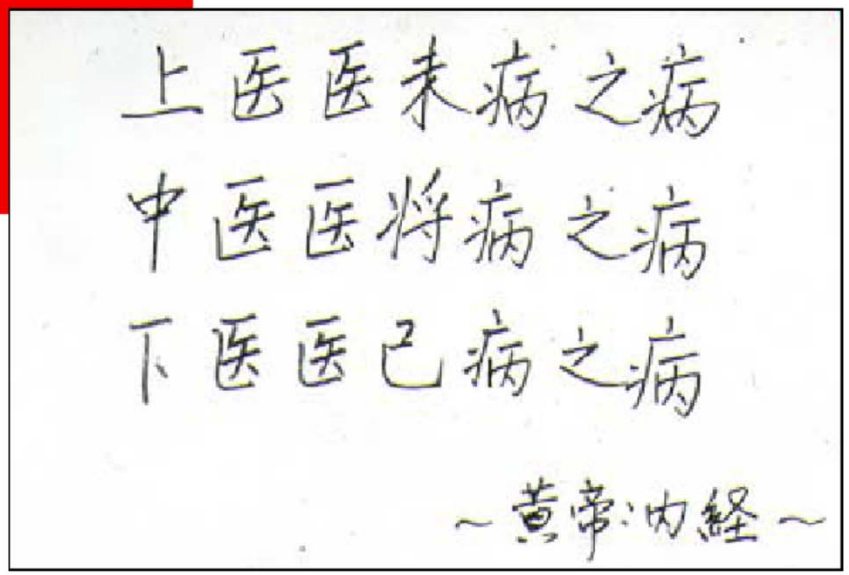
The New England Journal of Medicine
Downloaded from nejm.org on June 7, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

Article in the „New York Times“ June 4, 2014: «In a First, Test of DNA Finds Root of Illness» - tells about a miraculous cure of a young boy due to the Next-Generation Sequencing (NGS), described in The New England Journal of Medicine (Wilson et al. 2014)

- Joshua Osborn, 14, laid in a coma at American Family Children's Hospital in Madison, Wis. For weeks his brain had been swelling with fluid, and a battery of tests had failed to reveal the cause.
- DNA-based test for diagnosing elusive pathogens
- DNA was isolated from different tissues, sequenced and compared with database within 48 hours
- Joshua's cerebrospinal fluid contained DNA from a potentially lethal type of bacteria called Leptospira
- Leptospira was readily treated with penicillin.



Preventive medicine



"Superior Doctors Prevent the Disease.
Mediocre Doctors Treat the Disease Before Evident.
Inferior Doctors Treat the Full Blown Disease."

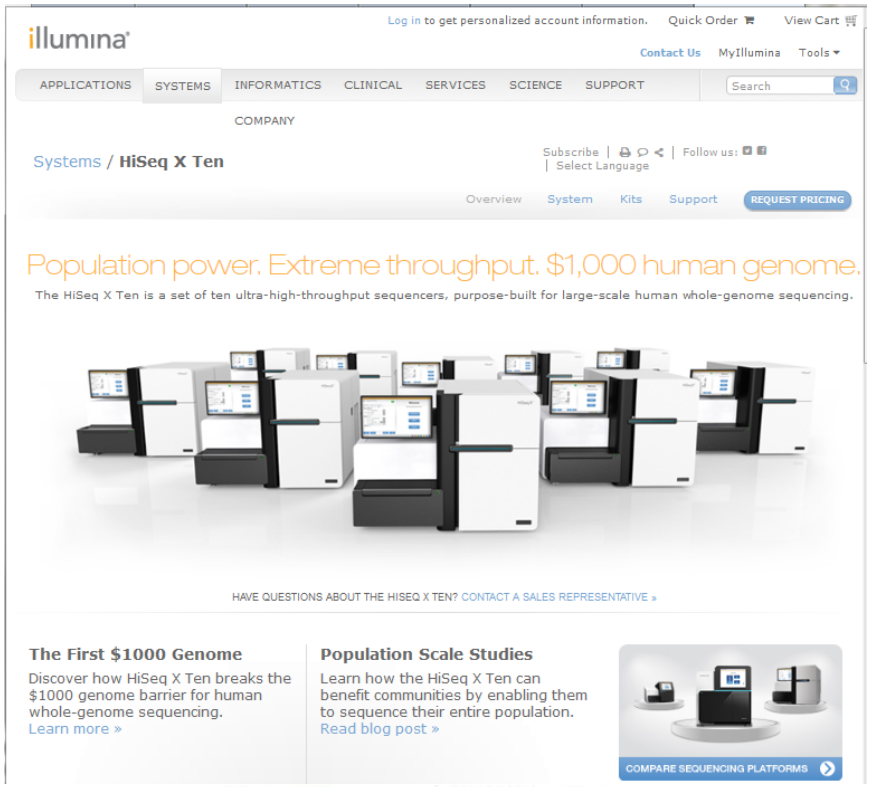
-Huang Dee: Nai - Ching (2600 B.C. 1st Chinese Medical Text

Genomics allows to predict deseases, establish their relations with particular genes and genotypes, and therefore creates a foundation to prevent them

When thinking about diseases, I never think about how to cure them, but instead I think about how to prevent them.

-Louis Pasteur (1822-1895)

Preventive medicine



- Preventive medicine based on the whole genome sequencing is becoming a reality!
- Illumina presented a new and the most powerfull sequencer **HiSeq X** at the Plant and Animal Genome conference in San-Diego in January, 2014
- In his presentation, Illumina's chief executive Jay Flatley said the **HiSeq X** would be able to deliver **a human genome for just under $1,000**
- He said the world is "entering the **supersonic age of genomics**".
- **1.6-1.8 Tb for 3 days = >500 human genomes!**
- **Qatar's human genome project** (http://www.qatartodayonline.com/qatar-genome-launched-at-wish)

Paleogenomics and sequencing of ancient DNA

Scientists create complete genetic map of a Neanderthal from a TOE - and put it online for free

- Scientists from Germany's Max Planck Institute sequenced genome from toe bone found in southern Siberia
- New techniques allowed them to sequence every position in the genome 50 times over for greater accuracy
- They hope it will help answer questions about our own genetic history and how we're related to Neanderthals

By DAMIEN GAYLE

PUBLISHED: 14:52 GMT, 20 March 2013 | UPDATED: 17:26 GMT, 20 March 2013

Share Tweet +1 Share 39 View comments

The first complete Neanderthal genome sequence has been completed and made available free-of-charge to researchers across the world.

Scientists from the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, have made the data available as a free download from their website.

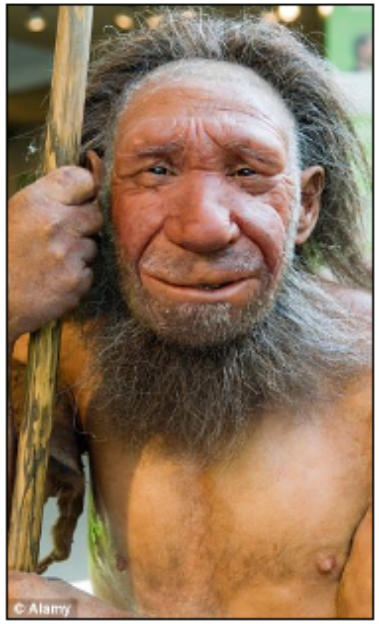
The group will present a paper describing the genome later this year.

'But we make the genome sequence freely available now to allow other scientists to profit from it even before it is published' said Dr Svante Pääbo, who led the project.

Dr Pääbo and his colleagues in 2010 presented the first draft of the Neanderthal genome from data collected from three bones found in a cave in Croatia.

They have now used a toe bone excavated in 2010 in Denisova Cave in southern Siberia to generate a high-quality genome from a single Neandertal individual.

The Leipzig team used sensitive techniques developed there over the past two years to sequence every position in the genome about 50 times over, using DNA extracted from 0.038 grams of the bone.



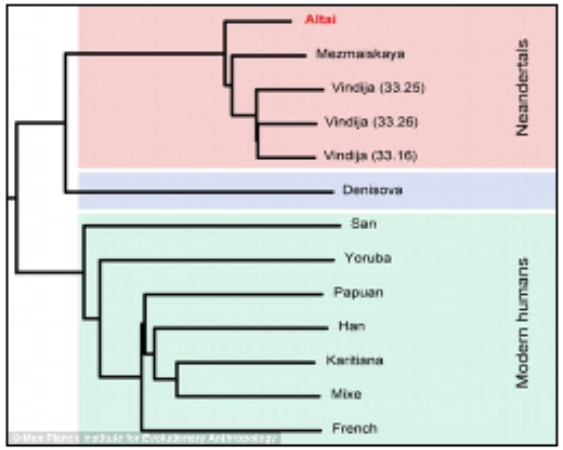
Sequenced: The first full Neanderthal genome has been sequenced and made available free-of-charge by the Max Planck Institute

The analysis of the genome together with partial genome sequences from other Neanderthals, and the genome from a small finger bone discovered in the same cave, shows that the individual is closely related to other Neanderthals in Europe and western Russia.

Remarkably, Neanderthals and their relatives, Denisovans, were both present in this unique cave in the Altai Mountains on the border between Russia, China, Mongolia and Kazakhstan.

In the 2010 draft version of the Neanderthal genome, each position was determined, on average, once. In the now-completed version of the genome every position was determined on average 50 times over.

This allows even the small differences between the copies of genes that this individual inherited from its mother and father to be distinguished.



This family tree relates this genome (top) to the genomes of Neanderthals from Croatia, Germany and the Caucasus as well as the Denisovan genome recovered from a finger bone also excavated at Denisova Cave

The Leipzig group has made the entire genome sequence freely available for the scientific community over the internet.

'The genome is of very high quality', said Dr Kay Prüfer, who coordinated the analyses. 'It matches the quality of the Denisovan genome, presented last year, and is as good as or even better than the multiple present-day human genomes available to date.'

Dr Pääbo added: 'We are in the process of comparing this Neanderthal genome to the Denisovan genome as well as to the draft genomes of other Neanderthals.'

'We will gain insights into many aspects of the history of both Neanderthals and Denisovans and refine our knowledge about the genetic changes that occurred in the genomes of modern humans after they parted ways with the ancestors of Neanderthals and Denisovans.'

The project, part of 30 years' worth of efforts by Dr. Pääbo's group to study ancient DNA, was made possible by financing from the Max Planck Society.

The bone used to sequence the genome was discovered by Professor Anatoly Derevianko and Professor Michael Shunkov from the Russian Academy of Sciences in 2010 during excavations at the Denisova Cave.

The cave is a unique archaeological site which contains cultural layers indicating it has been occupied by humans and our ancestors from as early as 250,000 years ago.

HOW THE DENISOVAN GENOME WAS SIMILARLY SEQUENCED

The Neanderthal genome was sequenced thanks to the discovery of just a toe bone, and it was an even smaller fragment of finger that allowed the same researchers to map out the entire genetic code of Denisovan man.

Evidence suggests that the Denisovans, a little-known ancient cousin of modern humans who lived in Siberia around 50,000 years ago, had dark skin, brown hair and brown eyes.

The existence of the Denisovans was only confirmed in 2010, but previous research has already suggested they co-existed with Neanderthals and interbred with our own species, Homo sapiens.

Scientists made the discovery after studying DNA from a piece of finger bone and two molars found at same Denisova Cave in the Altai Mountains of southern Siberia as the Neanderthal toe bone.

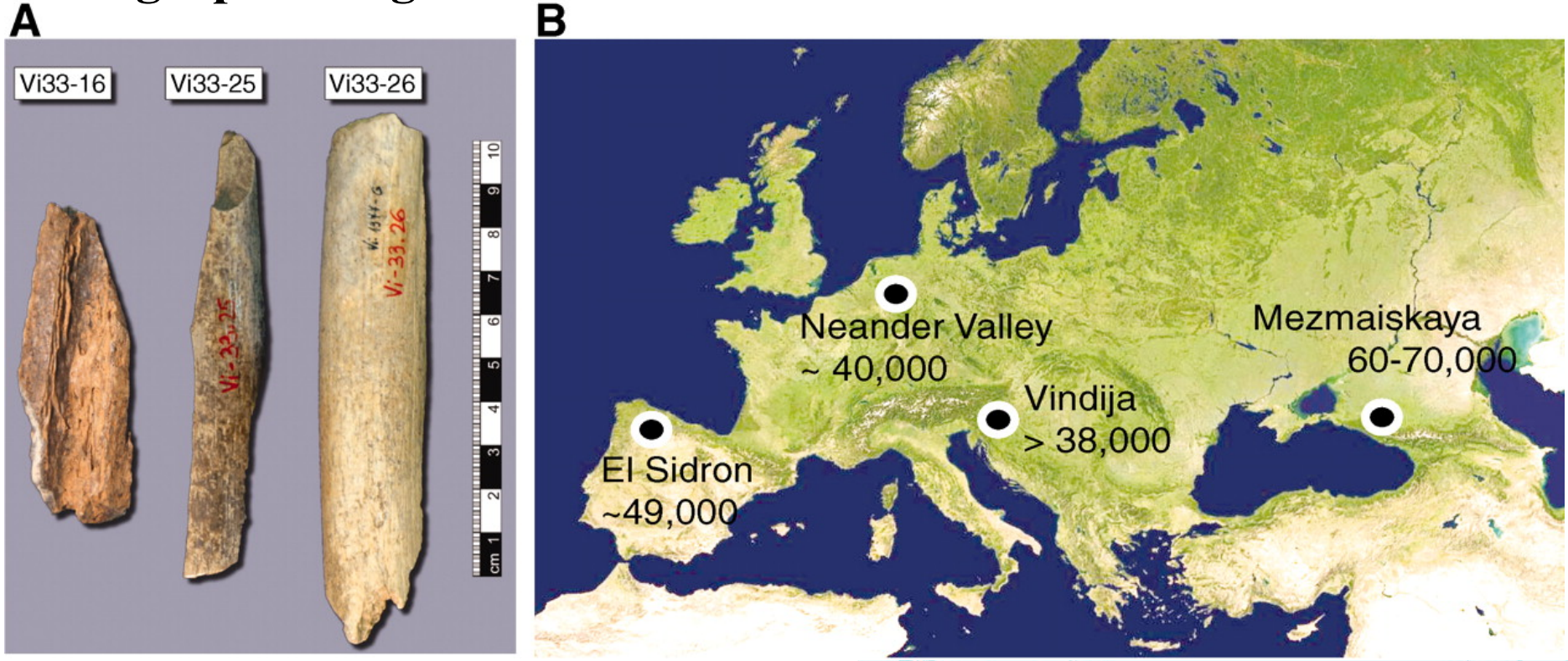
Because they had only a tiny sample of material from the finger bone, Svante Pääbo and his research team developed a treatment that unzipped the DNA so that each of its two strands can be used to generate molecules for sequencing.

This method allowed the team to generate an extremely thorough genome sequence (240X), similar in quality to what researchers can obtain for the modern human genome.

The scientists found that the Denisovans were more genetically similar to Australian aborigines and island populations from south-east Asia.

Paleogenomics and sequencing of ancient DNA

Geographic origin of the Neandertal bones used to isolated DNA

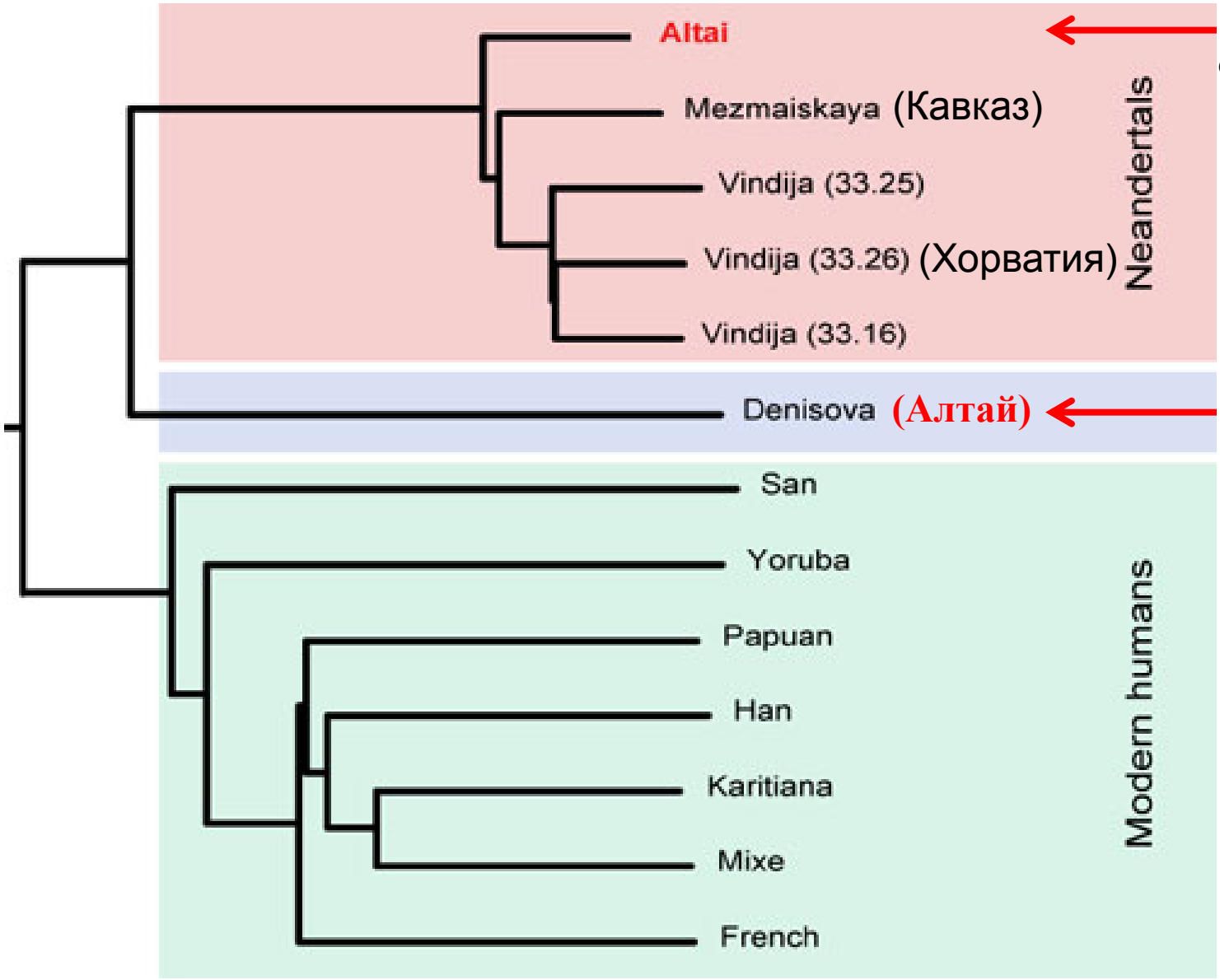


(A) The three bones from Vindija from which Neandertal DNA was sequenced.

(B) Map showing the four archaeological sites from which bones were used and their approximate dates (years B.P.)

Green et al. Science 2010; 328: 710-722

Paleogenomics and hominid paleophylogenomics

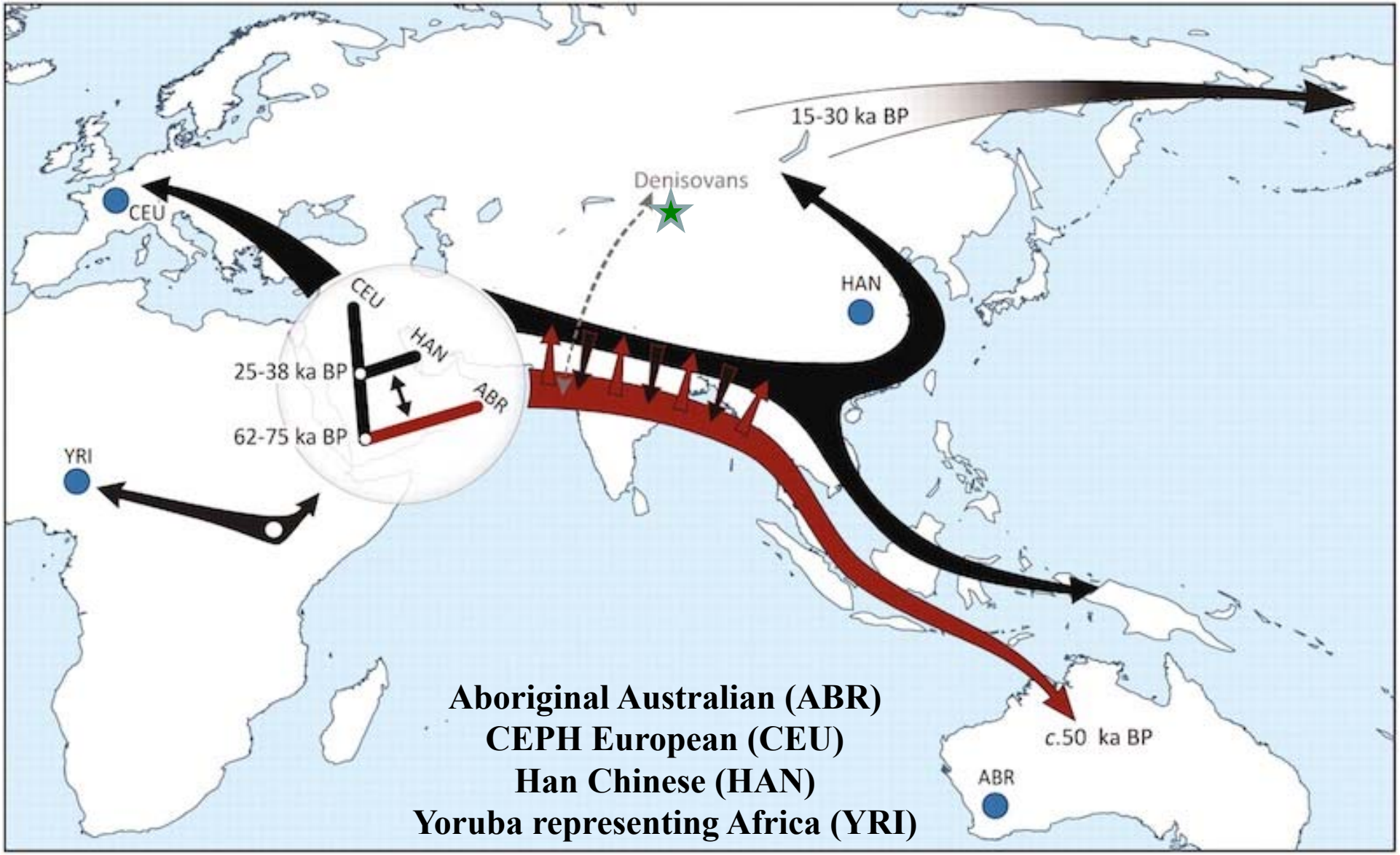


Neandertal genome assembled from DNA of a tooth found in the Denisova Cave

Genome assembled from DNA of a pedal phalanx found in the Denisova Cave in 2010 (Meyer et al. Pääbo 2012 Science 338(6104): 222-226)

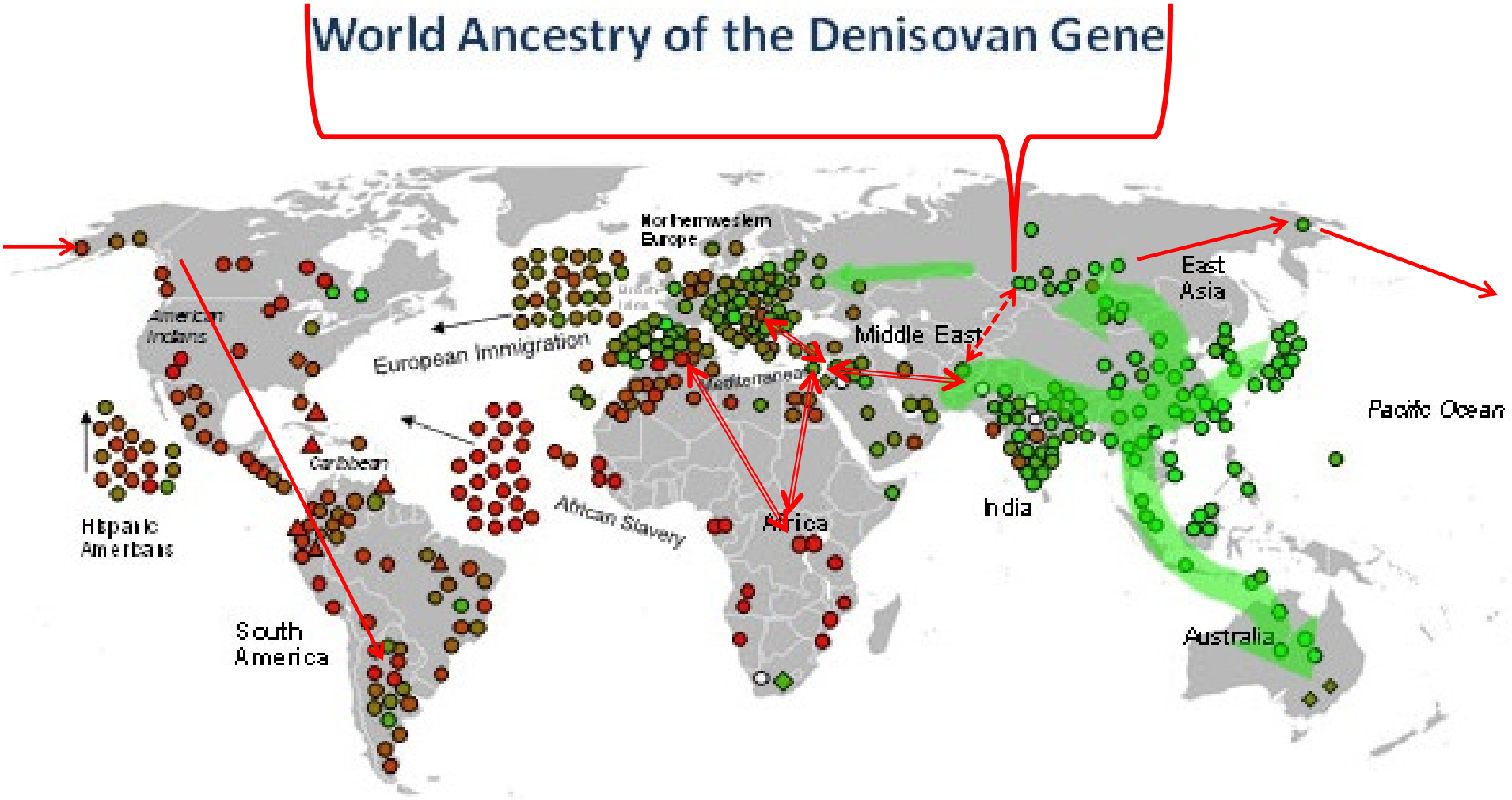
http://www.eva.mpg.de/neandertal/index.html

Historic migration of modern human

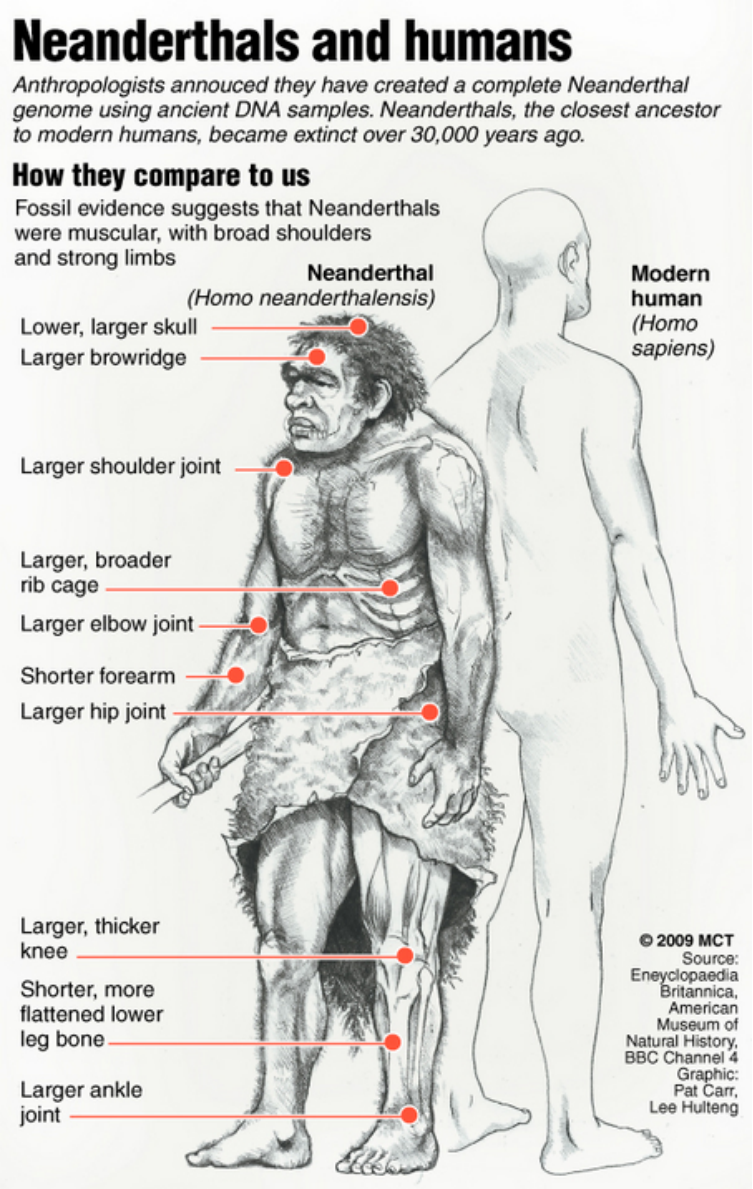


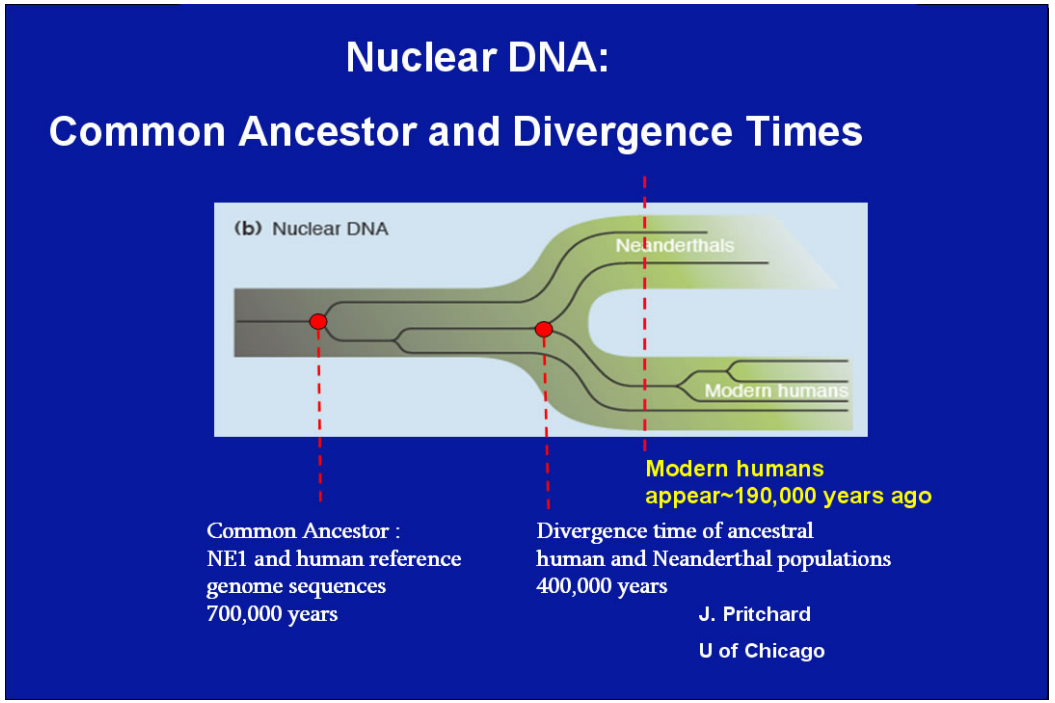
Morten Rasmussen et al. **An Aboriginal Australian Genome Reveals Separate Human Dispersals into Asia**
Science 2011: Vol. 334 no. 6052 pp. 94-98.

Paleogenomics and hominid ancestry



Paleogenomics and hominid paleophylogenomics

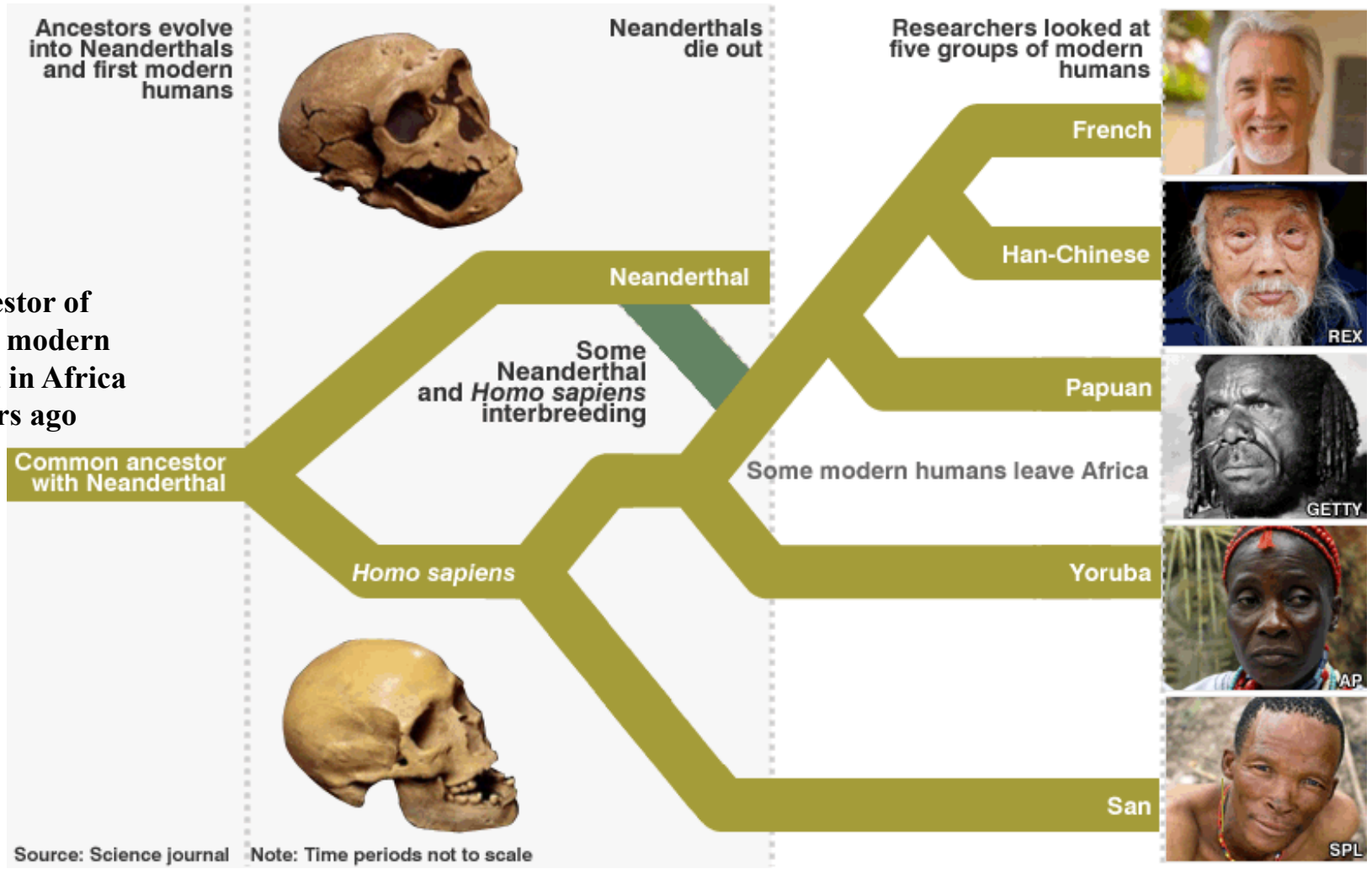




Analysis of genomic DNA from fossilized Neanderthal bones indicated that *Homo sapiens* and *Homo neanderthalensis* last shared a common ancestor approximately 700,000 years ago. The two hominids split into separate species approximately 400,000 years ago, with no evidence of any significant crossbreeding between the two after that time.

Paleogenomics and hominid paleophylogenomics

Common ancestor of Neandertal and modern human appeared in Africa ~700,000 years ago



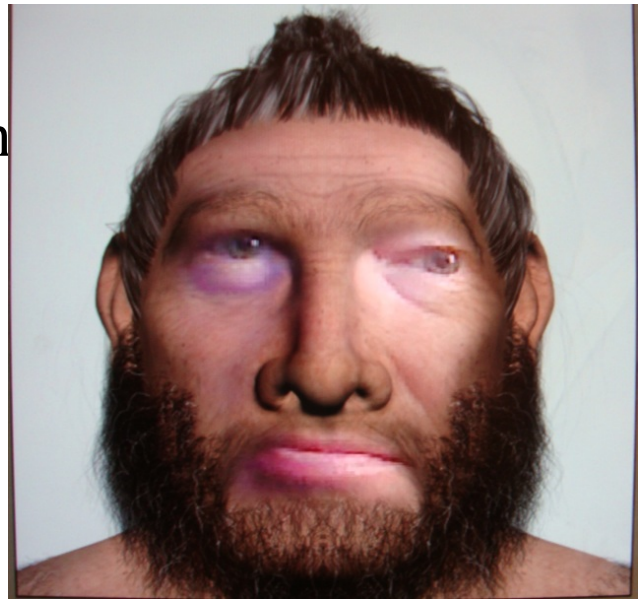
Split between Neandertal and modern human occured ~400,000 years ago

Dispersal of modern human from Africa to Eurasia began ~40,000-70,000 years ago

Paleogenomics and sequencing of ancient DNA

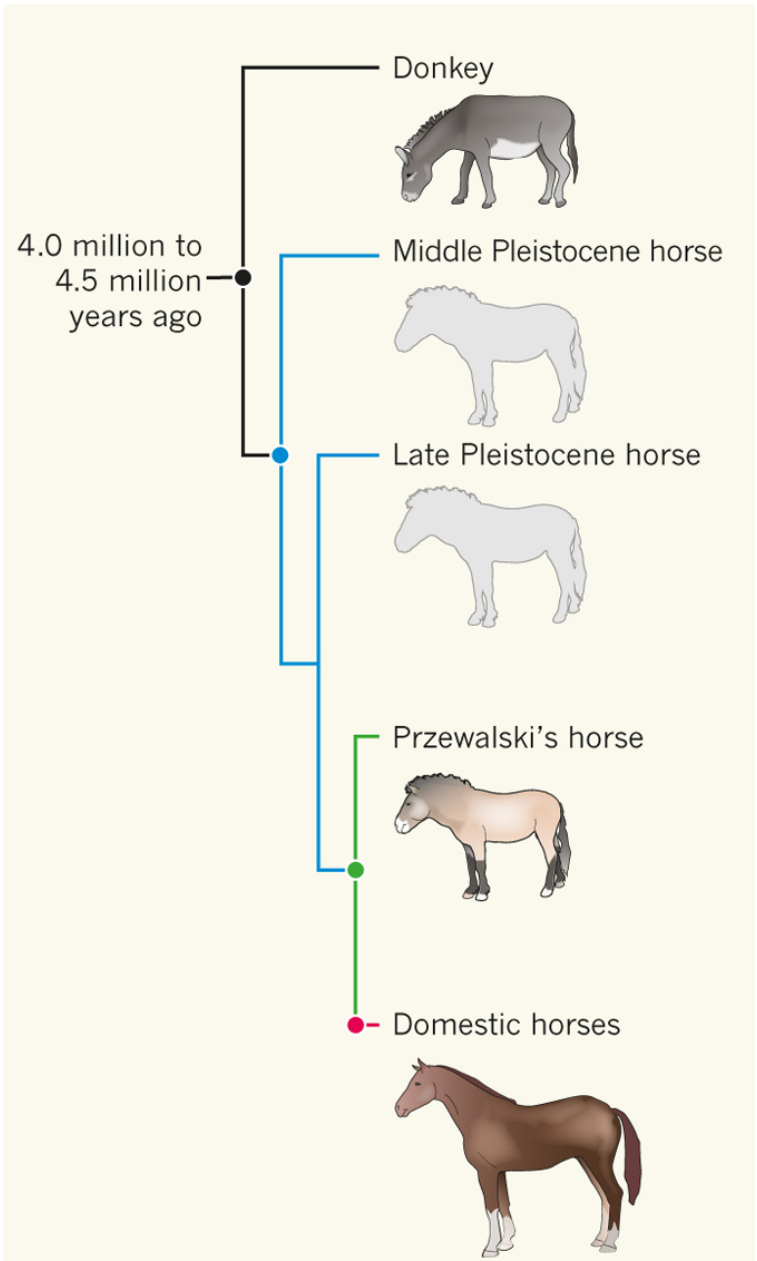
Special challenges:

- Ancient DNA is degraded by nucleases
- The majority of DNA in samples derives from unrelated organisms such as bacteria that invaded after death
- The majority of DNA in samples is contaminated by human DNA
- Determination of authenticity requires special controls, and analysis of multiple independent extracts



Green, R. E. *et al.* A draft sequence of the Neandertal genome. Science 328, 710–722 (2010)

Paleogenomics and paleophylogenomics



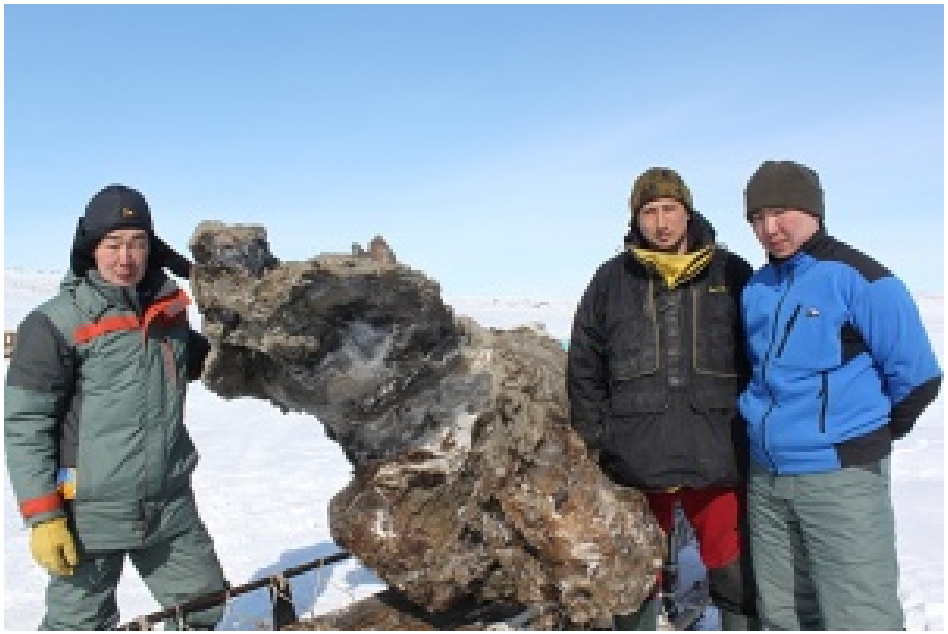
- The most ancient, 700,000 year old DNA was isolated from the remnants of the ancient horse found in the permafrost in Canada and was used to assemble a whole genome.
- Phylogenomic analysis demonstrated that the common ancestor of domestic horses, zebras and their relatives lived ~4 mln years ago (Orlando *et al*. Nature 2013: http://dx.doi.org/10.1038/nature12323).

Paleogenomics and sequencing of ancient DNA

Genome of wool mammoth (***Mammuthus primigenius***)was partially sequenced in 2008 using hairs of two females found in permafrost in Siberia and dated as ~20,000 and 60,000 year old (Miller et al. 2008 Nature 456: 387-390).

The best preserved wool mammoth was found in **2013 in Maly Lyakhovsky Island in the far north of Siberia**

Scientists from the Siberian Northeastern Federal University in Yakutsk and the Siberian Federal University in Krasnoyarsk have a joint project for the whole genome sequencing



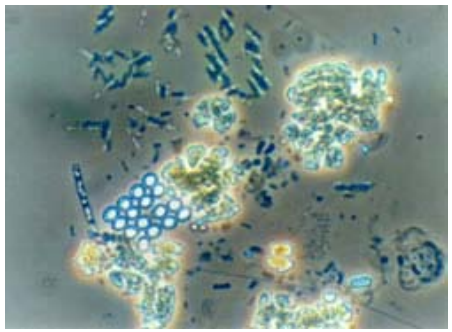
Paleogenomics and sequencing of ancient DNA

Dissection and sampling of the Maly Lyakhovsky mammoth by the scientists from the Siberian Northeastern Federal University and the Siberian Federal University in 2014 . The genome sequencing will be done at the Genome Research and Education Center of the Siberian Federal University (http://genome.sfu-kras.ru/en)

Metagenomics and sequencing of complex communities

Metagenomics (also **Environmental Genomics**, **Ecogenomics** or **Community Genomics**) is the study of genetic material recovered directly from environmental samples:



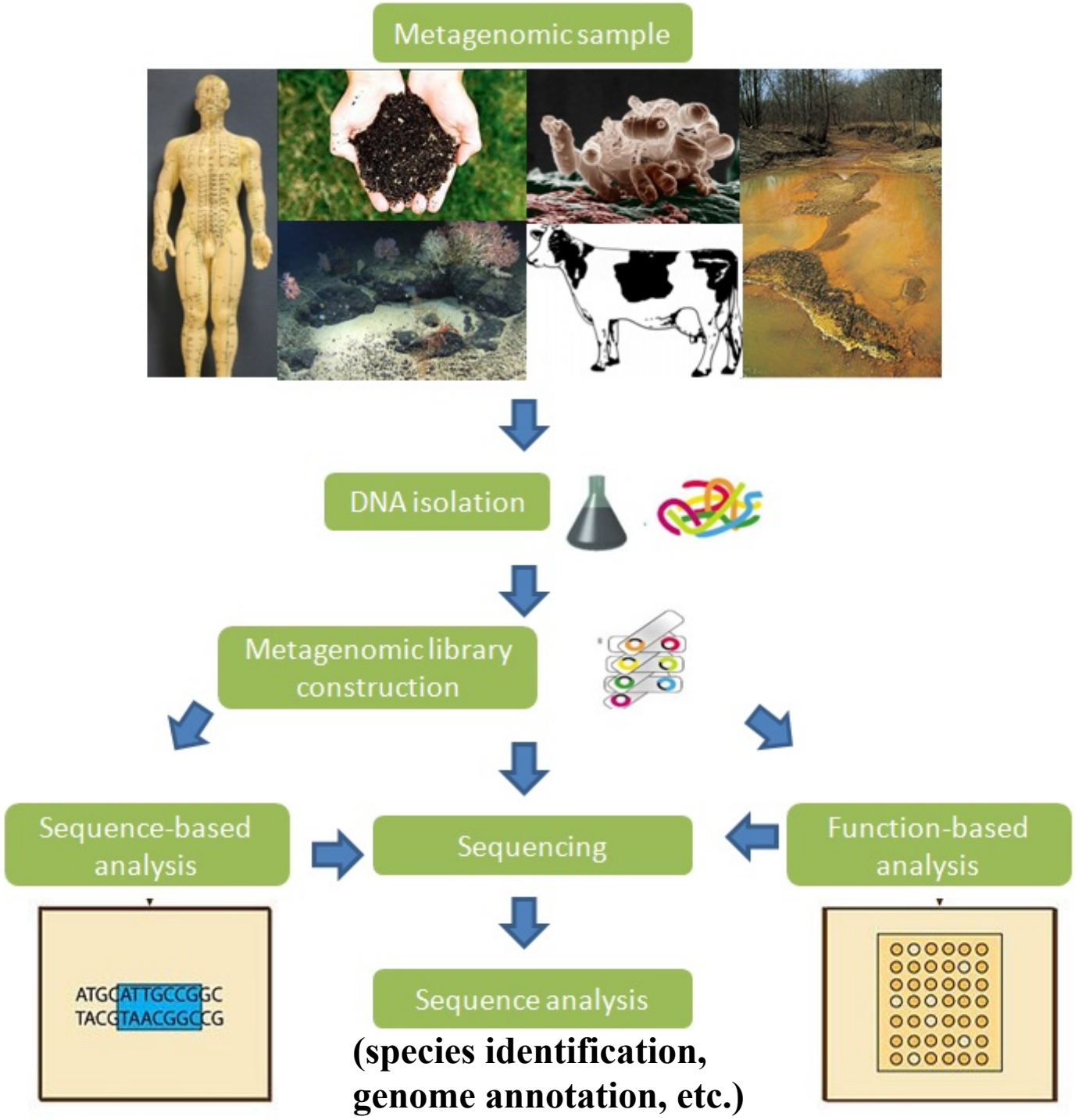



- external environments (ecological)

  hot spring, ocean, sludge, soil, etc.

- internal environments (organismal)

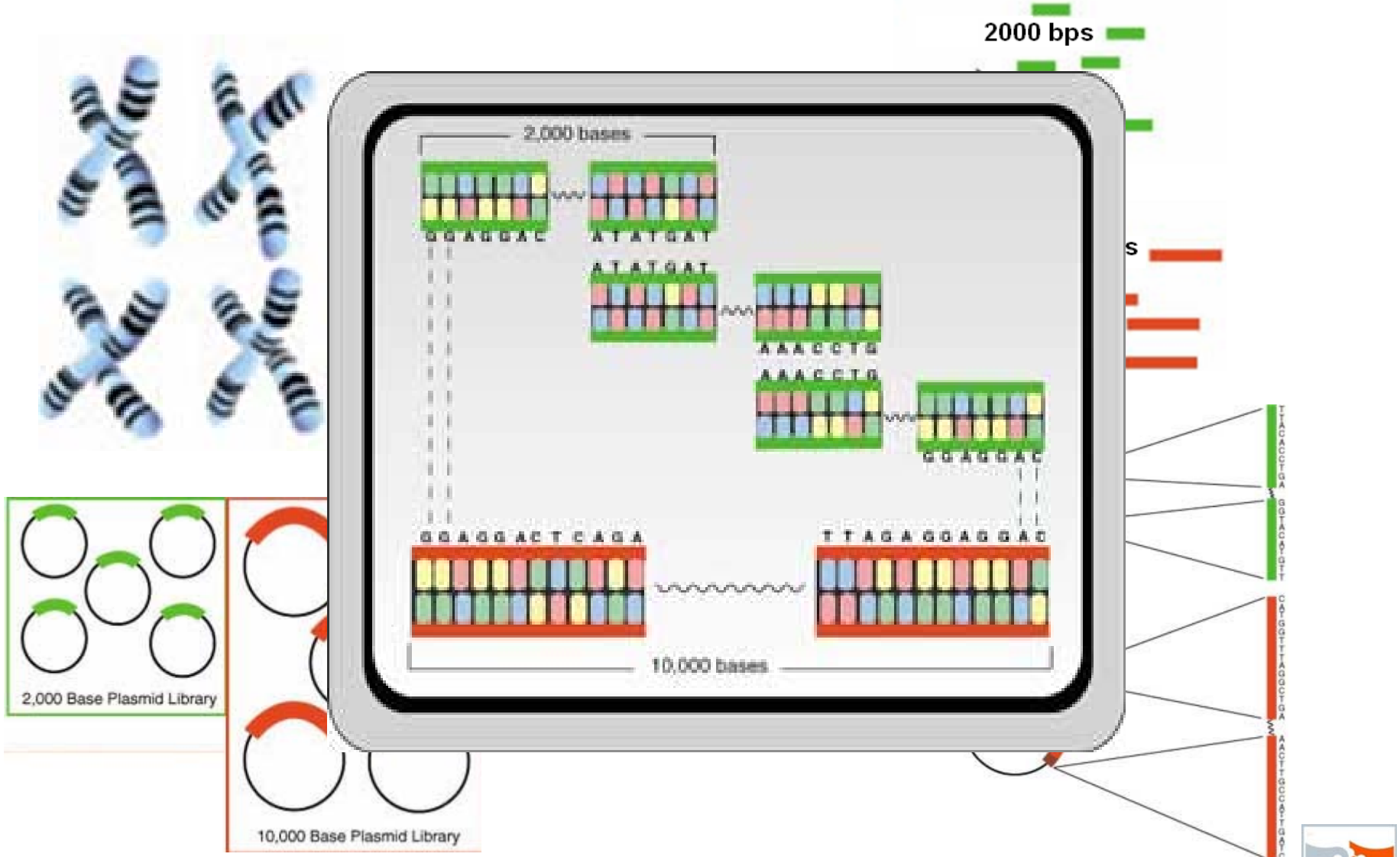
  guts, saliva, feces, lung, etc.


Metagenomic sample
DNA isolation
Metagenomic library construction
Sequence-based analysis
Sequencing
Function-based analysis
ATGCATTGCCGGC
TACGTAACGGCCG
Sequence analysis
(species identification, genome annotation, etc.)

Sampling in Metagenomics

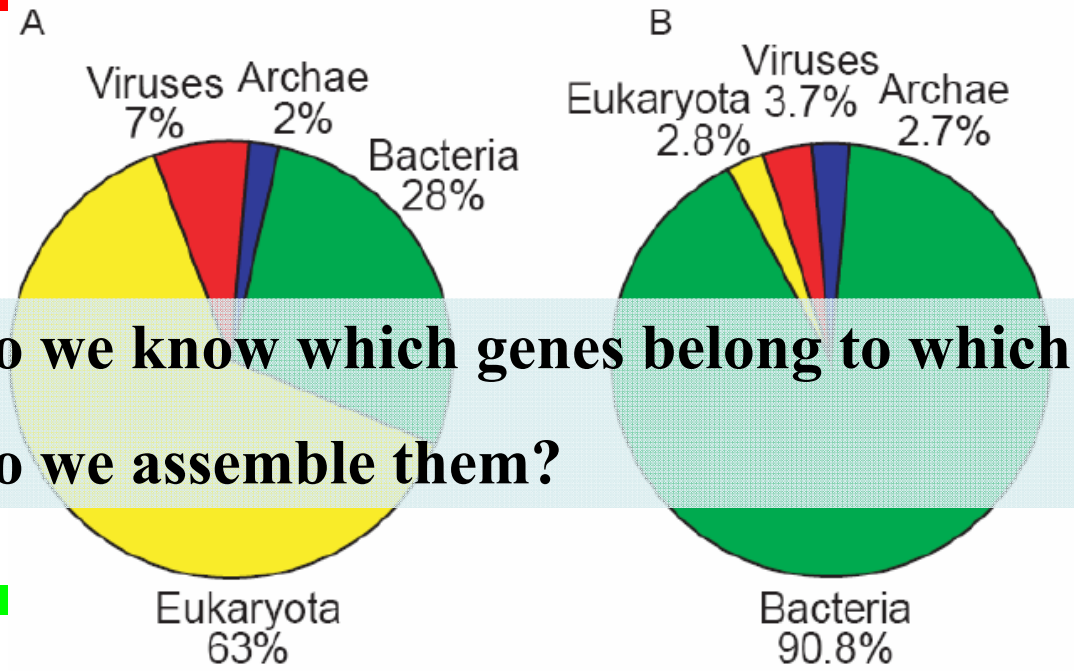
- Take a sample off of the environment
- Isolate and amplify DNA/mRNA
- Sequence it

Shotgun Sequencing



Computer assembly

ACT…GTC CTA ATC …GGGG



How do we know which genes belong to which genome?

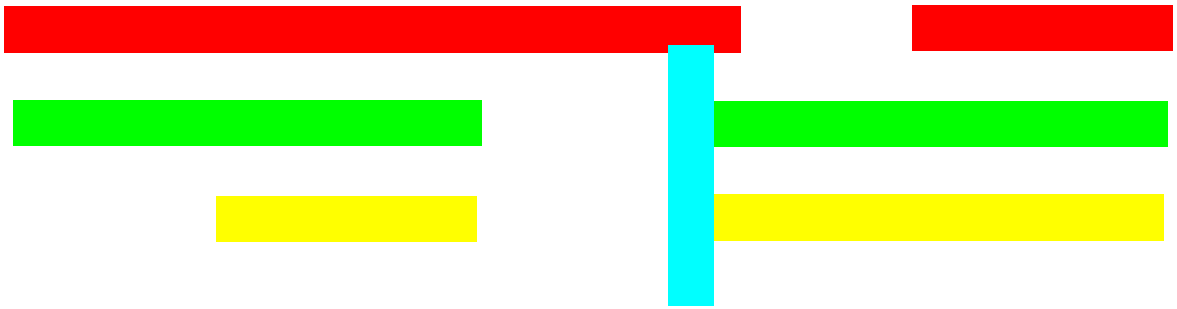
How do we assemble them?

Global Ocean Sampling (GOS) metagenomic data

The Best Case Scenario

Coverage is enough to assemble independent genomes

What normally happens

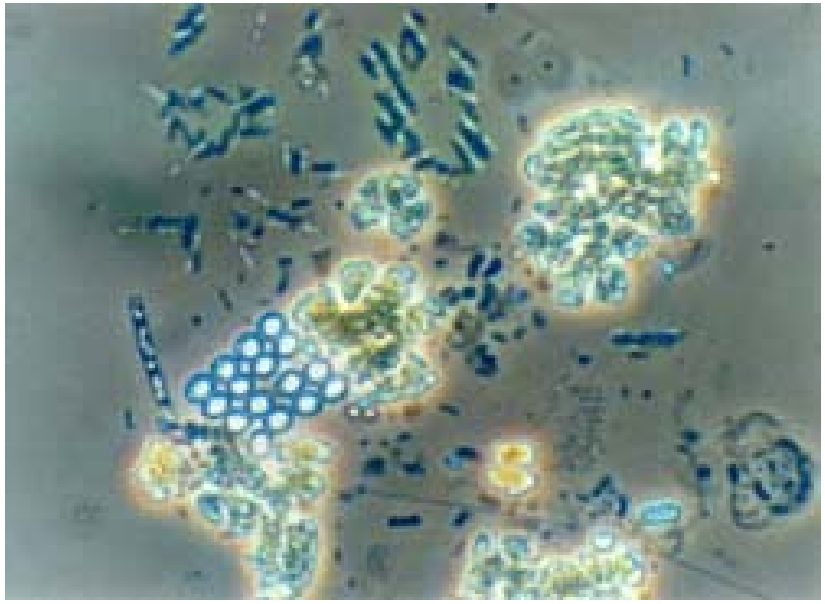


Coverage is not enough and assembly is fragmentary

Worst Case Scenario: Some fragments can not be assigned

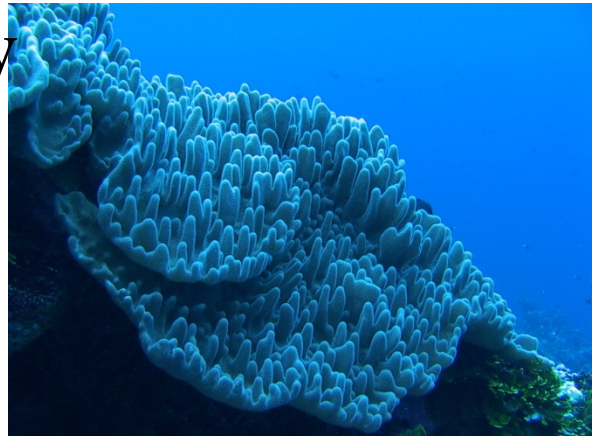
Down Side of Metagenomics

- often fragmentary
- often highly divergent
- rarely any known activity
- no chromosomal placement
- no organism of origin
- *ab initio* ORF predictions
- huge data



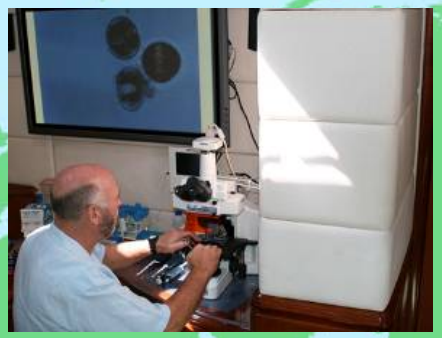
Marine Metagenomics

- Microbes account for more than **90% of ocean biomass**, mediate all biochemical cycles in the oceans and are responsible for **98% of primary production** in the sea.



- Metagenomics is a breakthrough sequencing approach to examine the open-space microbial species **without the need for isolation and lab cultivation of individual species**.

Marine Genome Sequencing Project Measuring the Genetic Diversity of Ocean Microbes



Dr. John Craig Venter

Sorcerer II Data from this area has already reach to 10% of GenBank.

The Entire Data Will Double Number of Proteins in Embank!

Sample Metadata from GOS (Global Ocean Sampling)

- **Site Metadata**
  - Location (lat/long, water depth)
  - Site characterization (finite list of types plus “other”)
  - Site description (free text)
  - Country
- **Sampling Metadata**
  - Sample collection date/time
  - Sampling depth
  - Conditions at time of sampling (e.g., stormy, surface temperature)
  - Sample physical/chemical measurements
  - “author”
- **Experimental Parameters**
  - Filter size
  - Insert size

Calit2's Direct Access Core Architecture Will Create Next Generation Metagenomics Server

Sargasso Sea Data

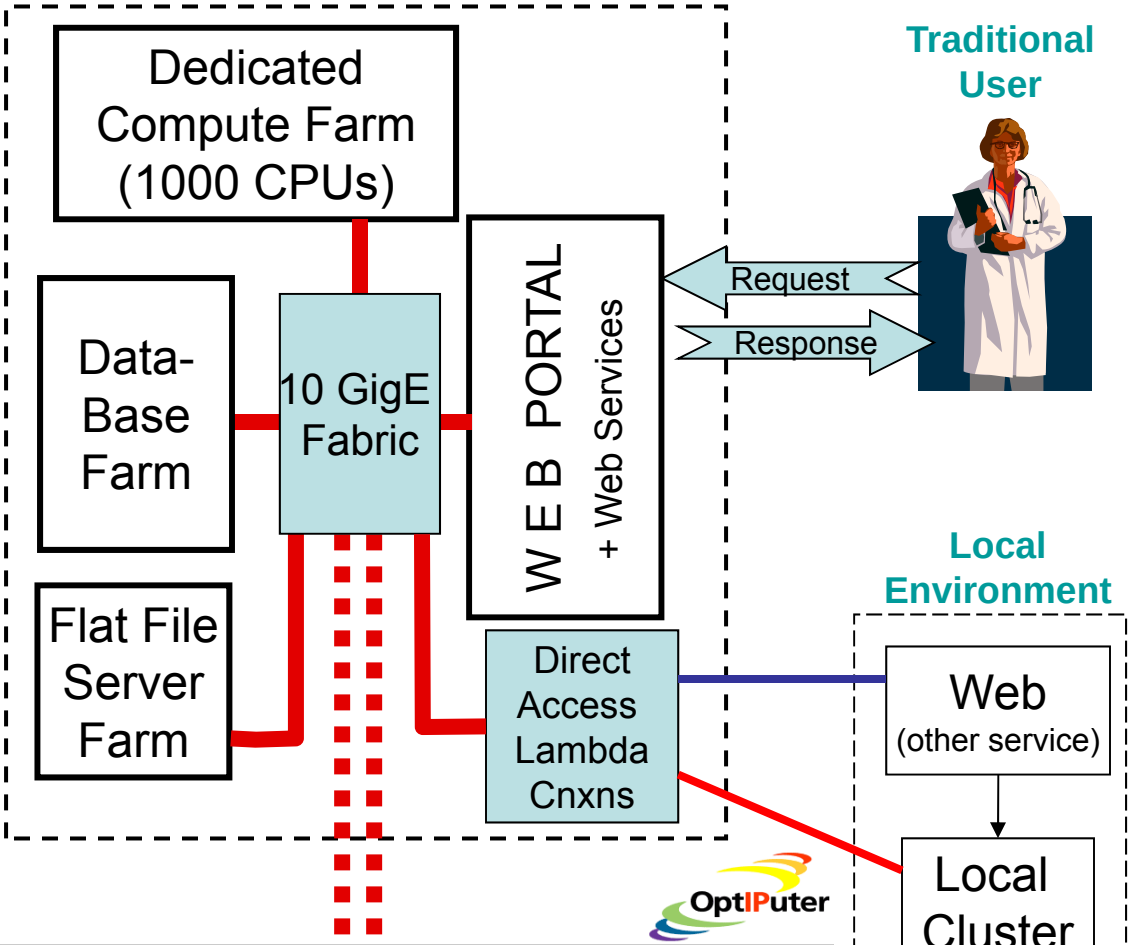
Sorcerer II Expedition (GOS)

JGI Community Sequencing Project

Moore Marine Microbial Project

NASA Goddard Satellite Data

Community Microbial Metagenomics Data



J. Craig Venter INSTITUTE

SDSC SAN DIEGO SUPERCOMPUTER CENTER

Source: Phil Papadopoulos, SDSC, Calit2

Marine Metagenomics

Drug discovery

Metabolic pathway discovery

Microbial genetic survey

Environmental survey

Symbiosis

Who is there?

Evolution study

Endosymbiosis

Organism discovery

Microbial genomic survey

Bioenergy discovery

Marine conservation

Biogeochemistry mapping

Ecological restoration

What is Nutrigenomics?

- Nutrigenomics is the science that examines the response of individuals to food compounds using post-genomic and related technologies.

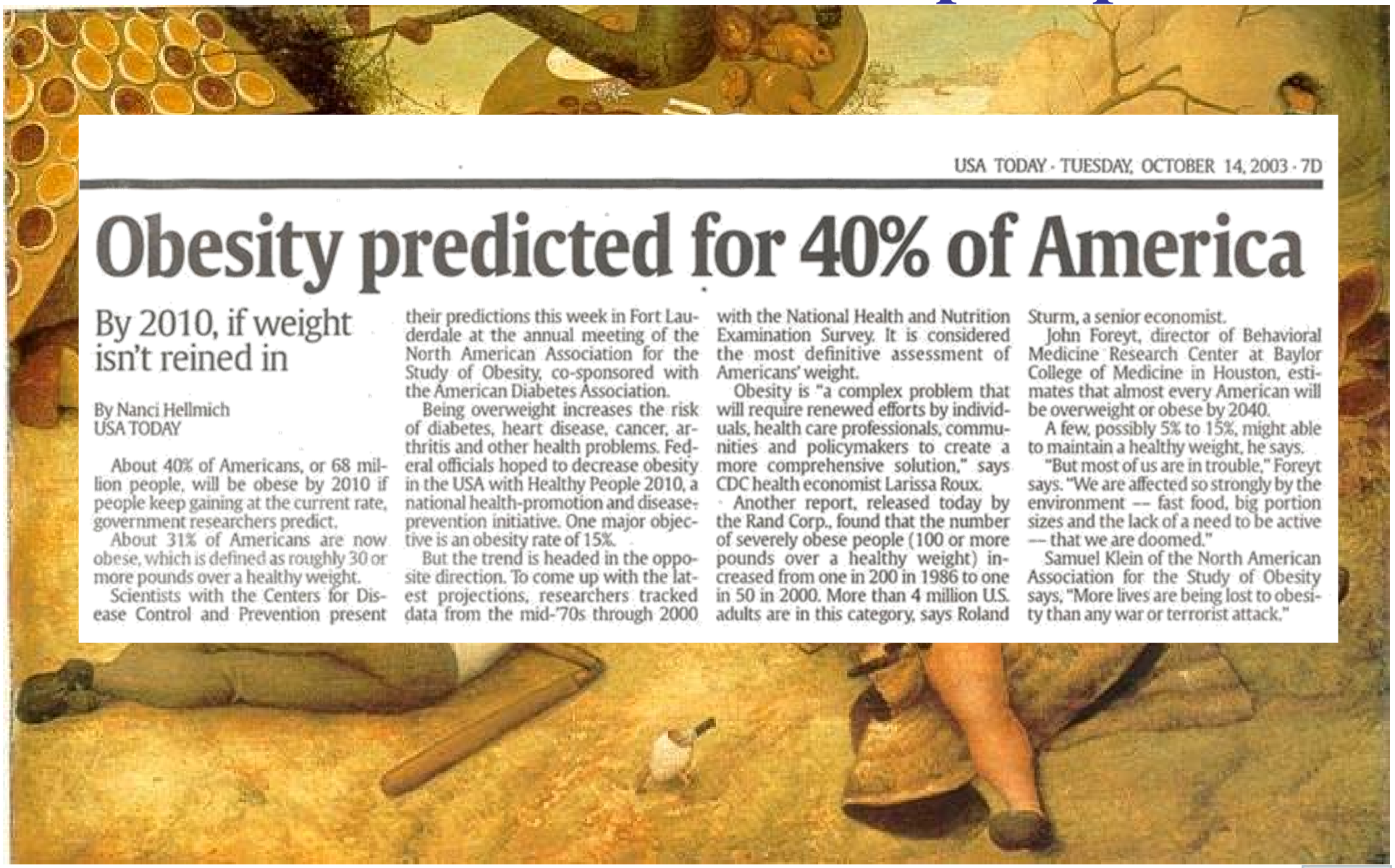
- The long-term aim of nutrigenomics is to understand how the whole body responds to real foods using an **integrated system biology approach**.

- Studies using this approach can examine people (i.e. populations, subpopulations - based on genes or disease - and individuals), food, life-stage and life-style without preconceived ideas.

Why is Nutrigenomics important?

- Most non-genetic diseases are **nutrition** related.
- **Diabetes, obesity and other nutrition related diseases are growing!!!** Of course genes are a factor.
- **Finding the right combination of nutrients for each genotype** can help in changing behavior and preventing many of these diseases.
- This combination may change with age, sex!

Problem 1: Nutrition – complex problem



USA TODAY · TUESDAY, OCTOBER 14, 2003 · 7D

Obesity predicted for 40% of America

By 2010, if weight isn't reined in

By Nanci Hellmich
USA TODAY

About 40% of Americans, or 68 million people, will be obese by 2010 if people keep gaining at the current rate, government researchers predict.

About 31% of Americans are now obese, which is defined as roughly 30 or more pounds over a healthy weight.

Scientists with the Centers for Disease Control and Prevention present their predictions this week in Fort Lauderdale at the annual meeting of the North American Association for the Study of Obesity, co-sponsored with the American Diabetes Association.

Being overweight increases the risk of diabetes, heart disease, cancer, arthritis and other health problems. Federal officials hoped to decrease obesity in the USA with Healthy People 2010, a national health-promotion and disease-prevention initiative. One major objective is an obesity rate of 15%.

But the trend is headed in the opposite direction. To come up with the latest projections, researchers tracked data from the mid-'70s through 2000 with the National Health and Nutrition Examination Survey. It is considered the most definitive assessment of Americans' weight.

Obesity is "a complex problem that will require renewed efforts by individuals, health care professionals, communities and policymakers to create a more comprehensive solution," says CDC health economist Larissa Roux.

Another report, released today by the Rand Corp., found that the number of severely obese people (100 or more pounds over a healthy weight) increased from one in 200 in 1986 to one in 50 in 2000. More than 4 million U.S. adults are in this category, says Roland Sturm, a senior economist.

John Foreyt, director of Behavioral Medicine Research Center at Baylor College of Medicine in Houston, estimates that almost every American will be overweight or obese by 2040.

A few, possibly 5% to 15%, might able to maintain a healthy weight, he says.

"But most of us are in trouble," Foreyt says. "We are affected so strongly by the environment — fast food, big portion sizes and the lack of a need to be active — that we are doomed."

Samuel Klein of the North American Association for the Study of Obesity says, "More lives are being lost to obesity than any war or terrorist attack."

More than one-third of U.S. adults (35.7%) are currently obese (BMI >30)!

http://www.cdc.gov/obesity/data/adult.html

Genes – Lifestyle – Calories

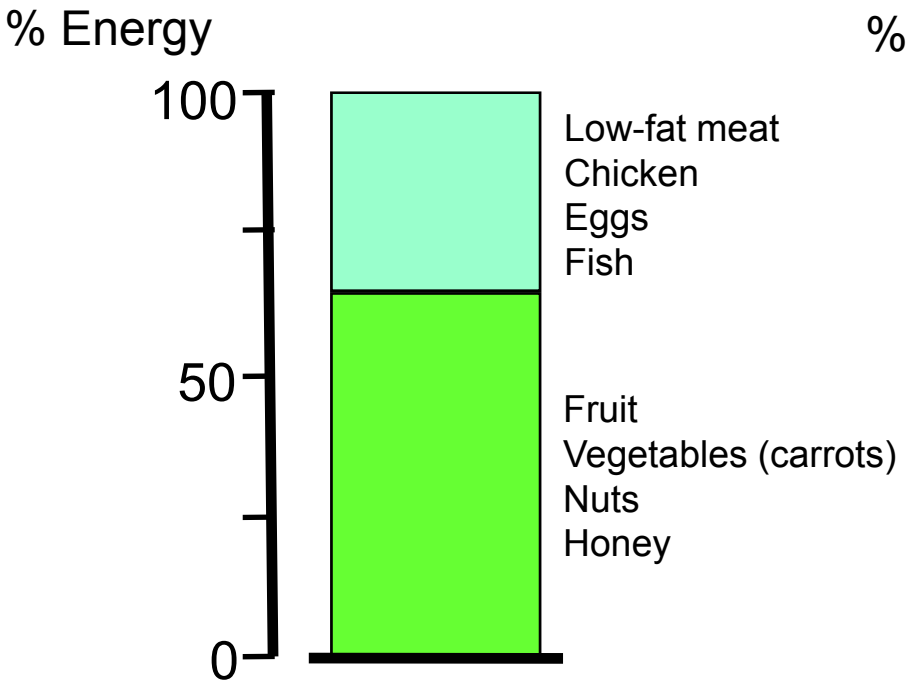
The same genes – The changed diet

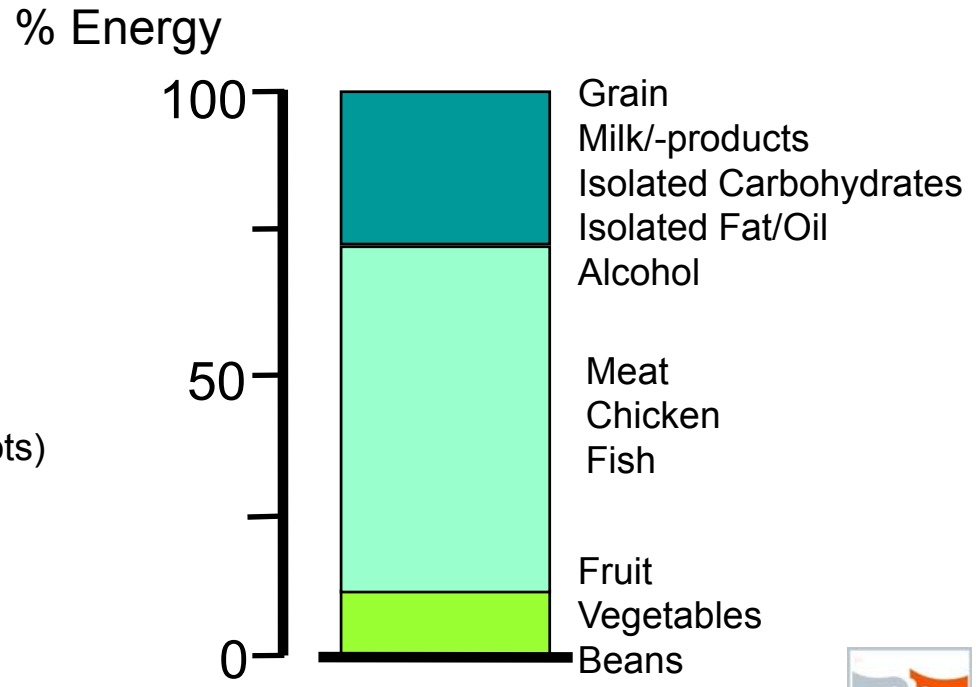
Paleolithic era

1.200.000 Generations between feast and famine

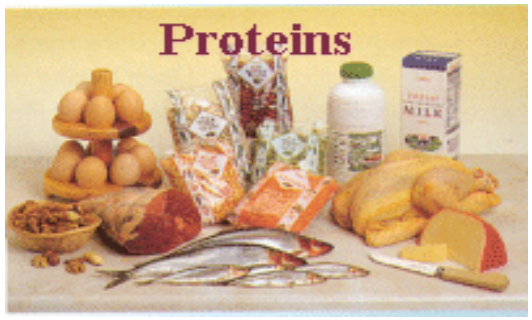
Modern Times

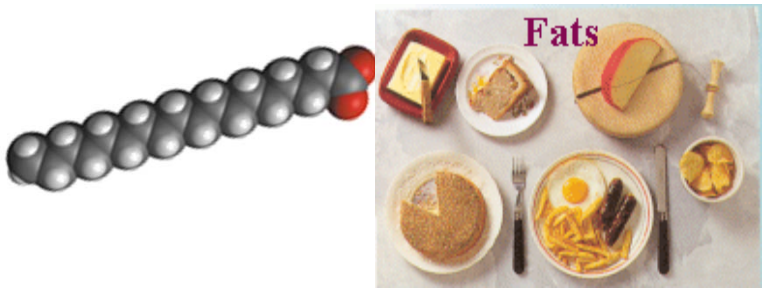
2-3 Generations in energy abundance

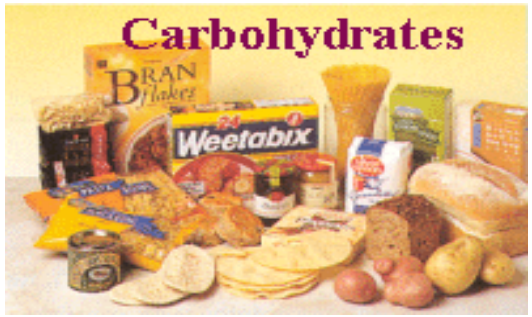


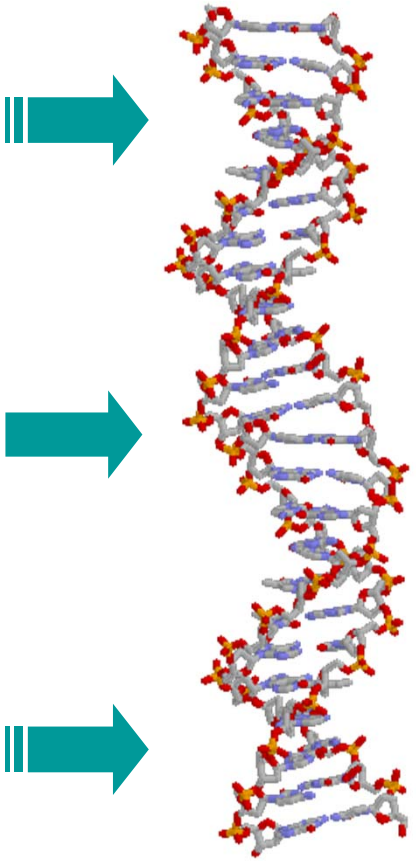


Molecular nutrition





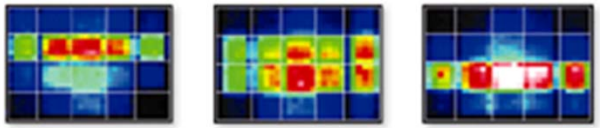




Problem 2:
Our “gene passports” and nutrition

Individual genotype
Functional phenotype

AA AB BB



Optimal Nutrition

Lifestyle

Improvement
Maintenance
of Health

“Eat right for your genotype??”

Personalized diets?

genelex
Science that benefits humanity

Nutritional Genetic Profile Request Form

Client Information

To order testing, either contact Genelex directly or complete this form and return it either by fax at (425) 825-1870 or mail to Genelex Corporation, 12277 134th Ct NE, Ste. 130 Redmond, WA 98052.

Name: _____ Phone: _____ E-mail: _____

Address: _____

City: _____ State: _____ Zip: _____

Nutritional Genetic Profile Requested

Item	Number ordered	Cost (per item)	Total
Nutritional Genetic Panel		$445.00	
Nutritional Genetic Collection Kit (Additional $410 due with samples)		$35.00	
International Shipping		$50.00	
Amount Due			

Payment: Prepayment is required. Send Cash, Check, or Money Order to the address shown above.

Cash ☐ Check or Money Order ☐ Credit Card (all major cards) ☐

Type of credit card: _____

Print cardholder's name: _____

Card number: _____ Expiration date: _____

For immediate consultation Call 800-TEST-DNA (800-837-8362)
Hours 7:00 AM to 6:00 PM PST, 10:00 AM to 9:00 PM EST, fax 425-825-1870,
e-mail: info@genelex.com
www.genelex.com

Consumers warned that time is not yet ripe for nutrition profiling

Erika Check

One day, information about your genome may well help you decide what breakfast cereal to eat. But that day's a long way off, the second International Nutrigenomics Conference in Amsterdam was told last week. In the meantime, researchers at the meeting heard, the emerging field badly needs a regulatory framework that will stop its first customers from being scared off.

Nutrigenomics researchers aim to learn how nutrients interact with genes to lead to health or disease. But people eat wildly different levels of nutrients over their lifetimes, and teasing apart the precise interactions is notoriously difficult.

The researchers who gathered in Amsterdam on 6–7 November were in optimistic mood, however. Their science is progressing quickly, and food industry executives have expressed interest in the idea of using genetic information to customize their products.

In January, the US National Institutes of Health used a 5-year, $6.5-million grant to create a National Center of Excellence for Nutritional Genomics at the University of California, Davis, and the Children's Hospital Oakland Research Institute (CHORI) in Oakland. In July, the European Commission set up the European NutriGenomics Organisation to coordinate work. Now the Netherlands looks set to embark on a $20-million nutrigenomics project, jointly funded by the government and the food industry.

But some researchers warn that the field is in danger of developing too quickly. They want experts to back off from the sometimes-extravagant claims for the field's potential, and instead to sit down and patiently work out a scientific vision and ethical framework for the discipline.

"Our aim is to bring the field a little bit back down to Earth, because people tend to start with a lot of science fiction," says Michael Müller, a genomicist at Wageningen University in the Netherlands who helped to organize the meeting.

The main fruits of this field are still years away, researchers say. So far, most of the studies on profiling gene expression — measuring genome-wide responses to nutrients — have been done in mice. And much more work is needed on the basic mechanisms by which nutrients turn genes on or off. But that hasn't stopped a handful of companies from selling nutritional profiles directly to consumers over the Internet.

Looks good, tastes good, and one day individuals may know exactly how much good it does them.

The companies test a tissue sample — such as a cheek swab — from a "patient". The patient can choose which genetic profile he or she wants to learn about, for example skin ageing or susceptibility to osteoporosis. The company then gives the patient a "personalized profile" based on its tests for single nucleotide polymorphisms (SNPs): genetic variants that have been linked to disease. For instance, one company, GeneLink of Margate, New Jersey, tells people what vitamins they should take, based on SNPs involved in cellular responses to certain toxins. GeneLink declined to comment on its products.

But many scientists argue that it's far too early for most of these tests to be useful. "The idea of marketing any individual genetic test at this point assumes there is information to justify the use of that test, and we really don't have evidence that any single genetic marker carries enough information to guide dietary treatments," says Ronald Krauss, director of atherosclerosis research at CHORI.

The direct-to-consumer tests also raise ethical issues that affect the whole field. For instance, some companies sell the results of their genetic profiles to other firms, which use the information for research on genes and disease. Although consumers must give their consent, they may not necessarily understand what they're agreeing to, says ethicist David Castle of the University of Guelph. Castle is collaborating with the University of Toronto Joint Center for Bioethics in soliciting comments on a joint working paper on ethics and nutrigenomics.

At the nutrigenomics meeting, Castle argued that even though the field is very young, scientists must begin talking to the public about such issues.

"This technology could end up affecting something that every person does every day, which is eat," Castle says. "It's not a situation where you want to roll out the science and the products and then go back and ask people how they feel about it." ■

NATURE | VOL 426 | 13 NOVEMBER 2003 |

Nutrients acts as dietary signals

Nutritional factors

↓

Transcription factors

↓

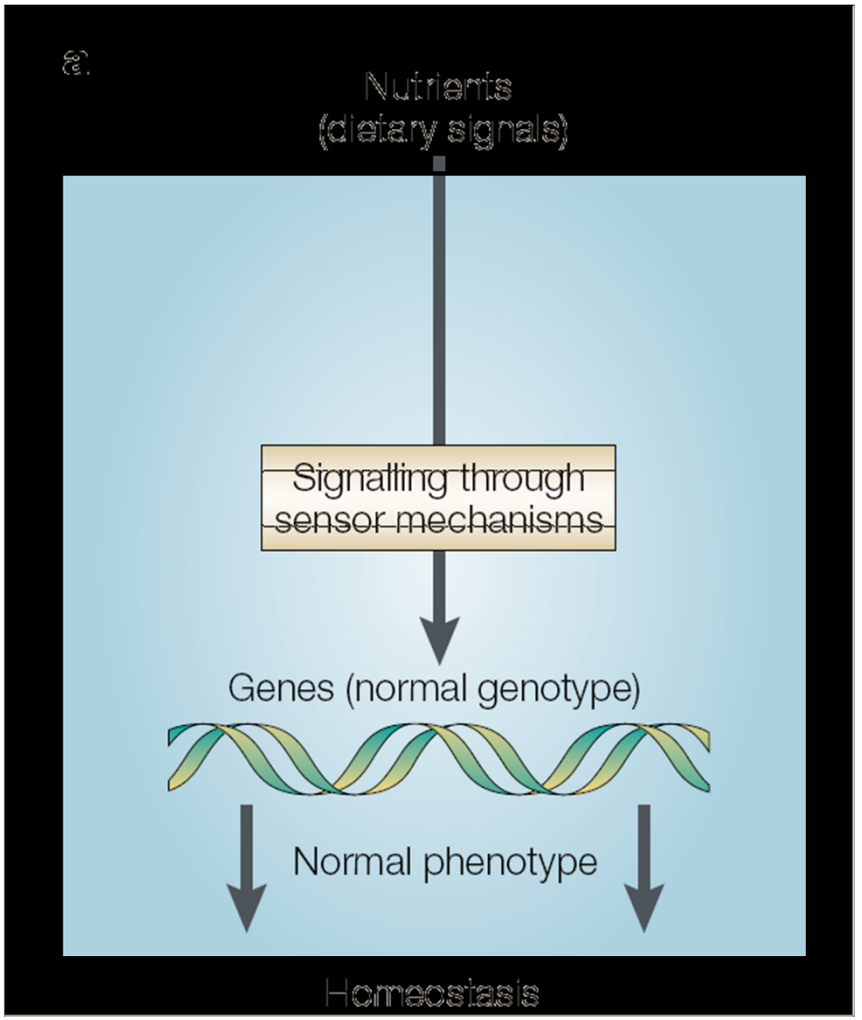
Gene transcription

↓

Energy homeostasis

Cell proliferation

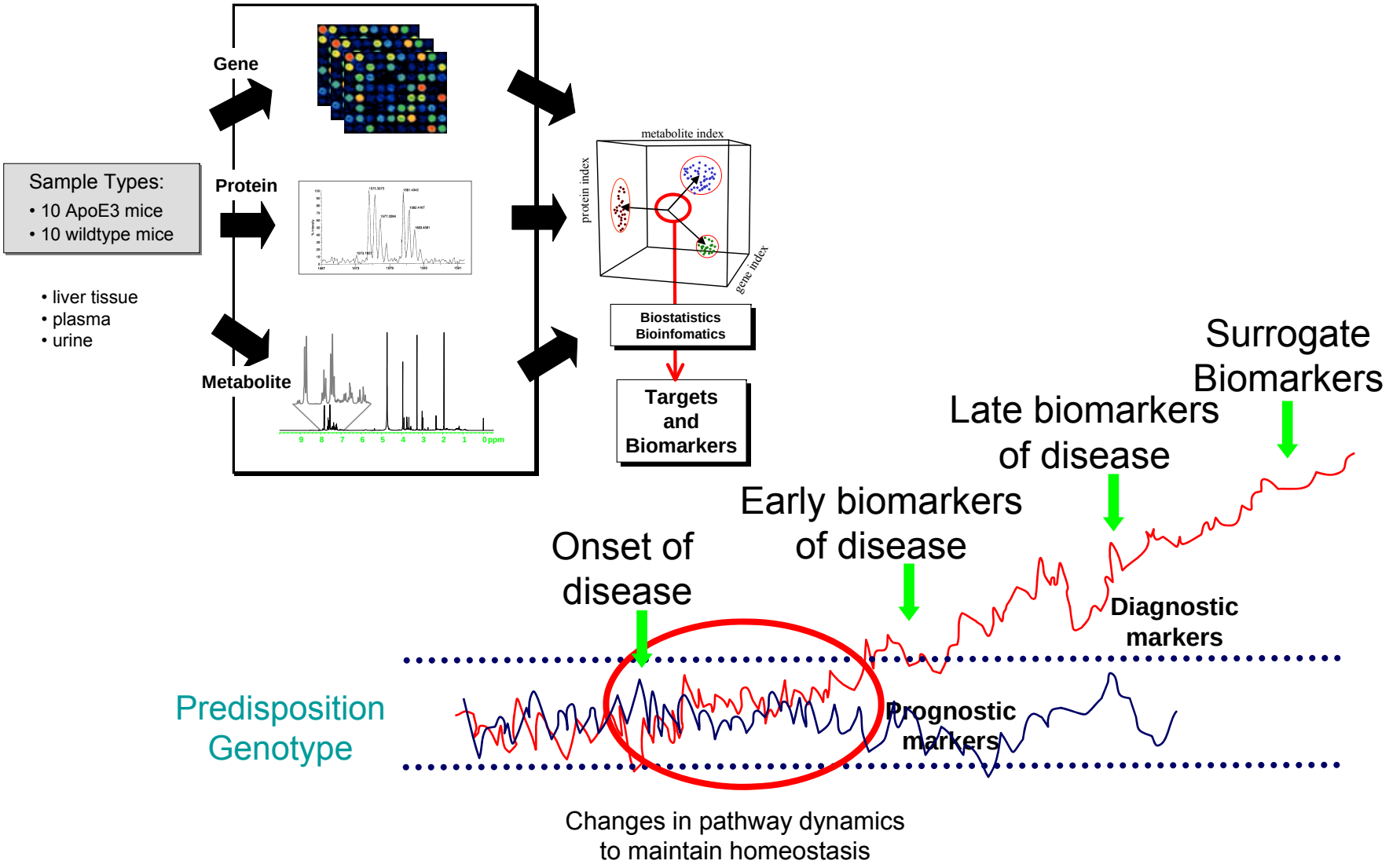
Nutrient absorption



Transcription-factor pathways mediating nutrient-gene interaction

Nutrient	Compound	Transcription factor
Macronutrients		
Fats	Fatty acids	PPARs, SREBPs, LXR, HNF4, ChREBP
	Cholesterol	SREBPs, LXRs, FXR
Carbohydrates	Glucose	USFs, SREBPs, ChREBP
Proteins	Amino acids	C/EBPs
Micronutrients		
Vitamins	Vitamin A	RAR, RXR
	Vitamin D	VDR
	Vitamin E	PXR
Minerals	Calcium	Calcineurin/NF-ATs
	Iron	IRP1, IRP2
	Zinc	MTF1
Other food components		
	Flavonoids	ER, NFκB, AP1
	Xenobiotics	CAR, PXR

Nutritional Systems Biology

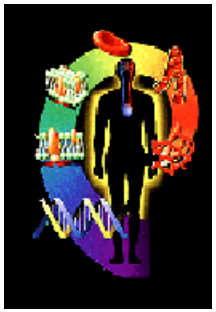


Nutrigenomics

Target Genes
Mechanisms
Pathways

Foods
Nutrition

Signatures
Profiles
Biomarkers



Molecular Nutrition & Genomics

- Identification of dietary signals
- Identification of dietary sensors
- Identification of target genes
- Reconstruction of signaling pathways

Nutritional Systems Biology

- Measurement of stress signatures
- Identification of early biomarkers

Small research groups
Small budgets

Large research consortia
Big money

Complexity

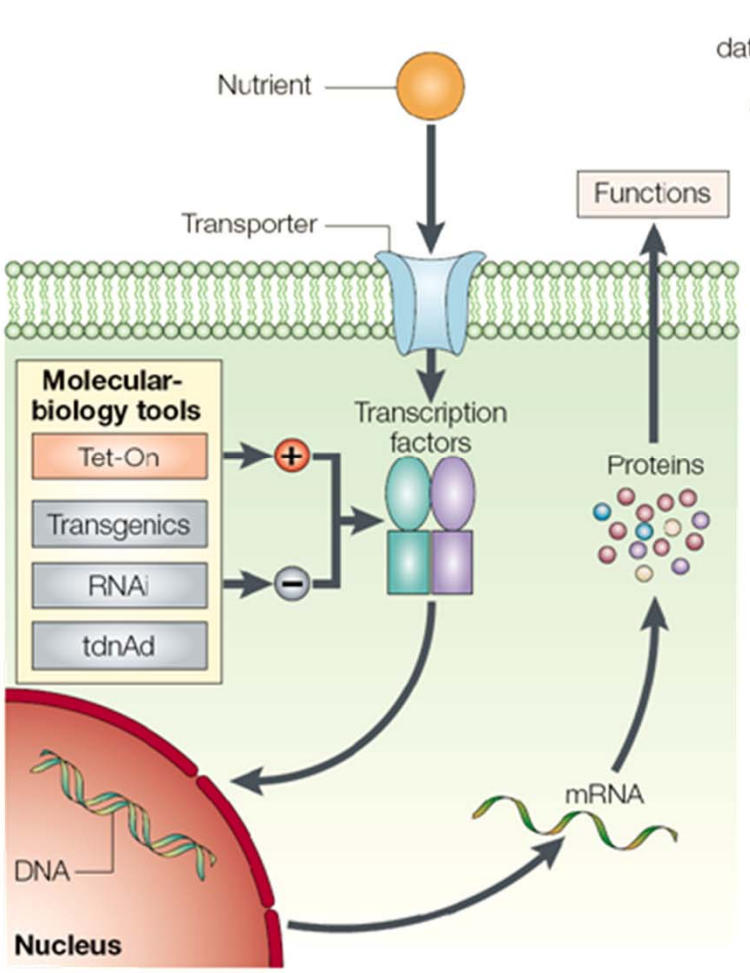
“Molecular Nutrition & Genomics” The strategy of Nutrigenomics

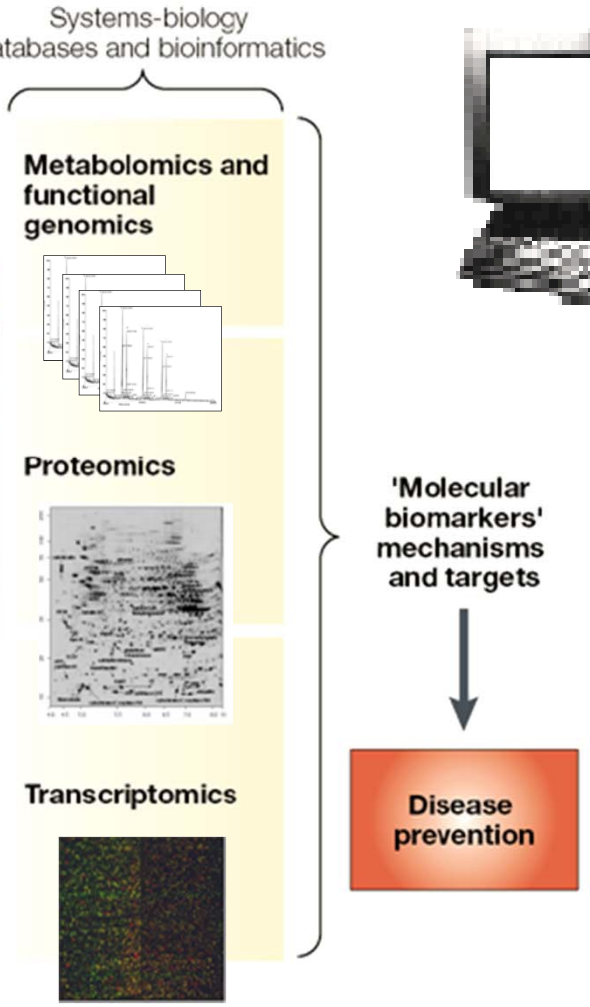
50000 (?) metabolites

80-100000 proteins

100000 transcripts

20-25000 genes

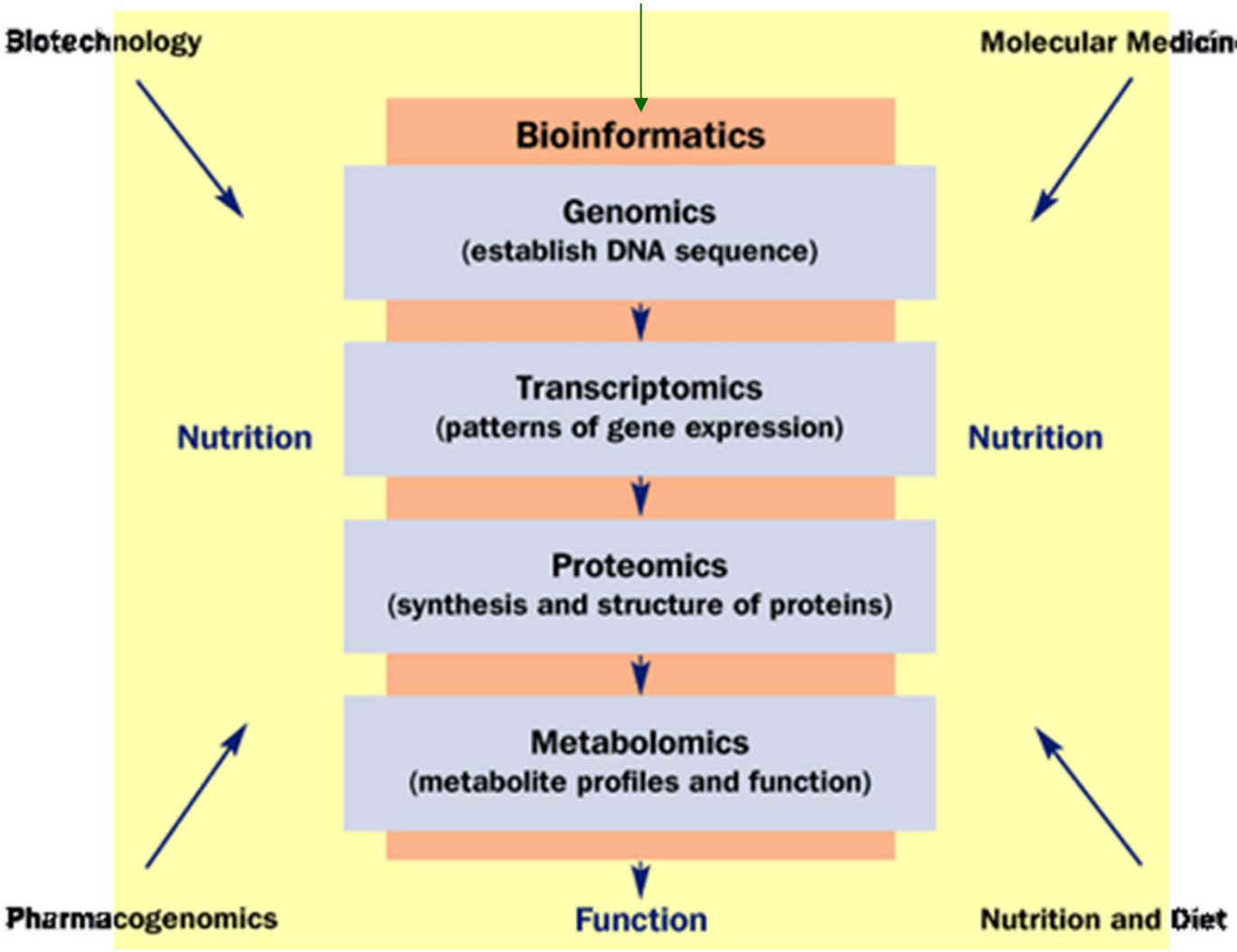




'Molecular biomarkers' mechanisms and targets

Disease prevention

Integration of enabling technologies in nutrigenomics



Two Strategies

(1) **The traditional hypothesis-driven approach**: specific genes and proteins, the expression of which is influenced by nutrients, are identified using genomics tools — such as transcriptomics, proteomics and metabolomics — which subsequently allows the regulatory pathways through which diet influences homeostasis to be identified. Transgenic mouse models and cellular models are essential tools.

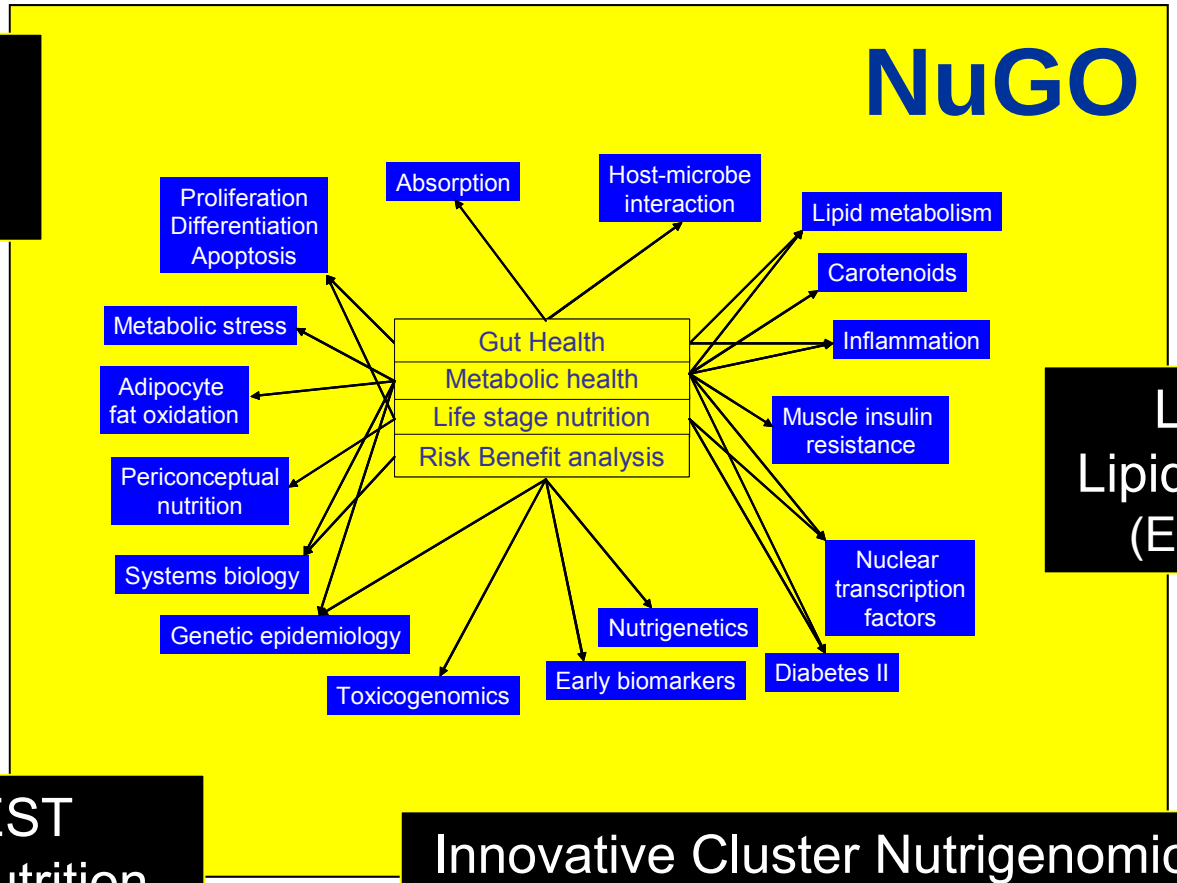
provide us with detailed molecular data on the interaction between nutrition and the genome.

(2) **The SYSTEMS BIOLOGY approach**: gene, protein and metabolite signatures that are associated with specific nutrients, or nutritional regimes, are catalogued, and might provide 'early warning'molecular biomarkers for nutrient-induced changes to homeostasis.

Be more important for human nutrition, given the difficulty of collecting tissue samples from 'healthy' individuals.

EU programs

DIOGENES
obesity
(EU, 12M€)



LIPGEN
Lipids & genes
(EU, 14M€)

EARNEST
early life nutrition
(EU, 14M€)

Innovative Cluster Nutrigenomics
Chronic metabolic stress
(Dutch, 21M€)

Conclusion and future perspective

(1) Nutrigenomics researchers must know the challenge of understanding polygenic diet related diseases.

(2) Short-term goals:

1. to identify the dietary signals.

2. to elucidate the dietary sensor mechanisms.

3. to characterize the target genes of these sensors.

4. to understand the interaction between these signalling pathways and pro-inflammatory signalling to search for sensitizing genotypes.

5. to find '**signatures**' (gene/protein expression and metabolite profiles).

(3) Long-term goals:

Nutrigenomics is to help to understand how we can use nutrition to prevent many of the same diseases for which pharmacogenomics is attempting to identify cures.

Future → **personalized diets**

Gerontogenomics

GerontoGenomics is the genomics of aging and senescence

Research

Somatic mutations found in the healthy blood compartment of a 115-yr-old woman demonstrate oligoclonal hematopoiesis

Henne Holstege,[1,10] Wayne Pfeiffer,[2] Daoud Sie,[3] Marc Hulsman,[4] Thomas J. Nicholas,[5] Clarence C. Lee,[6] Tristen Ross,[6] Jue Lin,[7] Mark A. Miller,[2] Bauke Ylstra,[3] Hanne Meijers-Heijboer,[1] Martijn H. Brugman,[8] Frank J.T. Staal,[8] Gert Holstege,[9] Marcel J.T. Reinders,[4] Timothy T. Harkins,[6] Samuel Levy,[5] and Erik A. Sistermans[1]

[1]*Department of Clinical Genetics, VU University Medical Center, 1007 MB Amsterdam, The Netherlands;* [2]*San Diego Supercomputer Center, UCSD, La Jolla, California 92093, USA;* [3]*Department of Pathology, VU University Medical Center, 1007 MB Amsterdam, The Netherlands;* [4]*Delft Bioinformatics Laboratory, Delft University of Technology, 2628 CD Delft, The Netherlands;* [5]*Department of Molecular and Experimental Medicine, Scripps Translational Science Institute, San Diego, California 92037, USA;* [6]*Advanced Applications Group, Life Technologies, Beverly, Massachusetts 01915, USA;* [7]*Department of Biochemistry and Biophysics UCSF, San Francisco, California 94143, USA;* [8]*Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands;* [9]*Centre for Clinical Research, University of Queensland, Herston, QLD 4006, Australia*

The somatic mutation burden in healthy white blood cells (WBCs) is not well known. Based on deep whole-genome sequencing, we estimate that approximately 450 somatic mutations accumulated in the nonrepetitive genome within the healthy blood compartment of a 115-yr-old woman. The detected mutations appear to have been harmless passenger mutations: They were enriched in noncoding, AT-rich regions that are not evolutionarily conserved, and they were depleted for genomic elements where mutations might have favorable or adverse effects on cellular fitness, such as regions with actively transcribed genes. The distribution of variant allele frequencies of these mutations suggests that the majority of the peripheral white blood cells were offspring of two related hematopoietic stem cell (HSC) clones. Moreover, telomere lengths of the WBCs were significantly shorter than telomere lengths from other tissues. Together, this suggests that the finite lifespan of HSCs, rather than somatic mutation effects, may lead to hematopoietic clonal evolution at extreme ages.

[Supplemental material is available for this article.]

Mutations are called somatic if they were acquired in a tissue cell during organismal development or later in life, rather than being inherited from a germ cell. As such, somatic mutations lead to genotypic and possibly phenotypic heterogeneity within and between tissues, and they may compromise growth or lead to a growth advantage (Frank 2010). Because somatic mutations often occur during cell division, frequently dividing cell types are more prone to acquire somatic mutations than tissues that rarely divide (Youssoufian and Pyeritz 2002). Consequently, frequently dividing cell types, i.e., epithelial cells, hematopoietic cells, and male germ cells are vulnerable to somatic mutations that may lead to tumor development or other diseases and disorders. Therefore, most studies regarding somatic mutations have been attempts to discover mechanisms leading to cancer and disease (Youssoufian and Pyeritz 2002; Erickson 2010; Hanahan and Weinberg 2011).

It has been estimated that the adult human blood compartment is populated by the offspring of approximately 10,000–20,000 hematopoietic stem cells (HSCs) (Abkowitz et al. 2002). HSCs self-renew about once every 25–50 wk to create two daughter cells equivalent to their parent, and they differentiate to create offspring clones with multipotent progenitor cells that generate the much larger number of diverse blood cells via hematopoiesis (Catlin et al. 2011). Over time, somatic mutations will gradually accumulate within the HSCs, and the genotypes of the HSCs along with their offspring clones will diverge and lead to new clones of varying sizes.

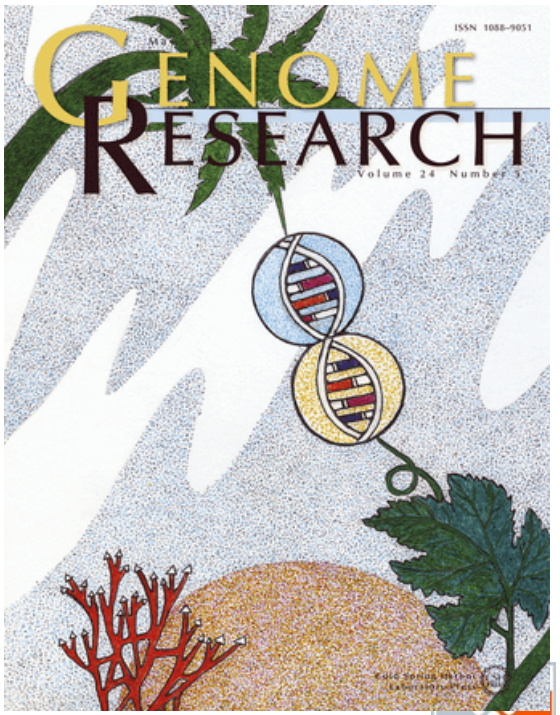
Recent publications show that the genomes of patients with acute myeloid leukemia (AML) contain hundreds of somatic mutations that accumulate with age (Ley et al. 2008; Mardis et al. 2009; Ding et al. 2012), and that most of these mutations occur as random events in HSCs before one of them acquires a specific pathogenic mutation leading to AML (Welch et al. 2012). Similar patterns of clonal evolution have also been shown for the development of chronic lymphocytic leukemia (CLL) (Landau et al. 2013). However, it is currently unknown to what extent healthy HSCs acquire somatic mutations and which types of mutations can be tolerated in the genome during a lifetime without causing disease.

We set out to determine the prevalence and types of single nucleotide and small insertion/deletion mutations that are somatic within the healthy blood genome. Since the occurrence of somatic copy number changes has been shown to increase with age in sev-

[10]**Corresponding author**
E-mail h.holstege@vumc.nl
Article published online before print. Article, supplemental material, and publication date are at http://www.genome.org/cgi/doi/10.1101/gr.162131.113. Freely available online through the *Genome Research* Open Access option.

- Individual genome in the multiple blood cells of **Hendrikje van Andel-Schipper (1890-2005)**, at one point the oldest woman in the world, were sequenced and compared (Holstege et al. 2014 *Genome Res*. 24(5): 733-742)

- She was remarkably healthy until her death
- **450 mutations were found in her cells, but none of them was detrimental**



- **genomes of 17 of the world's oldest living people (110-116 year old) have been sequenced and published recently** (Gierman et al. 2014 PLoS ONE 9(11): e112430 http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0112430)
- **Japanese project to sequence genome and metagenome of all centenarians**