Can nutrigenomics help us express ourselves?

Professor Lynne Cobiac

Associate Dean, Flinders Clinical and Molecular Medicine

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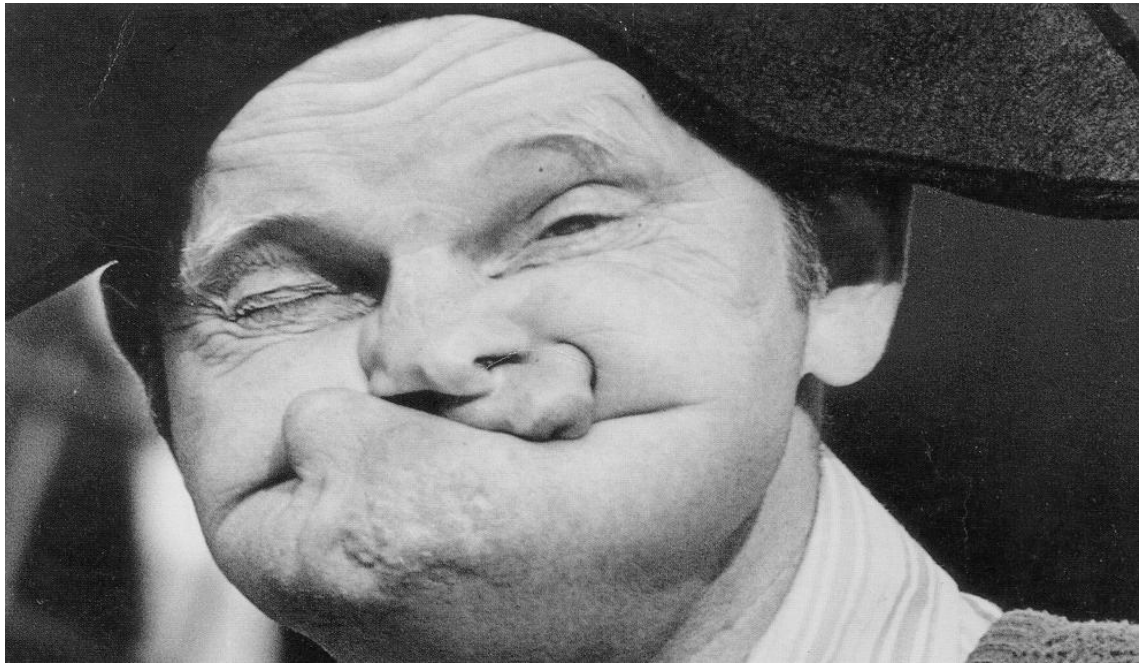
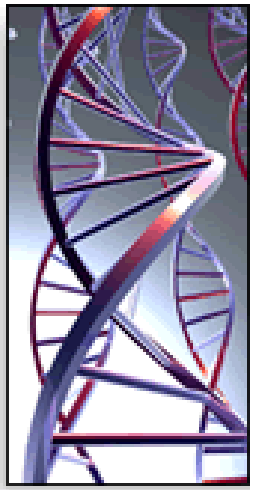
How does nutrition affect our genetic expression?

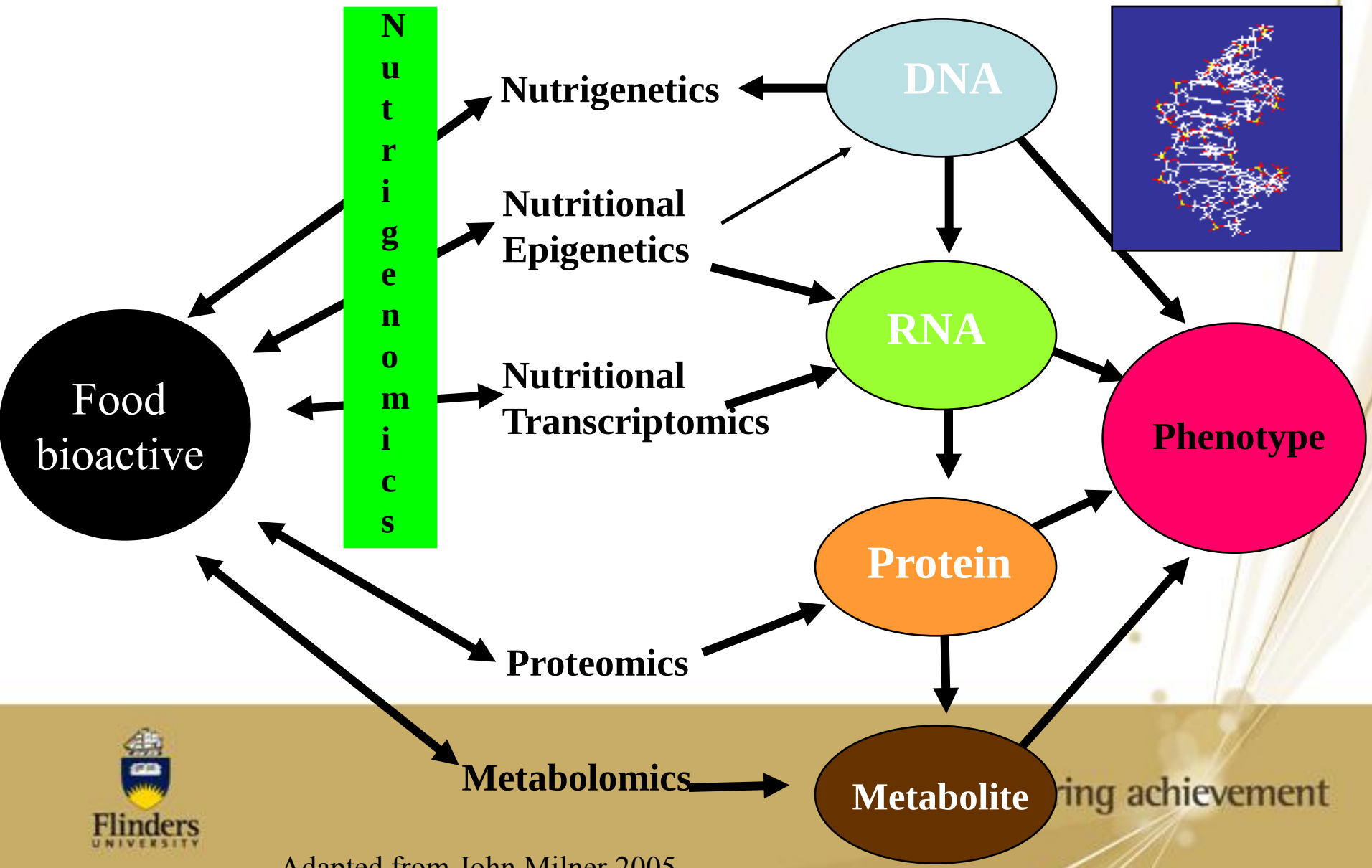




Overview

- Nutrigenomics
- Nutrient-gene interactions
- Epigenomics
- How do we distil the complex to the simple?
- How personal can you get?

Role of nutrigenomics



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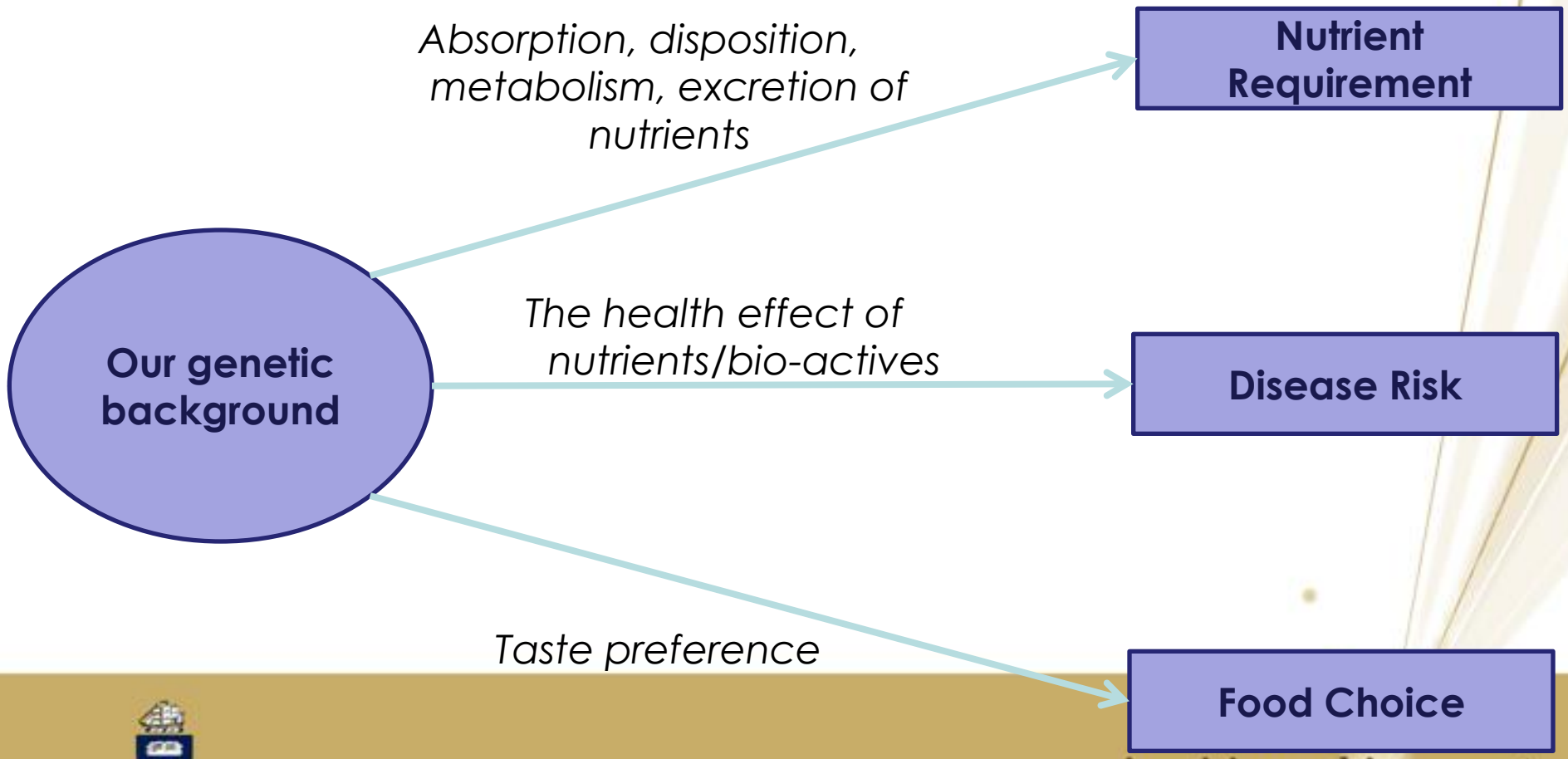
Adapted from John Milner 2005

Many types of nutrient-gene interactions



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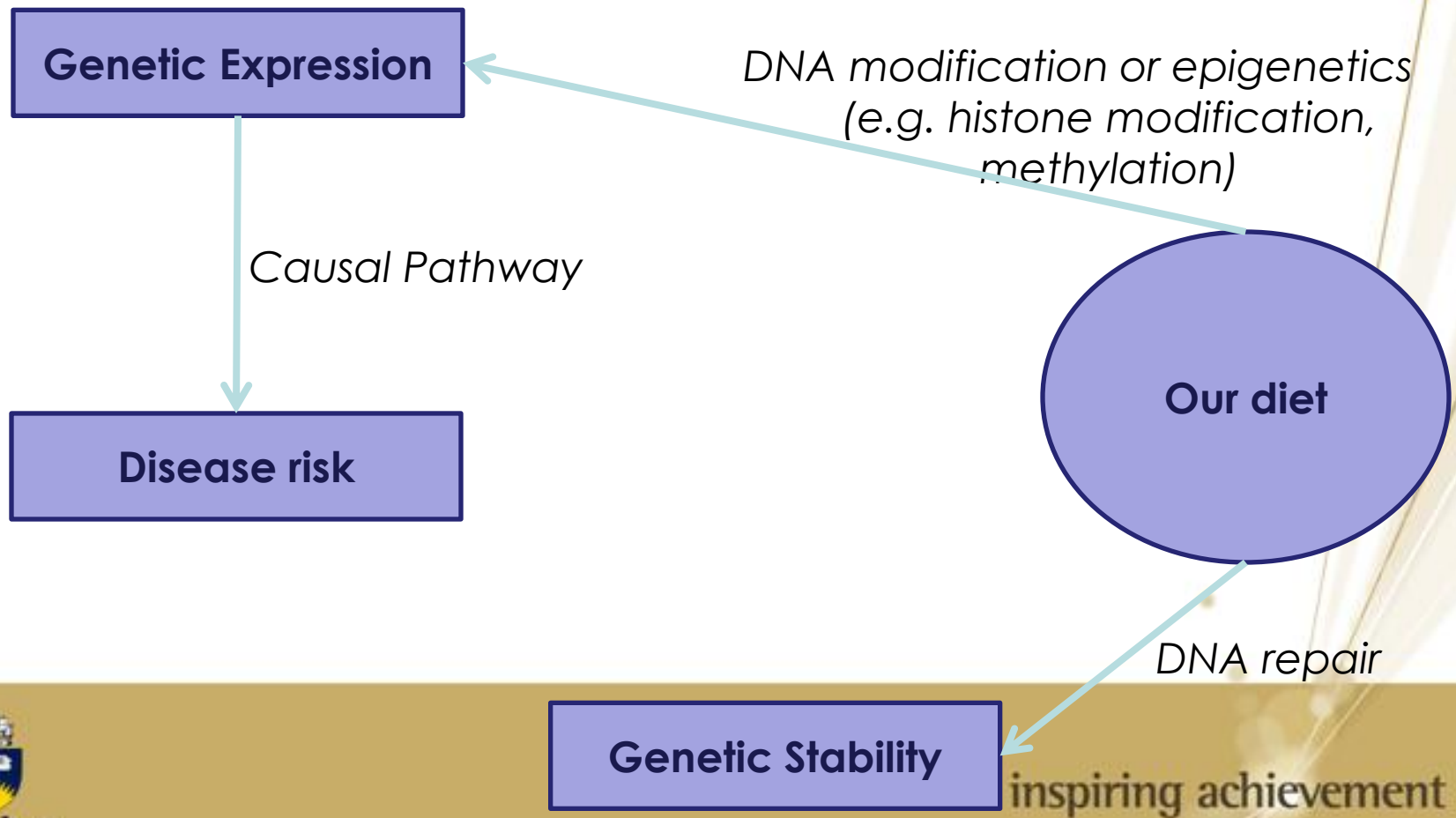


Testing is already here

Sciona™ Optimal health through genetics™

About Sciona

Sciona is a privately held, international company that provides personalized health and nutrition recommendations based on an individual's diet, lifestyle and unique genetic profile. The Company began on June 8, 2000, the same day President Clinton and Prime Minister Blair announced the completion of the first draft of the Human Genome Project. Sciona was founded on a simple premise: to use the scientific information uncovered in this landmark research project for the benefit of consumers and consumer product companies.
Since that time, Sciona has built a business around the application of evidence-based genetic information for the development of personalized products that help individuals optimize their health.

Genetic testing is getting faster and cheaper. Many tests require only a painless cheek swab to obtain DNA.

Epigenenomics: A unifying hypothesis for nutrition?

- DNA methylation, acetylation
- Histone modification
- Chromatin alteration & genomic stability
- miRNA expression

Can be heritable, associated with disease states and modified by nutrient factors & appear reversible

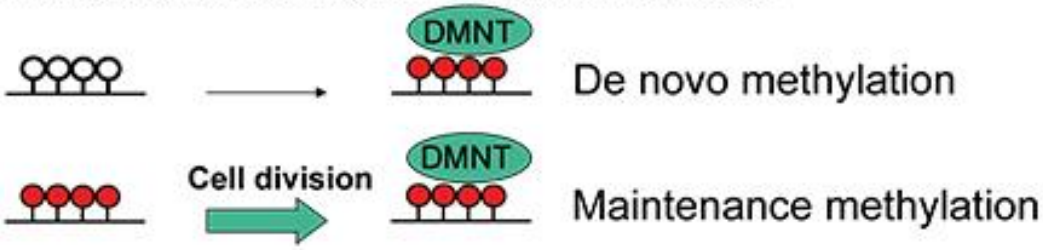
DNA methylation

Addition of a methyl group to a cytosine within C-G di-nucleotides which are frequently located in the regulatory regions of genes.

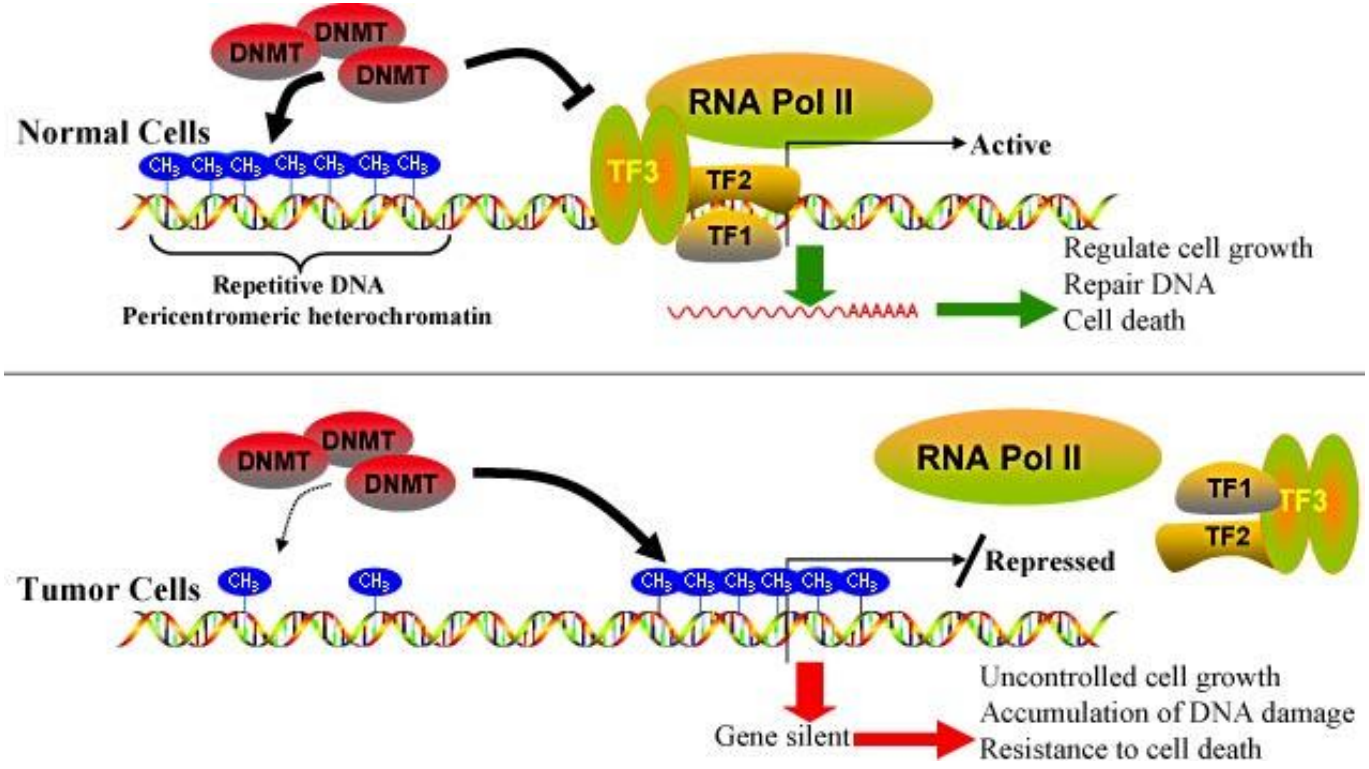
A mechanism for gene silencing:

- ⇨ preventing binding of regulatory factors
- ⇨ affecting chromatin status

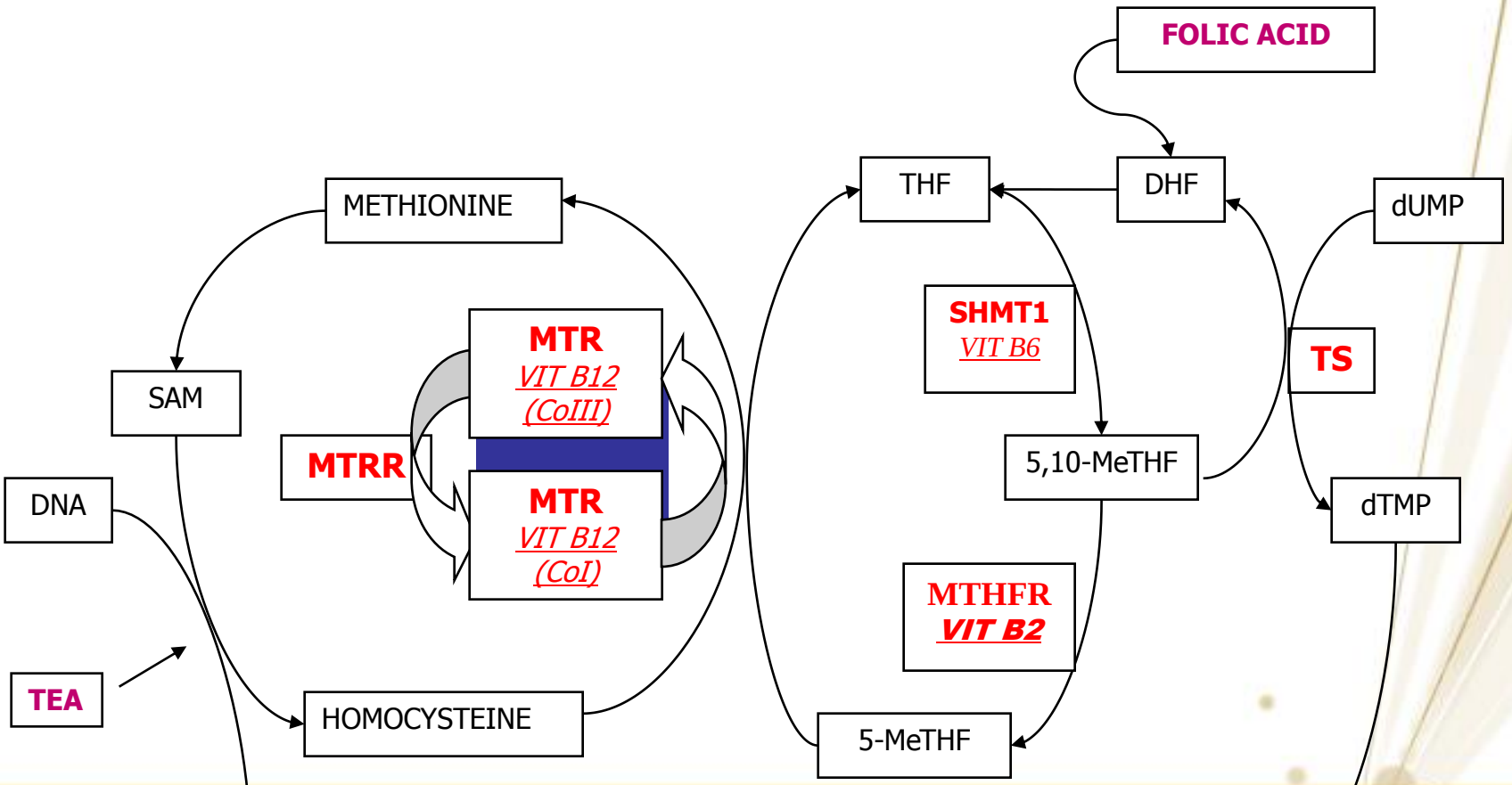
CpG methylation is a lasting form of epigentic modification



Methylation and disease risk



Nutrition & DNA methylation: tea & folate



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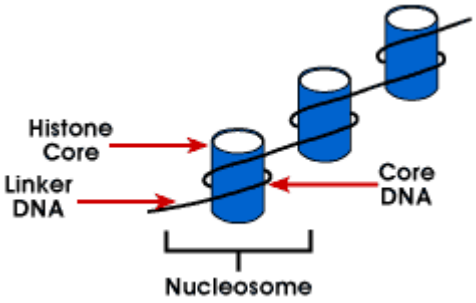
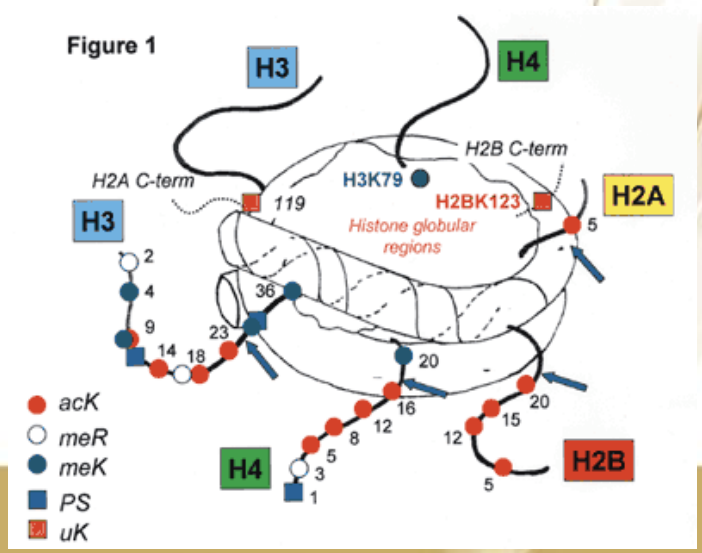
Histone modification

- **Chromatin**
  - General chromosome structure
- **Nucleosomes**
  - Histones – H2A, H2B, H3, H4
- **Modification of histone N-terminal tails**
  - Acetylation (mono, di and tri), phosphorylation, ubiquitination, poly (ADP) ribosylation, methylation (mono, di and tri-) etc
  - Generally reversible, enzymic eg histone acetyl transferases & histone deacetylases (HDAC)
  - Multiple residues can be modified on one histone
- ➢ **Alters chromatin structure** and thus controls access to the DNA by the proteins necessary for transcription.
- ➢ DNA methylation and histone modification are interdependent





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Butyrate: HDAC inhibitor

Energy source (mitochondrial β-oxidation)

Physiological function

Colonic mucosa homeostasis
- Cell cycle arrest
- Differentiation
- Apoptosis

Colonic cell

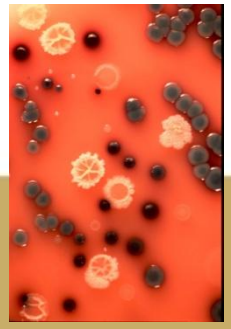
Colon lumen

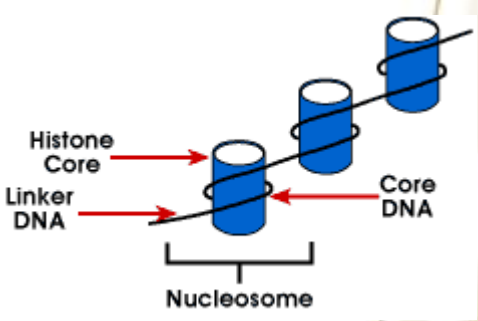
Butyrate metabolism

Resistant starch

Microbial fermentation

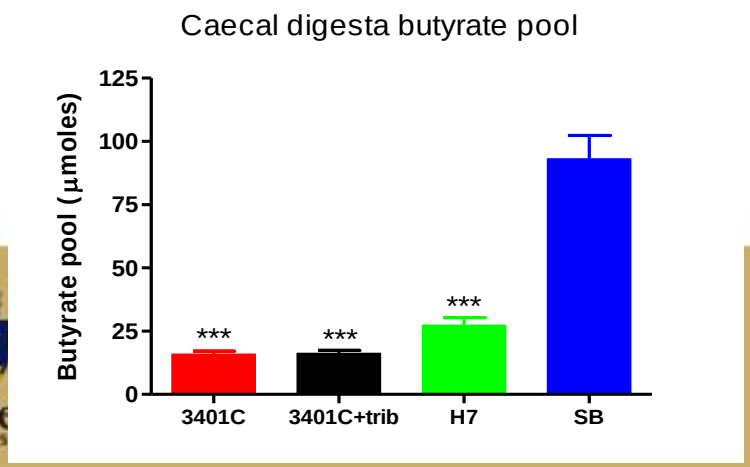
SCFA's (e.g. Butyrate)



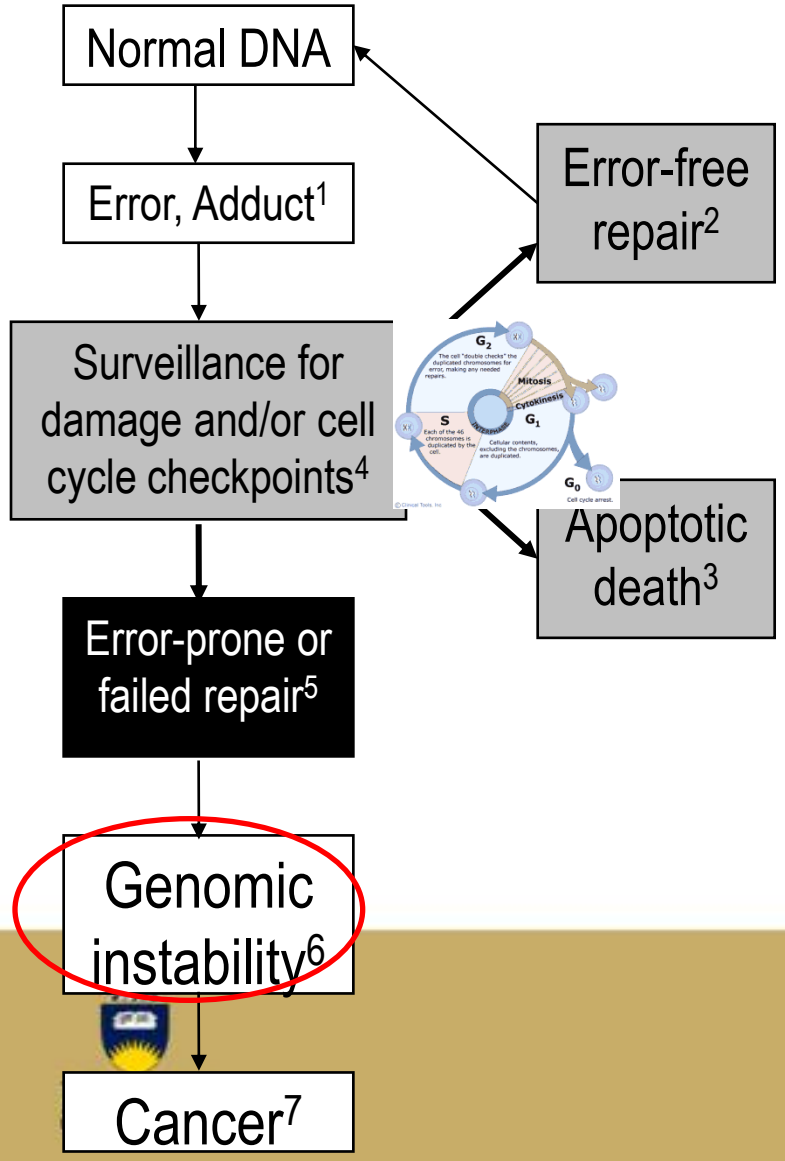


Animal studies – Starplus B

- reduces pH of digesta in large bowel
- promotes digesta bulking without increasing digesta passage rate
- comprehensive rat study showed no adverse effects of feeding acylated starches
- butyrylated *Starplus* (SB) does not affect rates of apoptosis or proliferation of healthy colonocytes
- SB increases rates of apoptosis in base of colonic crypts of carcinogen-treated rats
- SB reduces tumour burden in carcinogen-treated rats



Genomic stability

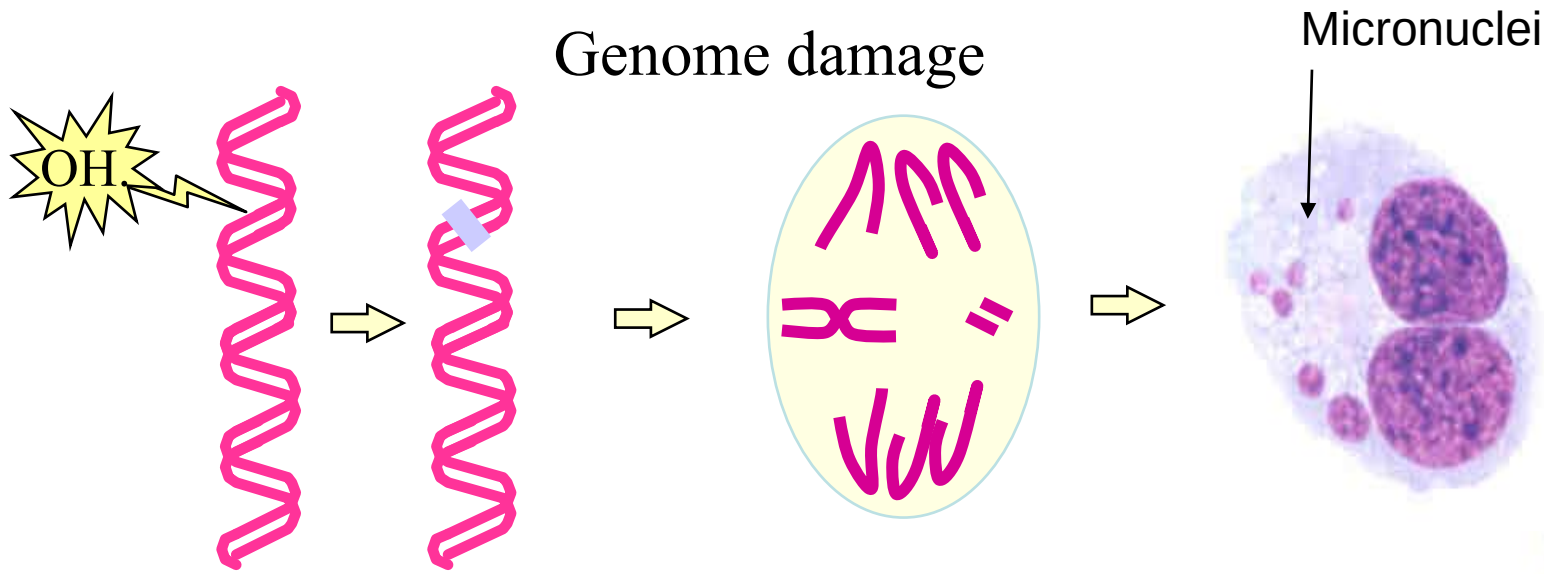


Measurable events

1. Adduct histochemistry
2. MGMT, other repair enzymes.
3. Apoptosis - TUNEL, morphology, DNA laddering
4. Checkpoint repair genes
5. Adducts fixed as mutations, e.g. K-ras
6. Ploidy, micronucleus assay
7. Cancer
8. Others: Proliferation, signal transduction, etc.

Epigenetics can affect all 8

Nutrition & genomic stability



- Oxidative stress
- Nutrient deficiency
- Excess calories

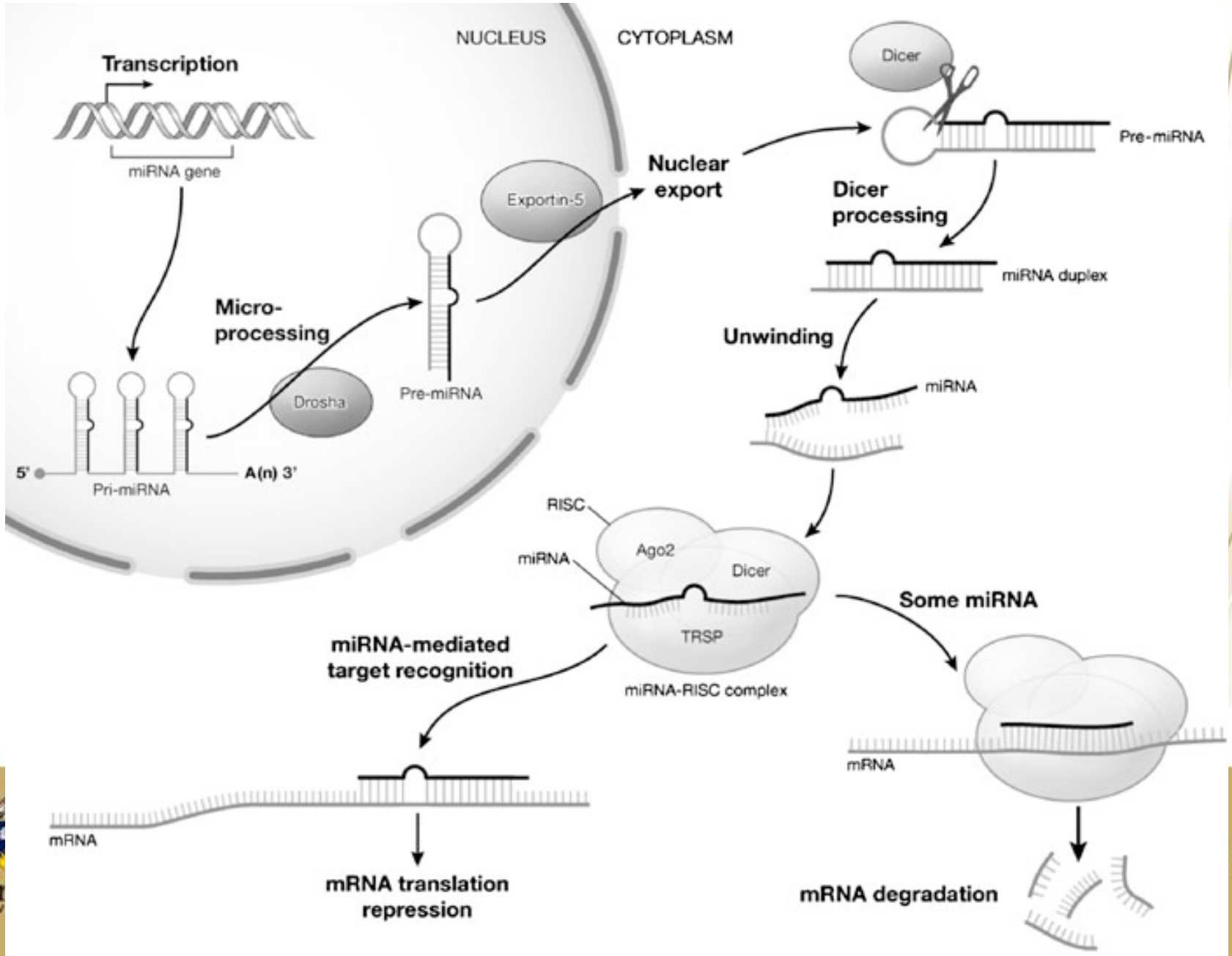
→

- Strand breaks in DNA
- Chromosome malsegregation
- Telomere shortening

→ Human cells with damaged & unstable genomes

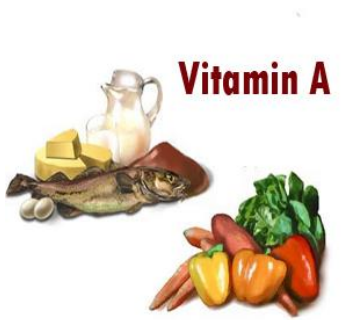
From M Fenech

miRNA


NUCLEUS
CYTOPLASM
Transcription
miRNA gene
Exportin-5
Nuclear export
Dicer
Pre-miRNA
Dicer processing
miRNA duplex
Micro-processing
Drosha
Pre-miRNA
Unwinding
miRNA
5'
A(n) 3'
Pri-miRNA
RISC
Ago2
miRNA
Dicer
TRSP
miRNA-RISC complex
Some miRNA
miRNA-mediated target recognition
mRNA
mRNA translation repression
mRNA
mRNA degradation

Diet & miRNAs

- Dietary folate
- Retinoic acid
- Curcumin (flavonoid)

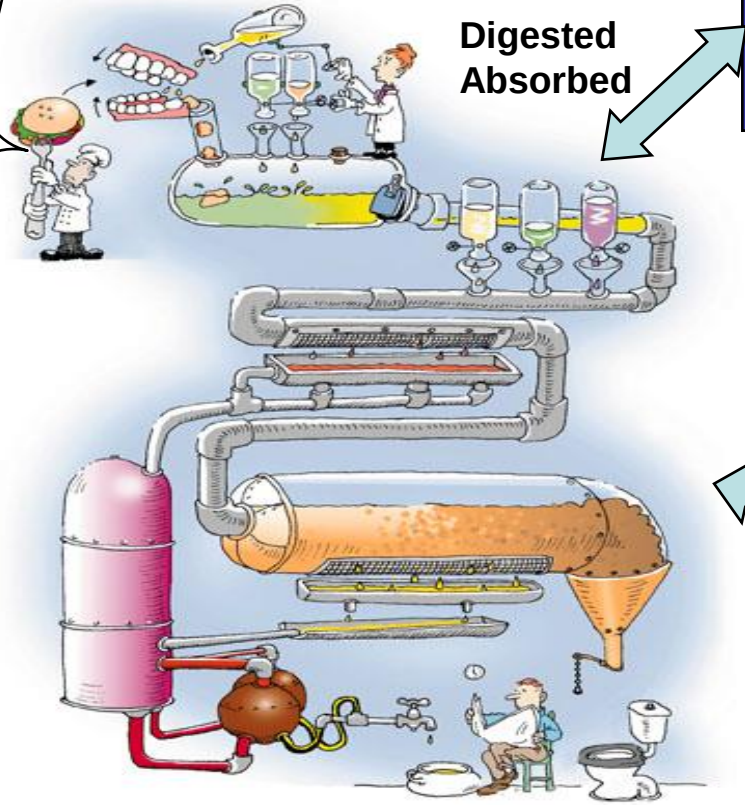


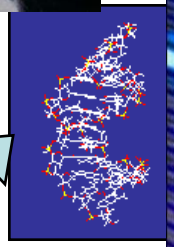
How does this work?

30,000 foods
25,000 bioactives
Processing
2000 kg per year & 80 years exposure!

10,000 taste buds
9000 olfactory genes
10,000 odours

Digested
Absorbed





30,000 g

300-500,000
Metabolites

500
Ext

Phenotypes: Result of genetic expression

- An individual's phenotype is ultimately a combination of the genotype (all genes and their alleles in the genome) and epigenome (all the chemical modifications of the chromatin) ….and impact of other environmental factors, such as nutrition.

Tell me what you eat, and I will tell you who you are.

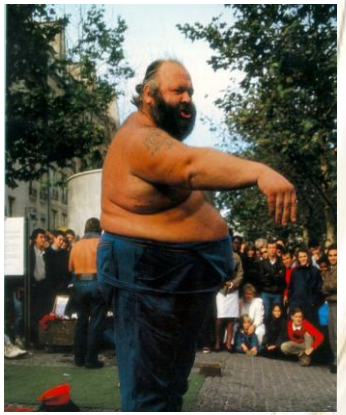
—Brillat-Savarin 1755-1826

How personal can you get?

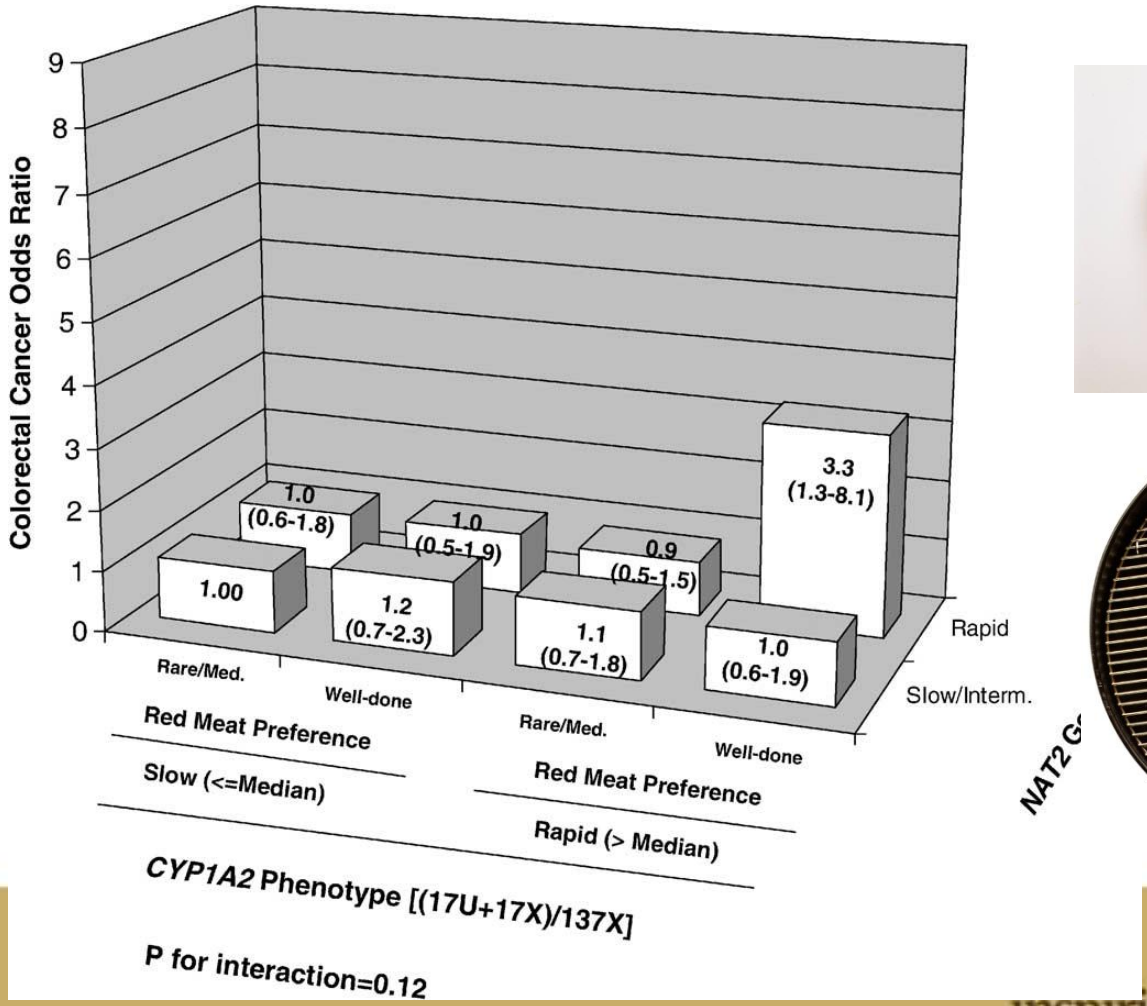
- Personalised diets are being promised but more likely to focus on sub-groups of the population
- Ethical & equity issues will need to be dealt with appropriately
- Promise us an interesting future!

Please Do Not Feed the Humans

Personalised diet only

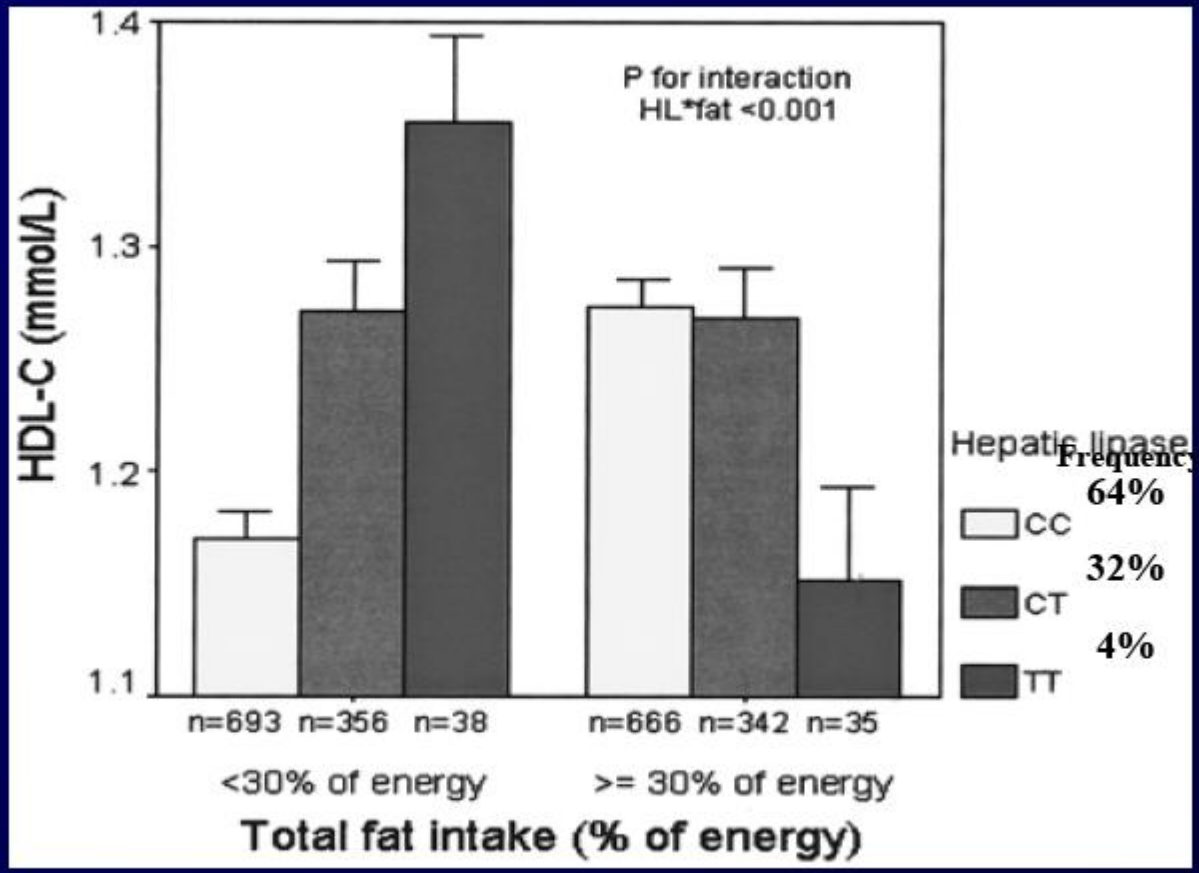


Disease risk modifier: Meat genotypes



Le Marchand et al 2002

Genetic Information May Also Identify Those Benefiting Most/Least From Dietary Change



Ordovas et al. (2002) *Circulation* 106:2315.

Old news…

- ***"Agassiz does recommend authors to eat fish because the phosphorus in it makes brains. But I cannot help you to a decision about the amount you need to eat. Perhaps a couple of whales would be enough."***

  Mark Twain (Samuel Langhorne Clemens) (1835-1910)