Personalized Medicine – to Narrow the Gap Between Knowledge and Clinical Practice

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Personalized Medicine

Predict, Prevent & Treat

www.upcp.org

What Is Personalized Medicine?

- The tailoring of medical treatment to the individual characteristics of each patient.
- The ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment.
- Preventive or therapeutic interventions can then be focused on those who will benefit, sparing expense and side effects for those who will not.

President's Council of Advisors on Science and Technology (PCAST) "Priorities for Personalized Medicine". September 2008

Personalized Medicine vs Evidence based Medicine

- There is an inherent, unresolved tension between genomics-enabled personalized medicine and the tenets of population-based, evidence-based medicine.
- However, there is no reason that the two approaches to caring for patients should be in opposition.

Feero WG et al. N Engl J Med 2010;362:2001-2011.

Leading Edge
Analysis

Cell

Getting Up Close and Personal with Your Genome

- Scan a person's genome for as little as $1000.
- Fun novelty or do valuable information ?

Bonetta, Cell *133: 753*-756, *2008*

The Practitioner

- Many patients, both genders, wide span of ages, diverse cultural and genetic backgrounds with various disease conditions.
- Is Lonely….
- Needs to oblige to set of rules and regulations
- Patient centered & shared decision making
- **10 minutes !!**

The Patient

- Is exposed to recent medical information
- Has an open access to medical information and searches for updates
  - Internet, disease forums, newspapers, open lectures,…
- Is more knowledgeable than in the past to his disease
- Knows better his/her own medical data, accumulates it and expects the physician to consider it.
- The law requires that the patient will take part in the medical decision
- Expects the physician to talk to him….

Preparing for a Consumer-Driven Genomic Age

James P. Evans, M.D., Ph.D., David C. Dale, M.D., and Cathy Fomous, Ph.D.

- Patients are no longer subordinate,
  - often know more than their clinicians about particular genetic topics.
- Patients embrace direct-to-consumer (DTC) genetic tests and turn to social networks.
- In the future, a primary role of health care professionals may be to interpret patients' DTC genetic test results and advise them about appropriate follow-up.

NEJM, 363:1099-1103, 2010

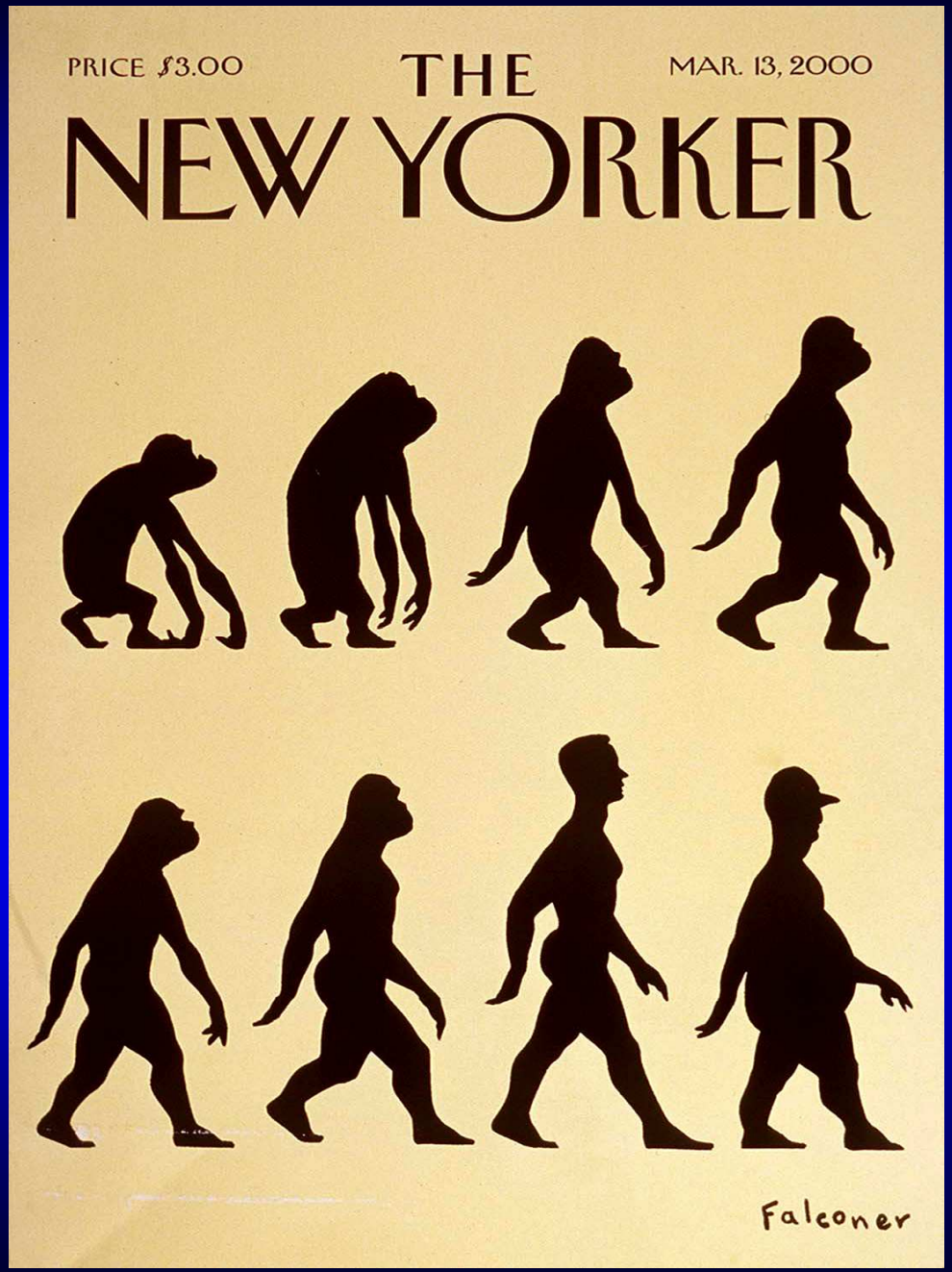
The Problem

- An ever-growing gap exists between accumulating knowledge derived from basic scientific and clinical research, new molecular mechanisms, recent medical and therapeutic guidelines and its use at the bed-side by the practitioner.

- There is an urgent need to Narrow the Gap Between Knowledge and Clinical Practice

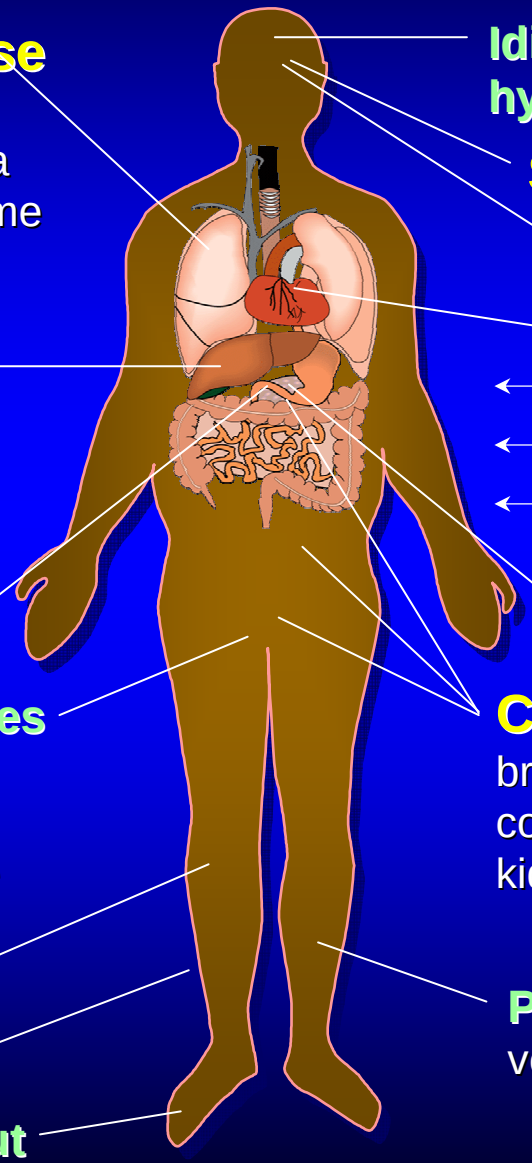
Vision

- To design and develop a **patient-centric bio-informatic tools and decision support system** to personalize the treatment to the specific patient needs based upon his/her clinical, genetic and metabolic characteristics.
- The system will be based on **combined software and nano- technology platform** enabling the physician to analyze in real-time clinical, genetic and metabolic parameters.
- The integrated system will be used **during the physician-patient encounter** in order to improve quality of care and reduce expenses.


PRICE $3.00
THE
MAR. 13, 2000
NEW YORKER
Falconer

Our Patient

Medical Complications of Obesity



Pulmonary disease
abnormal function
obstructive sleep apnea
hypoventilation syndrome

Nonalcoholic fatty liver disease
steatosis
steatohepatitis
cirrhosis

Gall bladder disease

Gynecologic abnormalities
abnormal menses
infertility
polycystic ovarian syndrome

Osteoarthritis

Skin

Gout

Idiopathic intracranial hypertension

Stroke

Cataracts

Coronary heart disease

Diabetes

Dyslipidemia

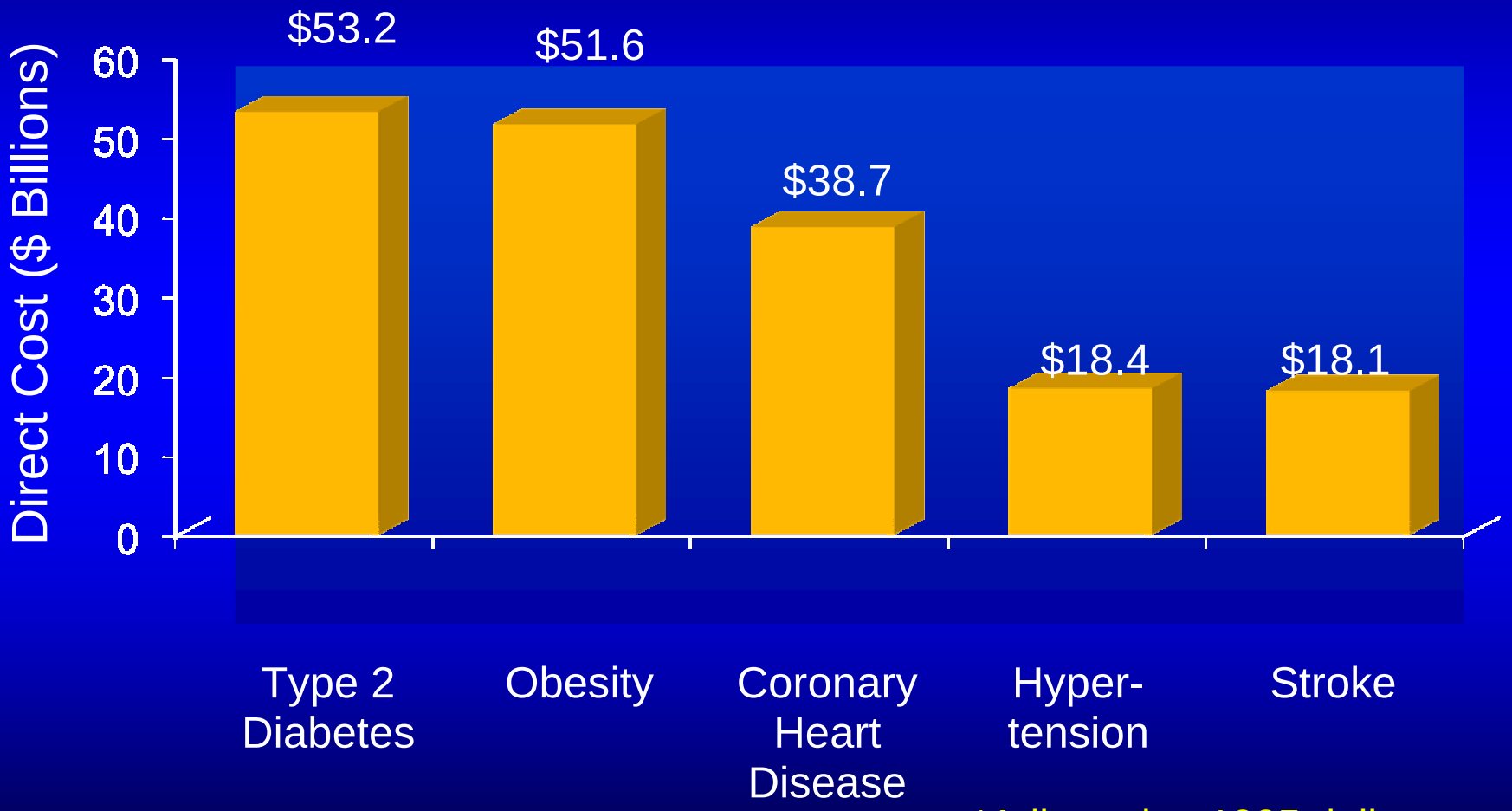
Hypertension

Severe pancreatitis

Cancer
breast, uterus, cervix
colon, esophagus, pancreas
kidney, prostate

Phlebitis
venous stasis

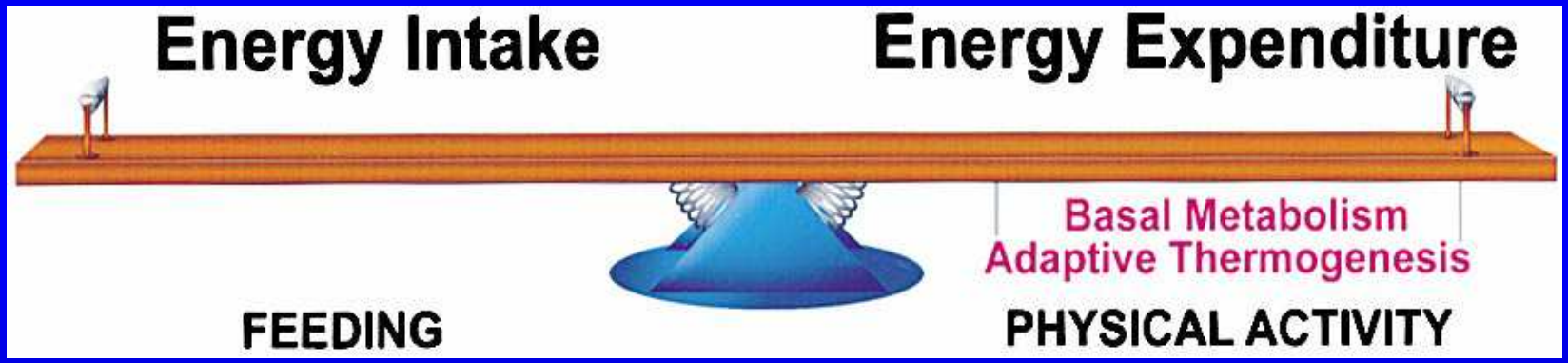
Direct Cost of Chronic Diseases in the United States



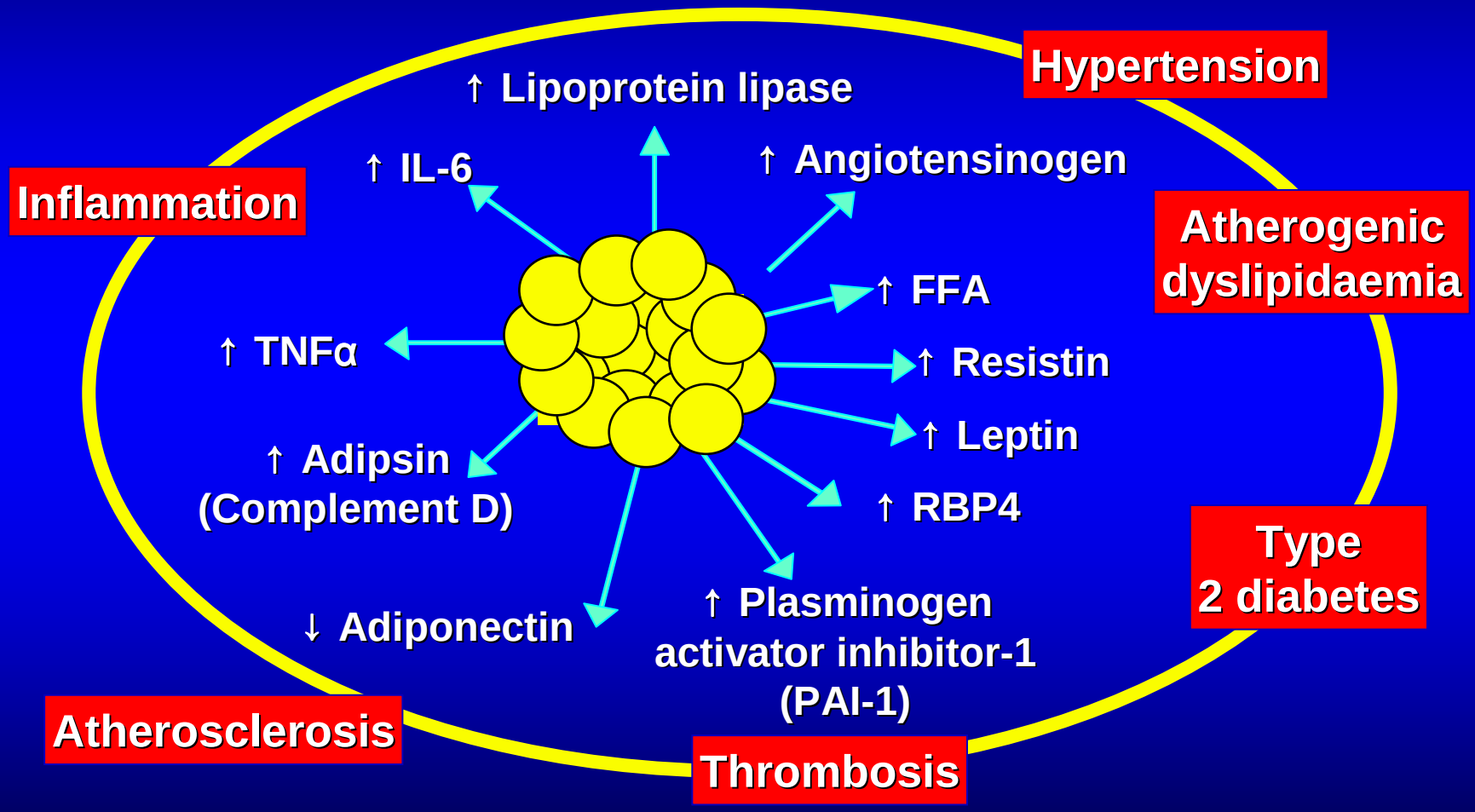
*Adjusted to 1995 dollars.

Wolf AM, Colditz GA. *Obes Res*. 1998;6:97-106.
Hodgson TA, Cohen AJ. *Med Care*. 1999;37:994-1012.

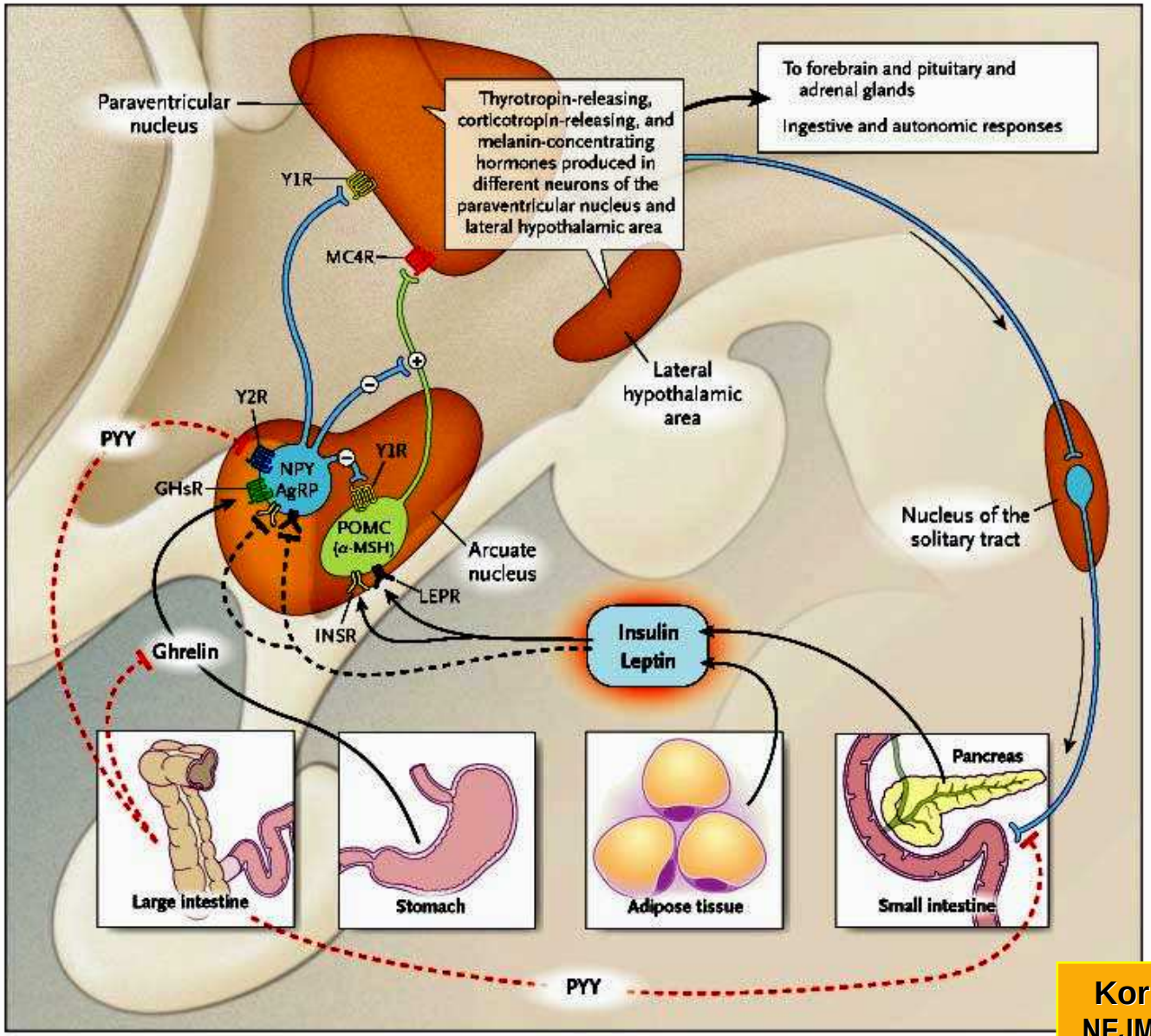
Key Component of the Energy Balance System



Cardiometabolic Risk Factors Promoted by Intra-abdominal Adiposity



To Eat or Not to Eat — the Brain and the Belly Love Story



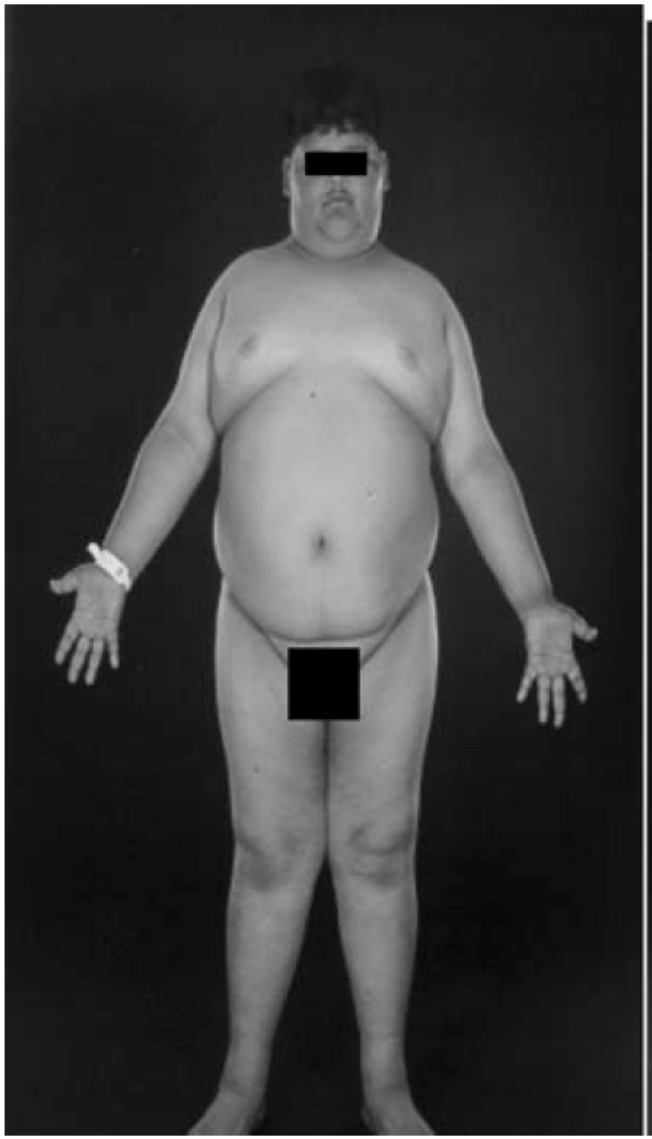
Korner and Leibel
NEJM 349:926-928, 2003

Monogenic Obesity – Leptin Deficiency

(a)

Farooqi and O'Rahilly Annu. Rev. Med. 2005. 56:443–58

Monogenic Obesity – MC4R Mutation



9 year- old with MC4R mutation

16 year- old sibling with Normal MC4R

Prevalence of Single-Gene Defects Causing Severe Early-Onset Obesity

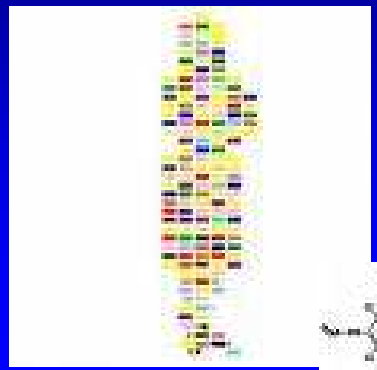
LEP (7q):	**0.5%**
LEPR (1p):	**0.5%**
POMC (2p):	**0.8%**
PCSK1 (5q):	**0.4%**
MC4R (18q):	**3%**
BDNF (11p):	**rare**
NTRK2 (9q):	**rare**

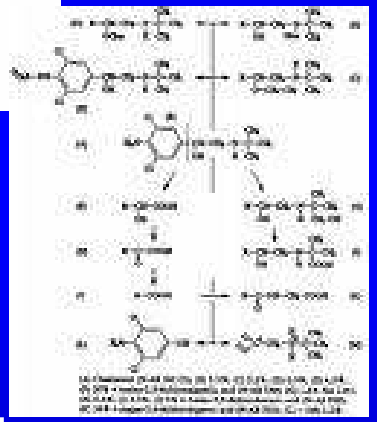
From S O'Rahilly and S Farooqi

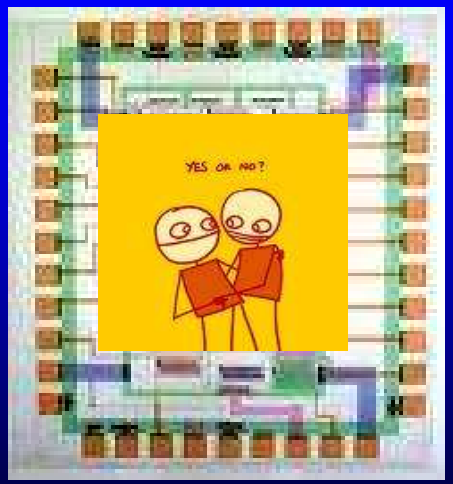
Obesity Associated genes

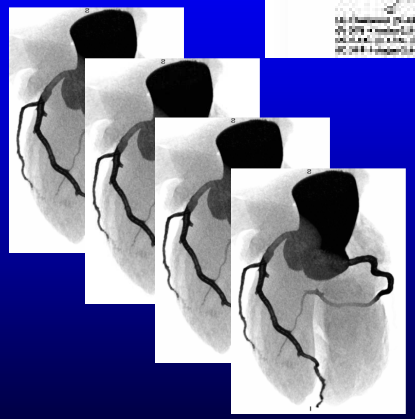
- **Orexigenic Genes**
  - Neuropeptides and Receptors
- **Anorectic Genes:**
  - Gut Hormones and Receptors:
  - Adipocyte-derived Peptides and Receptors
  - Pancreas Derived Peptides and Receptors
- **Energy Expenditure**
  - Adipocyte-Derived Peptides and Receptors
  - CNS-Derived Peptides and Receptors:

Our Patient









Our Patient = Data Bases

Electronic Patient Record

Virtual Clinical Data

Tissue Sample Bank

Genetic Profile

Proteomics

Imaging Data

Laboratory Data

Drugs + side effects Toxicology

Drugs Interactionsn

Molecular Mechanisms

Clinical Guidelines

Patient ID

Anonomity

Our Patient = Populations

Proteomics

Genetic Profile

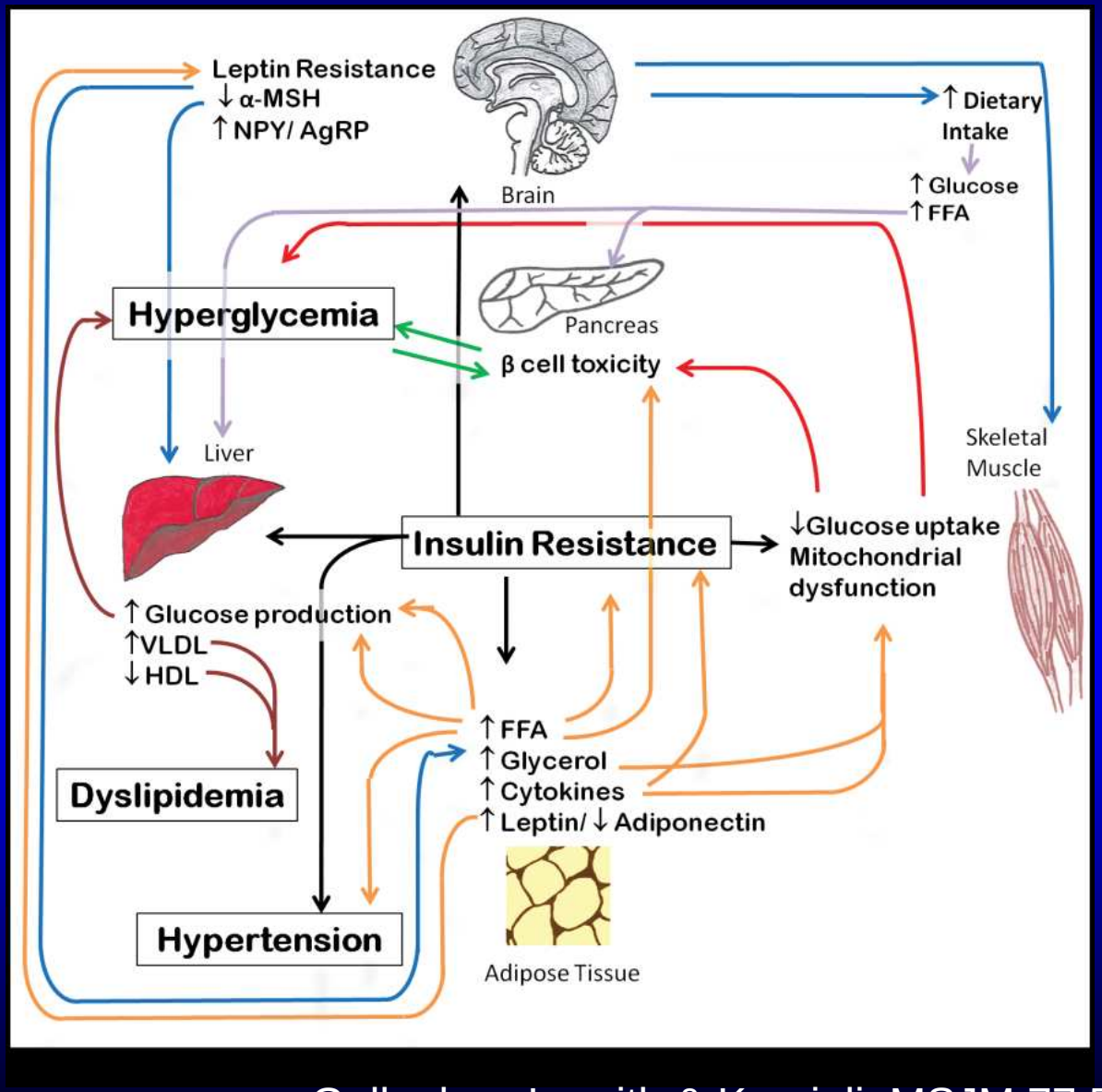
Relevant Populations

Target Genes

Epigenetics

Control Population

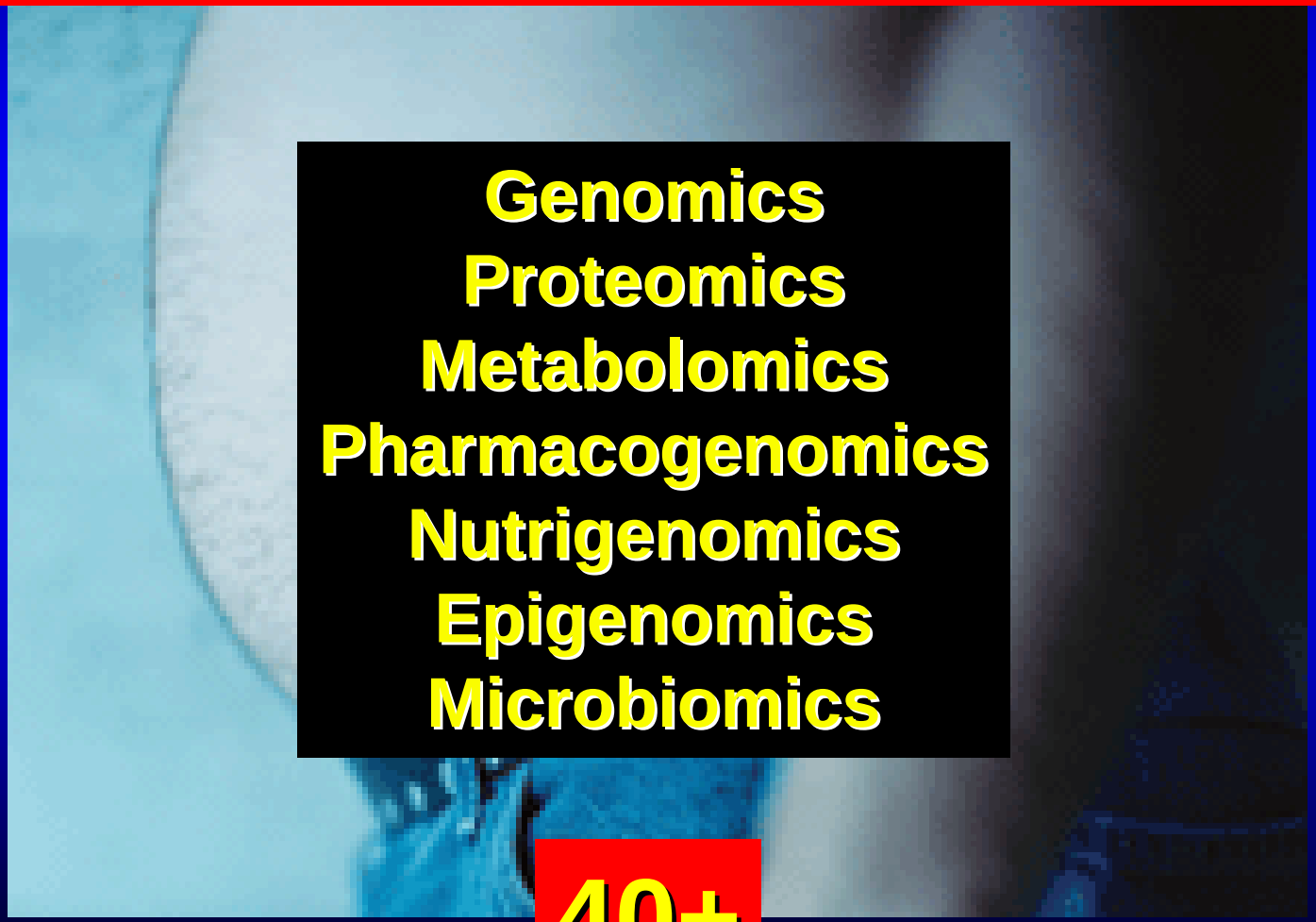
Our Patient = Physiological and Molecular Mechanisms



Gallagher, Leroith & Karnieli, MSJM 77:511–523, 2010

Our Patient

How many subtypes of DM2 do we have ?



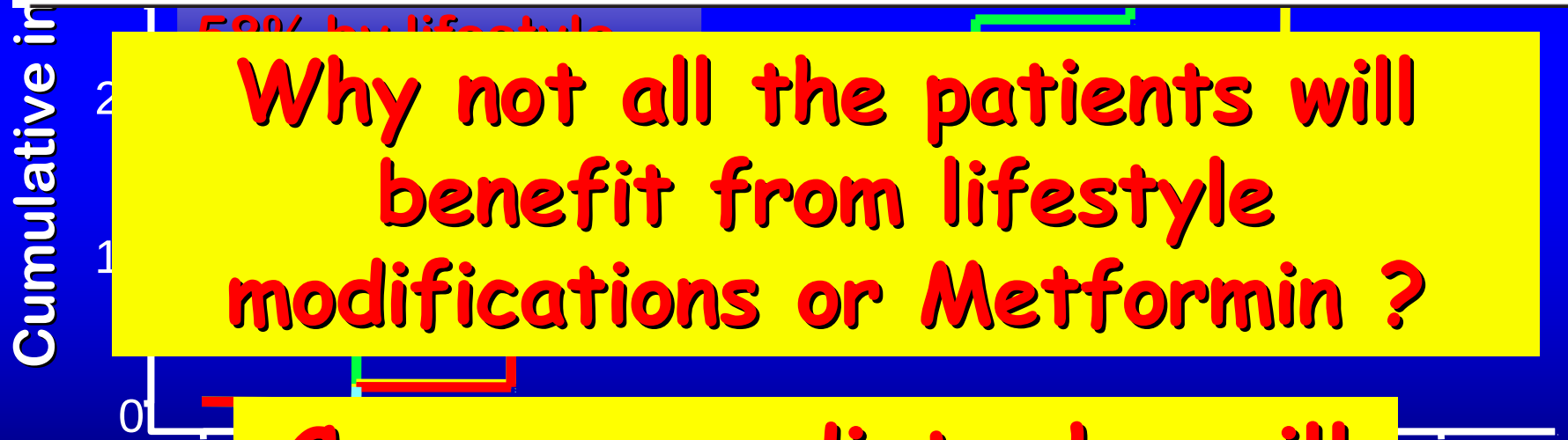
Genomics
Proteomics
Metabolomics
Pharmacogenomics
Nutrigenomics
Epigenomics
Microbiomics

40+

Prevention of Diabetes

Table 1. *Type 2 Diabetes Mellitus Prevention Trials.*

Trial	No. of Subjects	Intervention	Duration, yr	Risk Reduction Versus Control Group, %
Diabetes Prevention Program[52]	3234	Diet + exercise	3	58
Finnish Diabetes Prevention Study[53]	522	Diet + exercise	3	58
Da Qing IGT and Diabetes Study[54]	577	Diet + exercise	6	43
Diabetes Prevention Program[52]	3234	Metformin	3	31
TRIPOD[77]	133	Troglitazone	2.5	55
DREAM[56]	2365	Rosiglitazone	3	60
STOP-NIDDM[78]	714	Acarbose	3	25



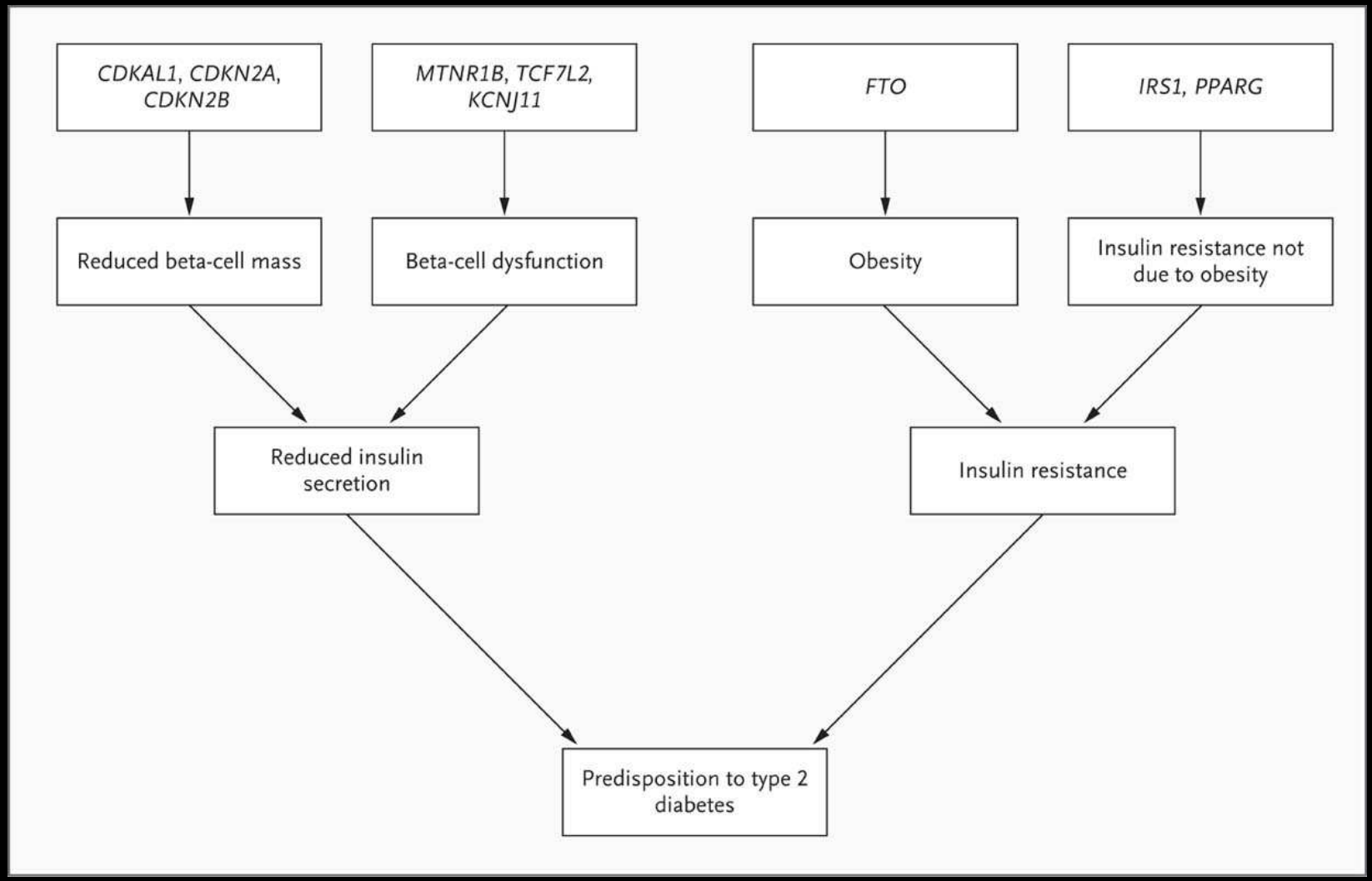
Why not all the patients will benefit from lifestyle modifications or Metformin ?

Can we predict who will develop Diabetes ?

393-403, 2002

Can We Predict, Prevent and Treat Diabetes Tailored to the the Specific Patient ?

Pathways to Type 2 Diabetes Implicated by Identified Common Variant Associations



McCarthy MI. N Engl J Med 2010;363:2339-2350

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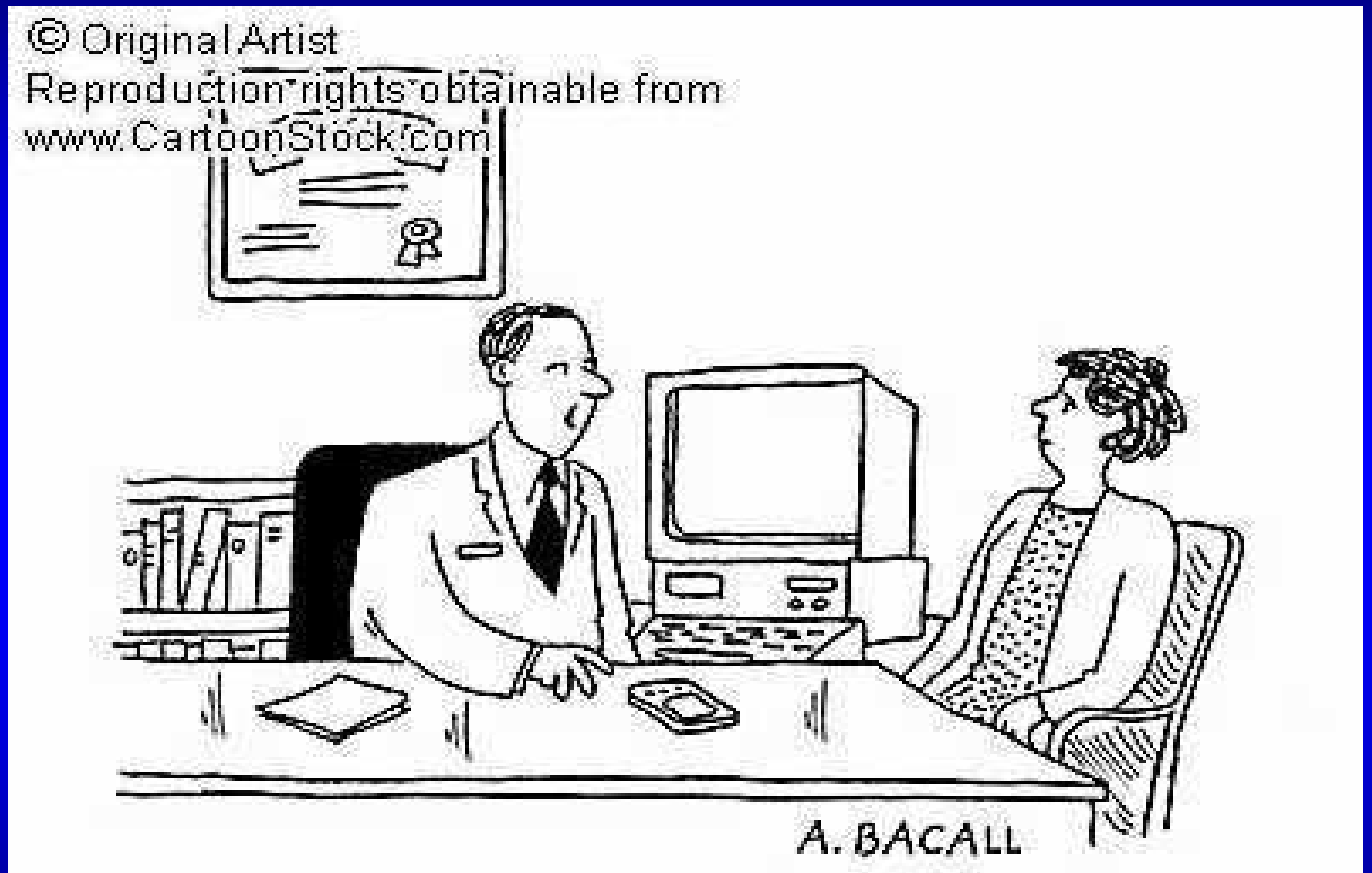
Six Functional Categories:

- Receptors;
- Transporters & Channels;
- Nuclear Receptors;
- Metabolic Enzymes;
- Secreted Factors;
- Signal Transduction Proteins;
- Transcription Factors.

Decision Support Systems



That's my diagnosis.
If you want a second opinion….
I will ask my computer

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ORIGINAL ARTICLE

Clinical Risk Factors, DNA Variants, and the Development of Type 2 Diabetes

Valeriya Lyssenko, M.D., Anna Jonsson, M.Sc., Peter Almgren, M.Sc., Nicoló Pulizzi, M.D., Bo Isomaa, M.D., Tiinamaija Tuomi, M.D., Göran Berglund, M.D., David Altshuler, M.D., Peter Nilsson, M.D., and Leif Groop, M.D.

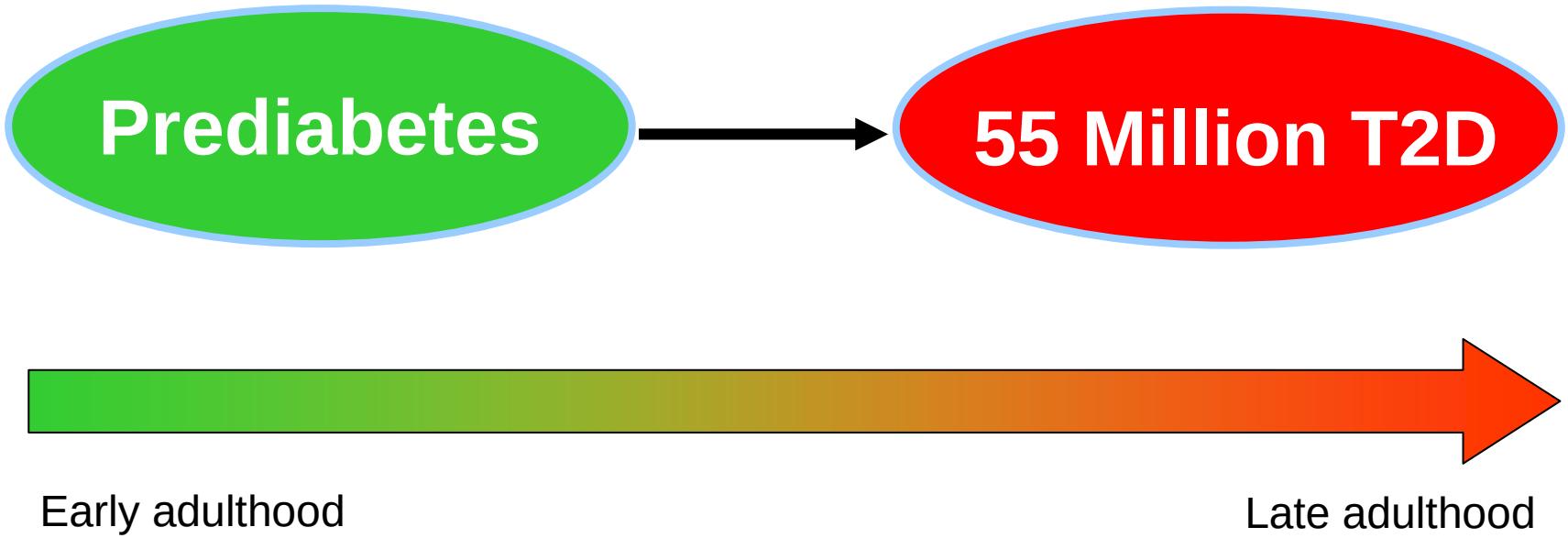
Lyssenko et al. NEJM 359, 21: 2220-2232, 2008

Predictors To Develop Type 2 Diabetes

- **Family history** of the disease, an **increased BMI**, **elevated liver-enzyme** levels, current **smoking** status, and **reduced measures of insulin secretion and action.**
- Variants in **11 genes** (*TCF7L2, PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX)*
  - independent of clinical risk factors;
- Common genetic variants associated with the risk of diabetes had a small effect on the ability to predict the future development of type 2 diabetes.

Lyssenko et al NEJM 359, 21: 2220-2232, 2008

Prevalence of Type 2 Diabetes in Europe



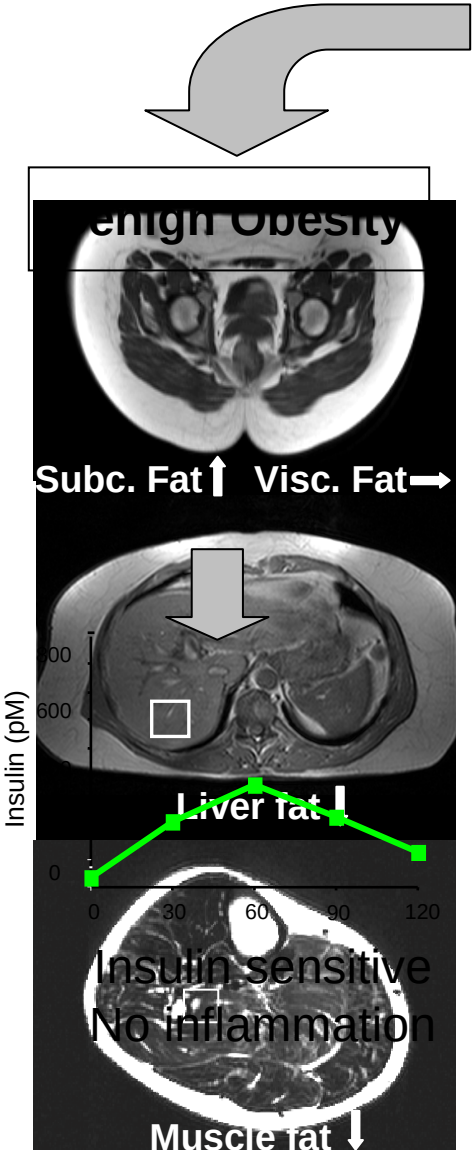
TÜbingen **F**amily study (TÜF): **prediabetic individuals (N=2000)**

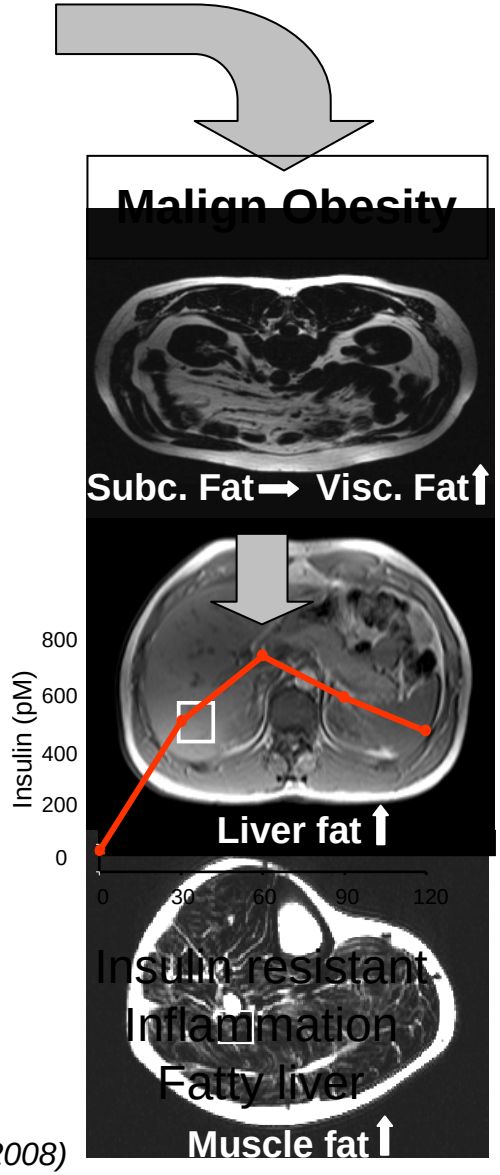
TULIP **Lifestyle Intervention (N=400)**

Subphenotypes of Obesity

The role of ectopic fat storage

n=500

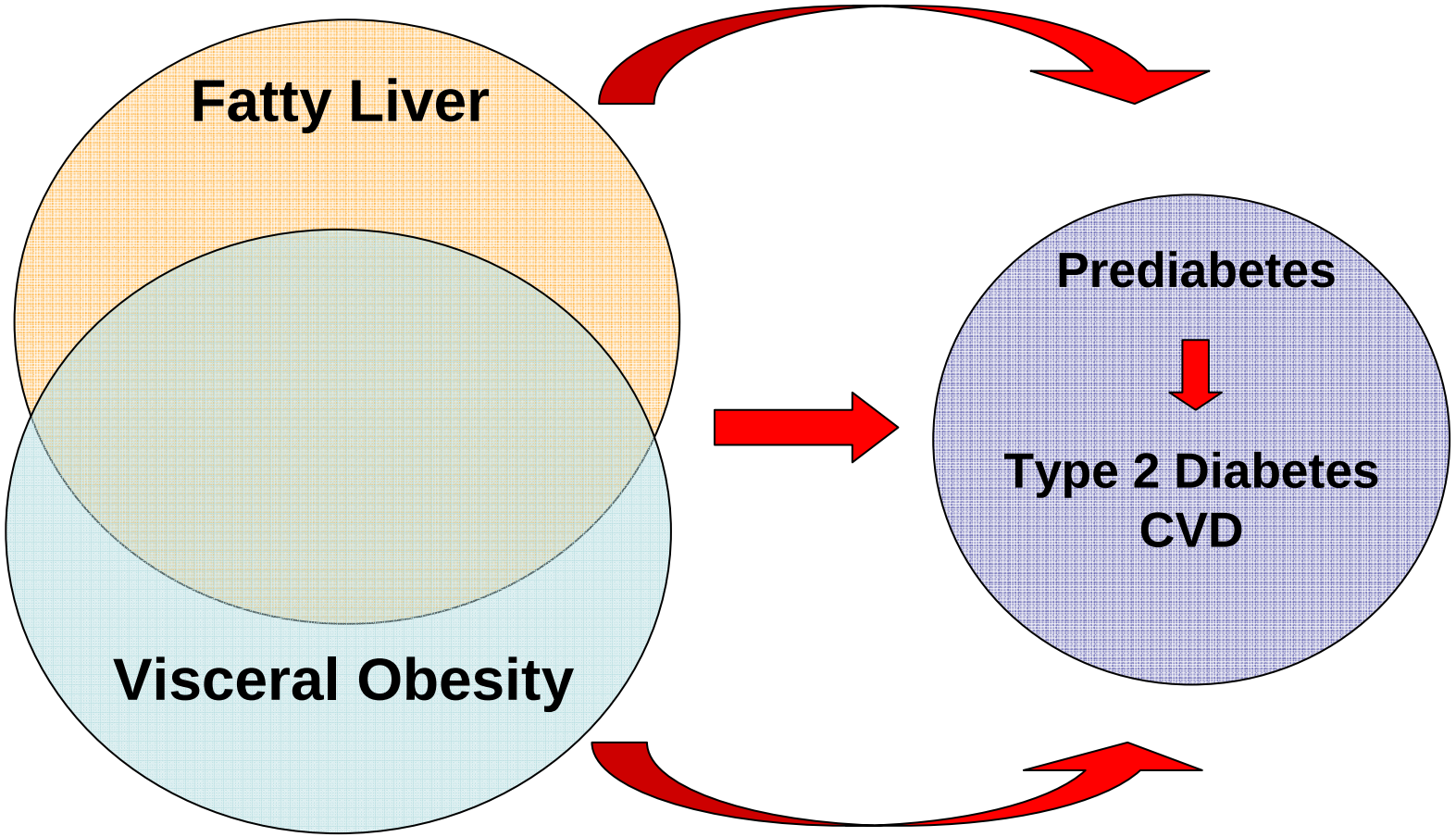




Stefan et al., Arch Intern Med. (2008)

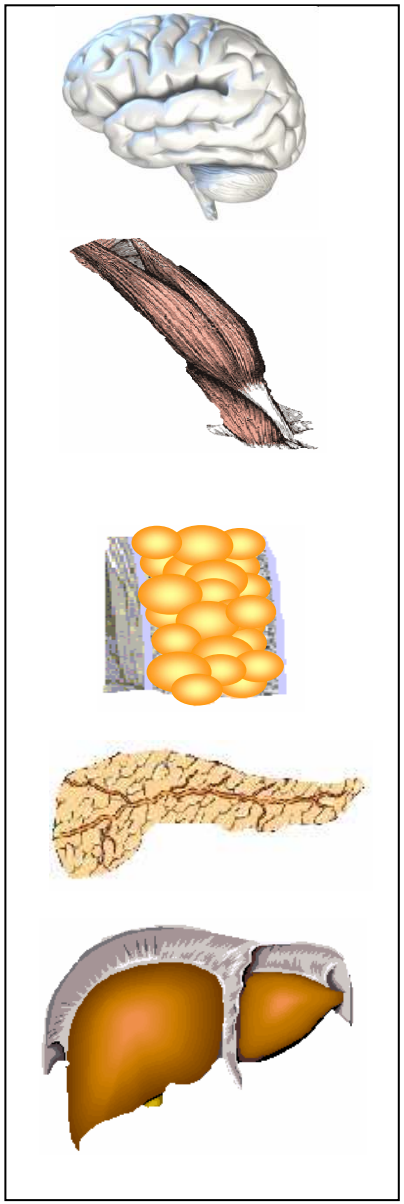
Kantartzis et al., Diabetologia 2010, Kantartzis et al., Diabetologia 2011

Contribution of different fat depots for the progression to diabetes



Stefan et al., Arch Intern Med. (2008)
Kantartzis et al., Diabetologia 2010, Kantartzis et al., Diabetologia 2011

Subphenotypes of prediabetes in TULIP



→ Insulin resistance of the brain

Tschritter et al., **Diabetologia 2011**
Tschritter et al., **Diabetologia 2007**
Tschritter et al., **PNAS 2006**

→ Exercise non-responders

Kantartzis et al., **Gut 2009**
Thamer et al., **JCEM 2008**
Stefan et al., **JCEM 2007**

→ The metabolically benign versus malignant obesity

Kantartzis et al., **Diabetologia 2010**
Stefan et al., **Arch. Int. Med. 2008**

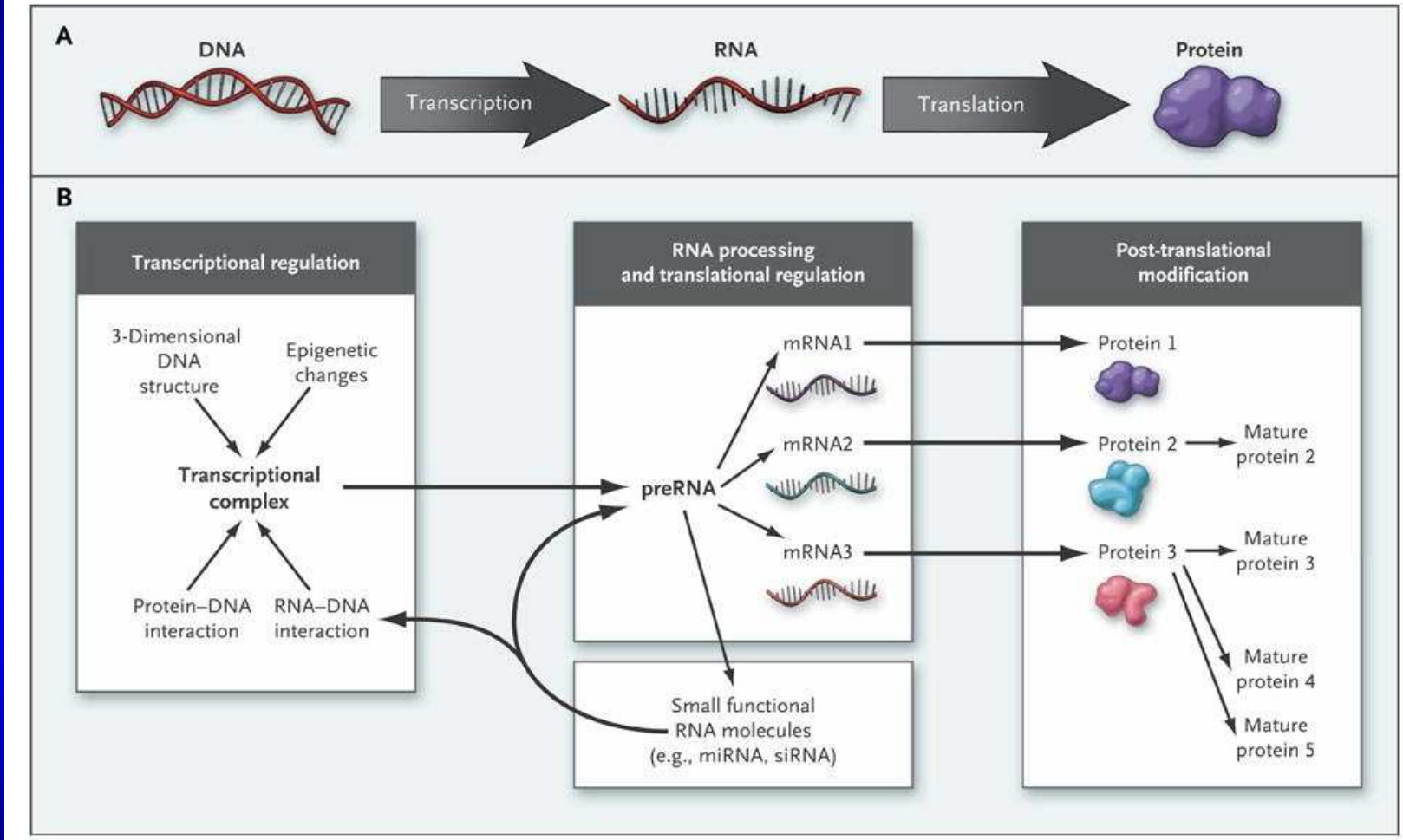
→ Incretin resistance
TCF7L2 →IR and PG interaction

Schäfer et al. **Diabetologia 2007**
Müssig et al. **Diabetes 2009,**
Diabetologia 2010
Haupt et al., **JCEM 2009**
Haupt et al., **Diabetologia 2009**

→ The metabolically malignant fatty liver predicts diabetes

Stefan & Häring **Diabetes 2011**
Stefan et al., **NEJM 2009**
Peter et al., **Diabetes 2010**
Stefan et al., **Diabetes 2008**
Hennige et al., **PLoS ONE 2008**

The Complexity of the Central Dogma of Molecular Biology.



Feero WG et al. N Engl J Med 2010;362:2001-2011.

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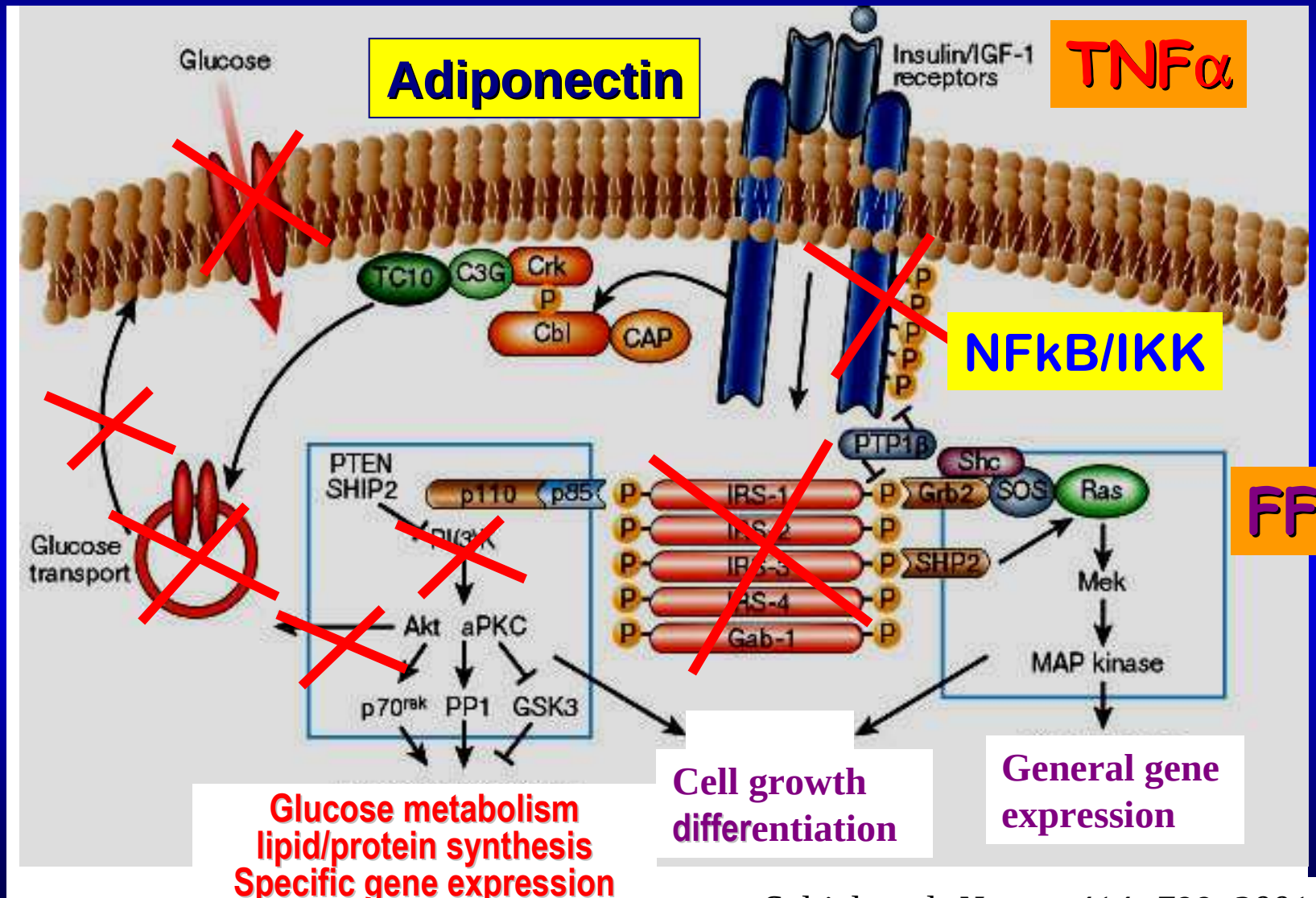
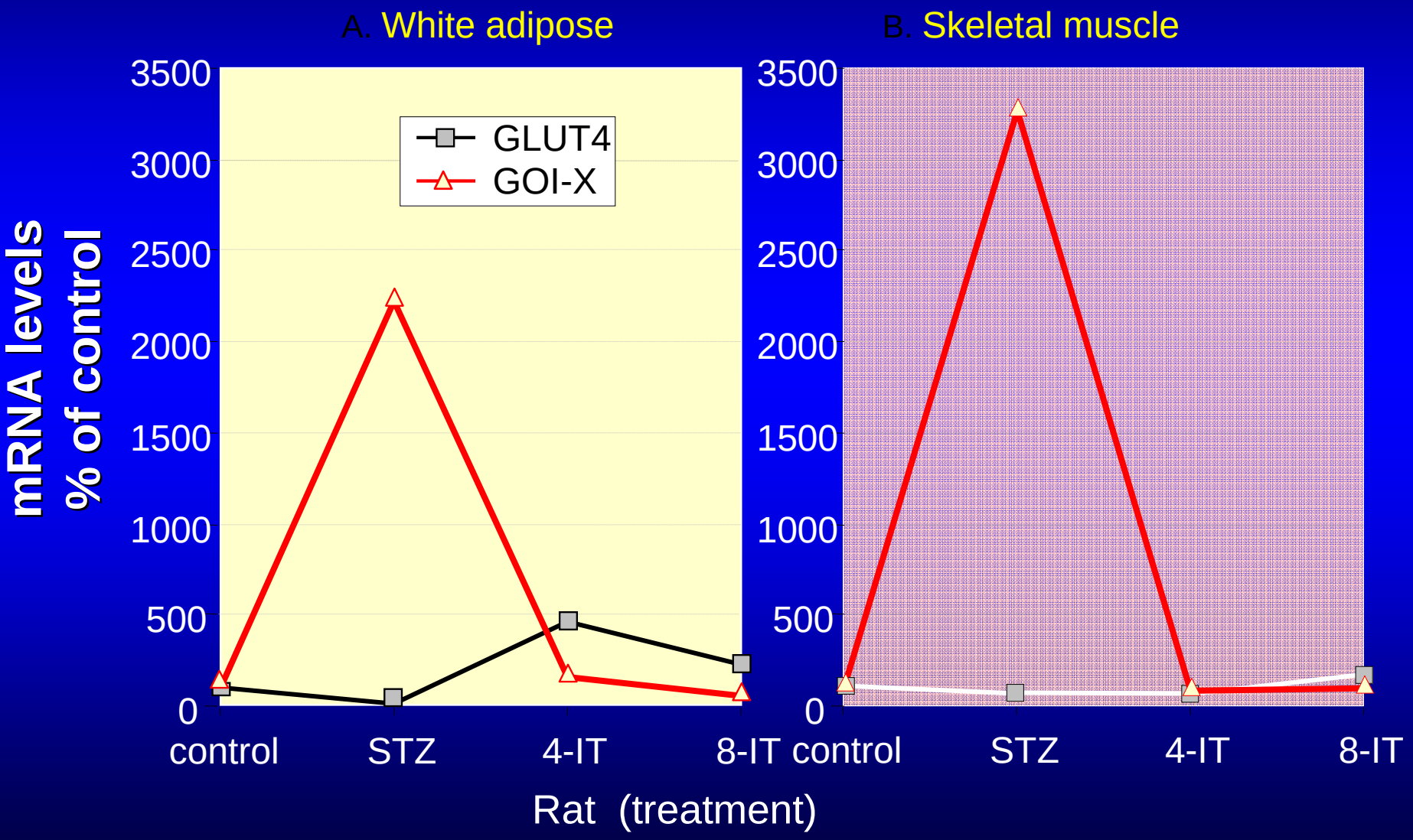
Potential Defects Associated With Type 2 Diabetes

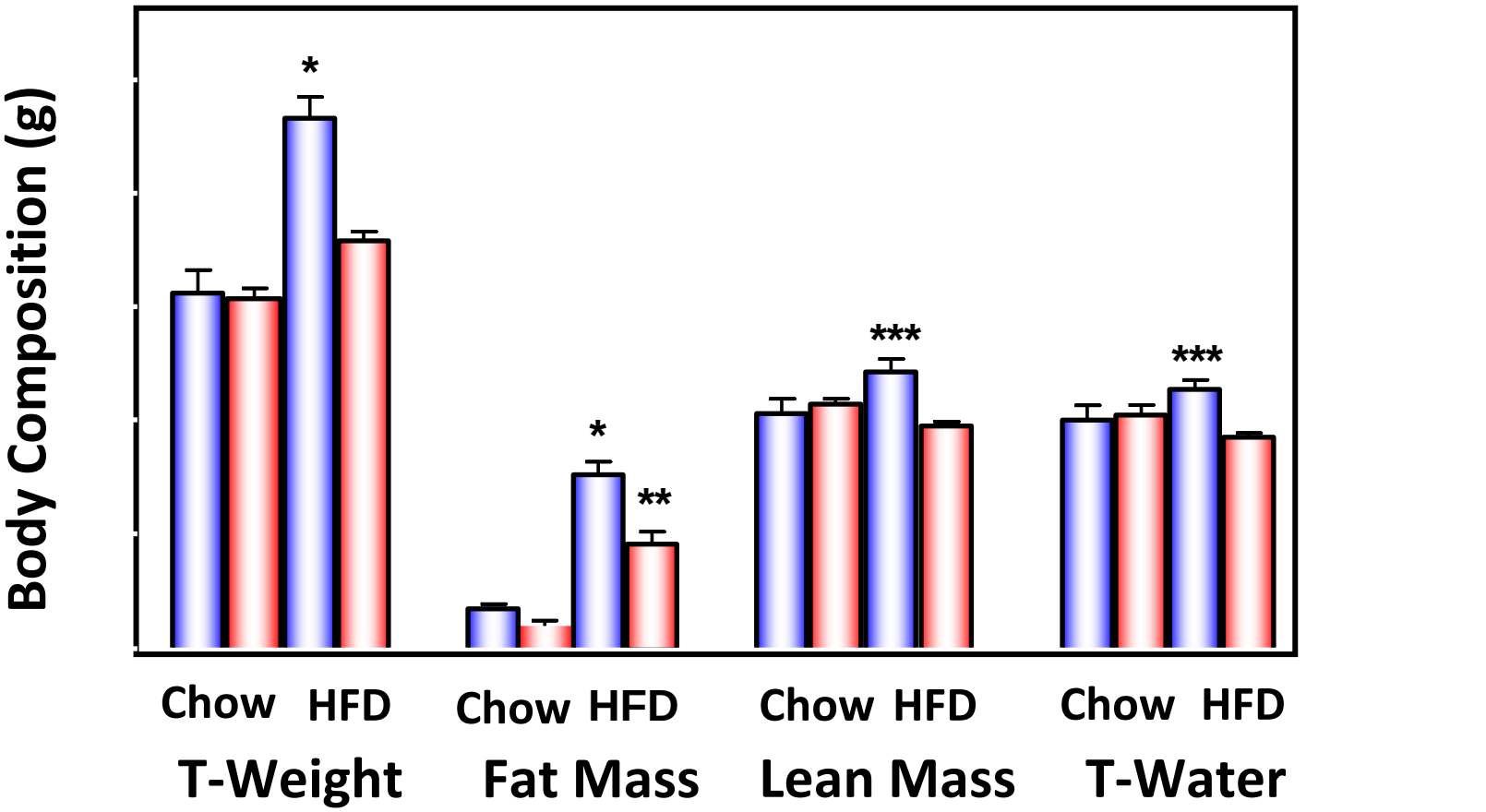


Saltiel et al, *Nature 414: 799, 2001*

mRNA Levels of CYP2E1 in Rat: (Real-time PCR analyses)

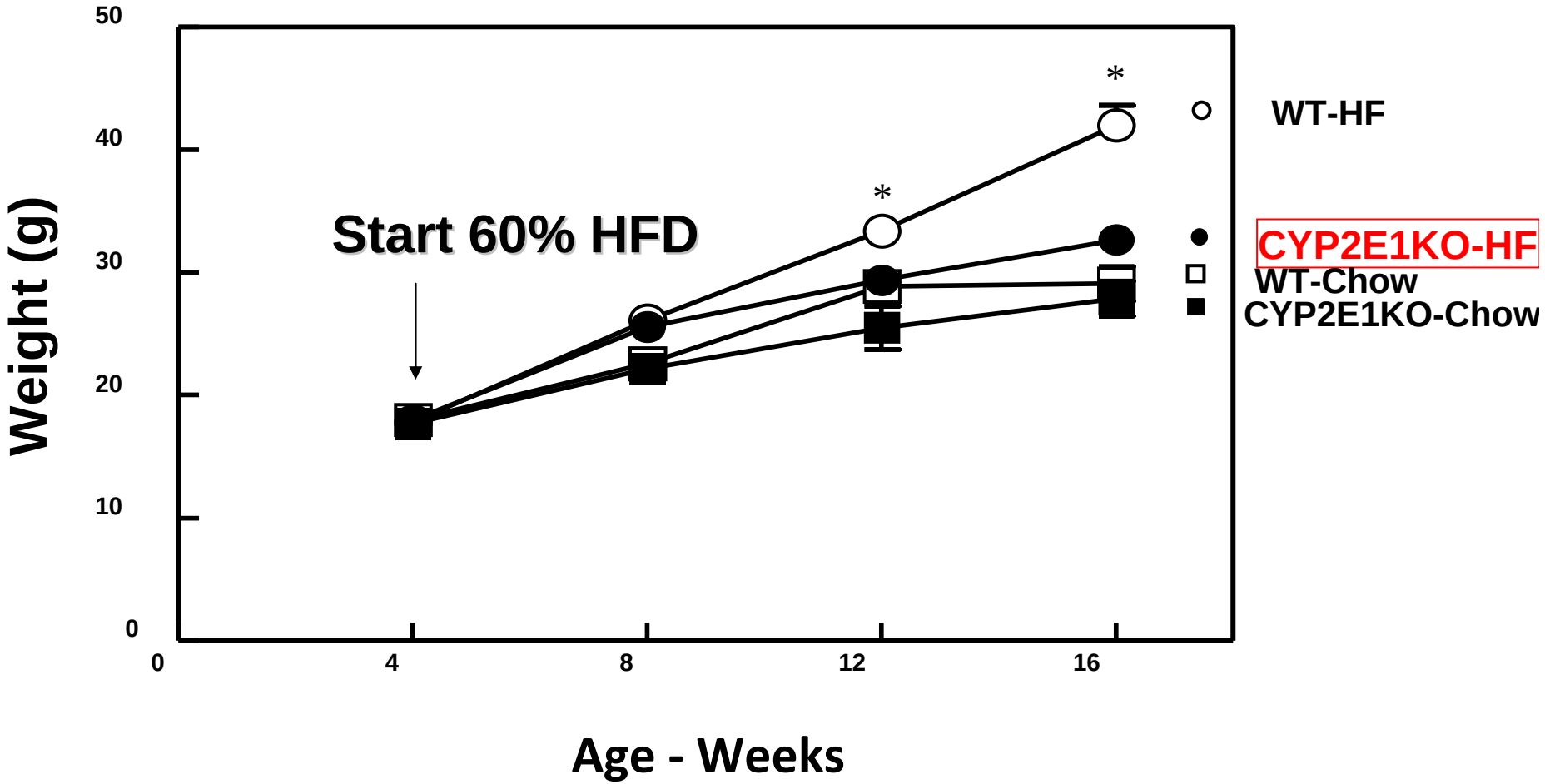


CYPKO Mice Are Protected From HFD-induced Obesity



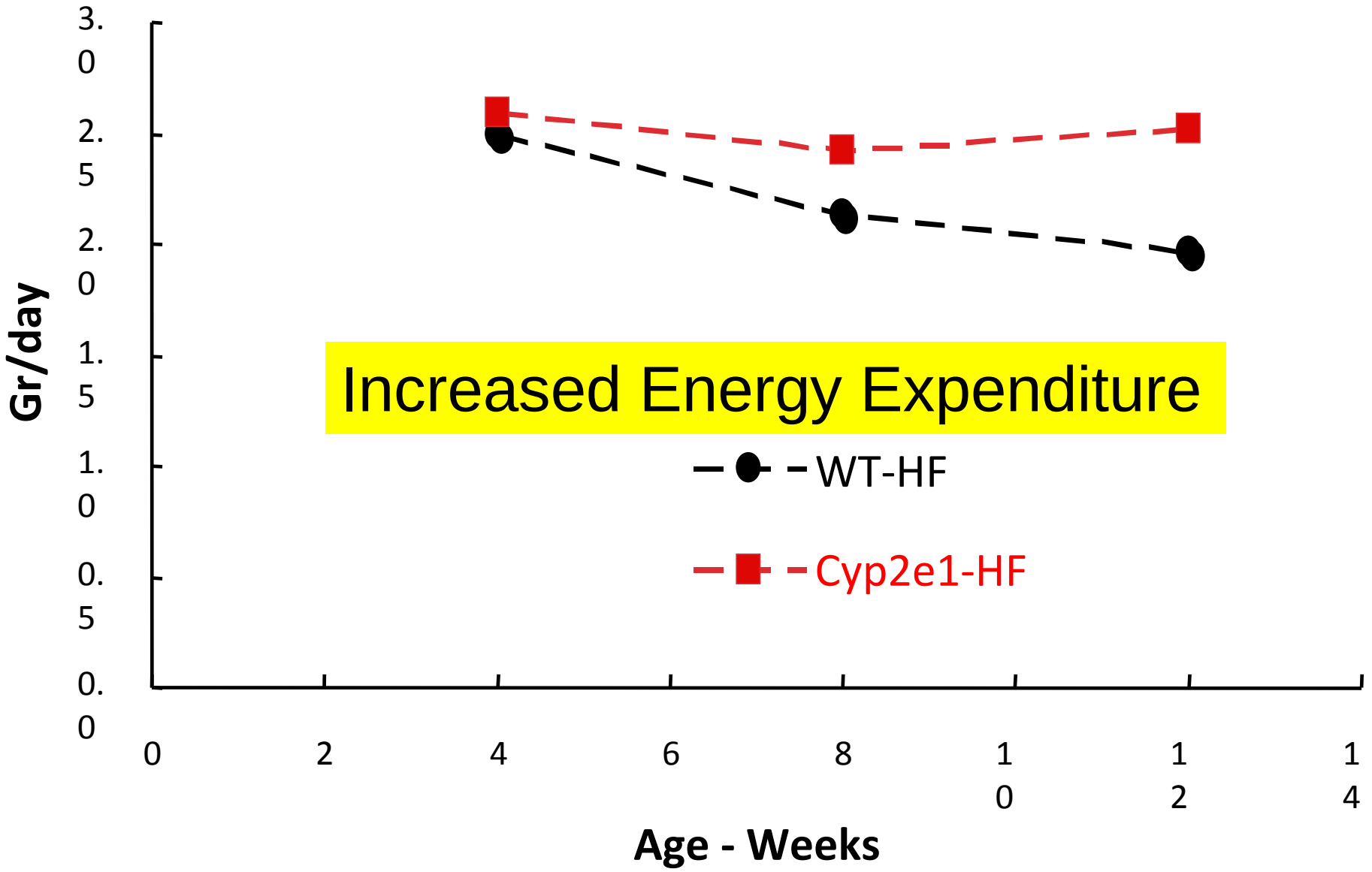
Zong et al. Am. J. Physiol, 302: in press 2012

CYP2E1 Null Mice Gain Less Weight



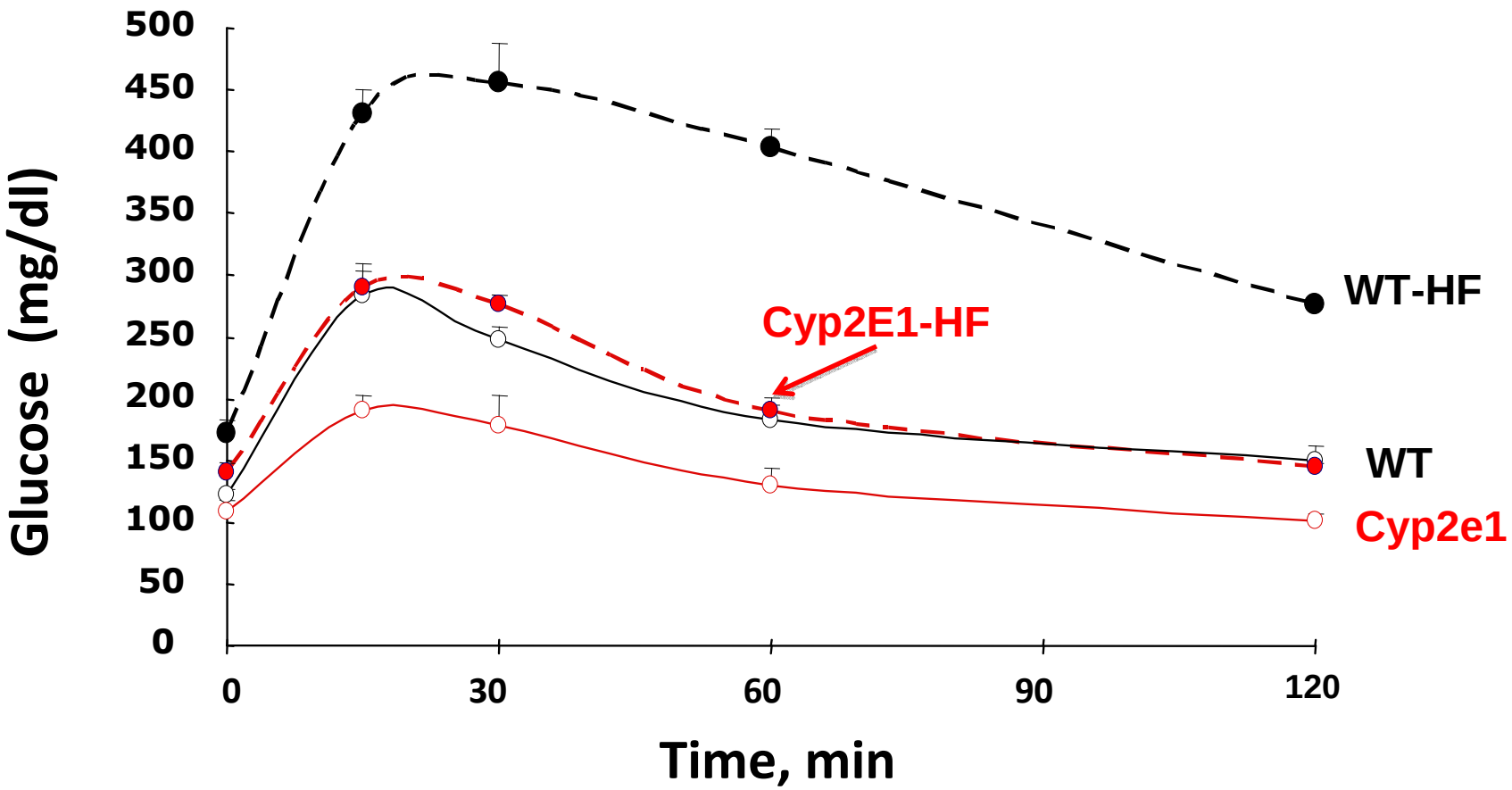
Zong et al. Am. J. Physiol, 302: in press 2012

Food Intake CYP2E1 Null Mice



What About Glucose Tolerance ?

IPGTT In Cyp2E1 KO Mice – 12 Weeks HF



Zong et al. Am. J. Physiol, 302: in press 2012

What are Our Treatment Options ?

The New York Times

Heart Attack Risk Seen in Drug for Diabetes

By STEPHANIE SAUL

An analysis of trials for Avandia concluded that the drug might significantly increase the risk of heart attacks.

Avandia (Rosi) + Actos (Pio) 2006
Prescriptions per Year: 22.6 Million
Sales per Year : $ 3.6 Billion

U.S. drug safety official recommends Avandia be wit

By Gar
Publish

US Sales declined 70%
EU – Withdrawn

Warnings

By GARDINER HARRIS

A federal drug advisory committee voted to recommend that the diabetes drug Avandia remain on the market, despite finding that it raised the risks of heart attacks.

July 31, 2007 | HEALTH | NEWS

Acomplia (Rimonabant) Story

Articles

Weight loss – 5-8 Kgs/year

Side effects: Anxiety & Depression

Never approved by FDA

Retracted from EU market

ant:

Lancet 2007; 370: 1706–1

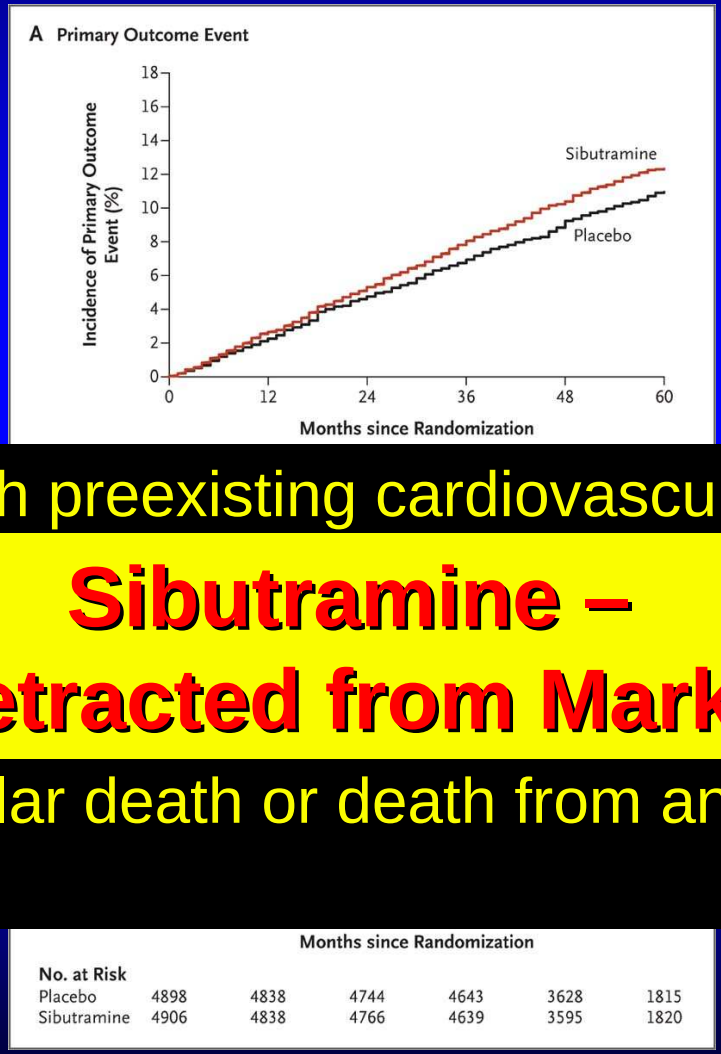
See Comment page 167

The Parker Institut
Musculoskeletal Statistics Uni
Frederiksberg Hospital,
Frederiksberg, Denmark
(R Christensen MSc,
P K Kristensen BSc,
Prof H Bliddal MD);

d safe anti-obesity
is of all published
nt rimonabant.

Methods We searched The Cochrane database and Controlled Trials Register, Medline via Pubmed, Embase via WebSpirs, Web of Science, Scopus, and reference lists up to July, 2007. We collected data from four double-blind, randomised controlled trials (including 4105 participants) that compared 20 mg per day rimonabant with placebo.

Incidence of a Primary Outcome Event and Death from Any Cause, According to the Time from Randomization



Subjects with preexisting cardiovascular conditions who wer
treatmer al
myocard but not of cardiovascular death or death from any cause.

Sibutramine – Retracted from Market

James WPT et al. N Engl J Med 2010;363:905-917

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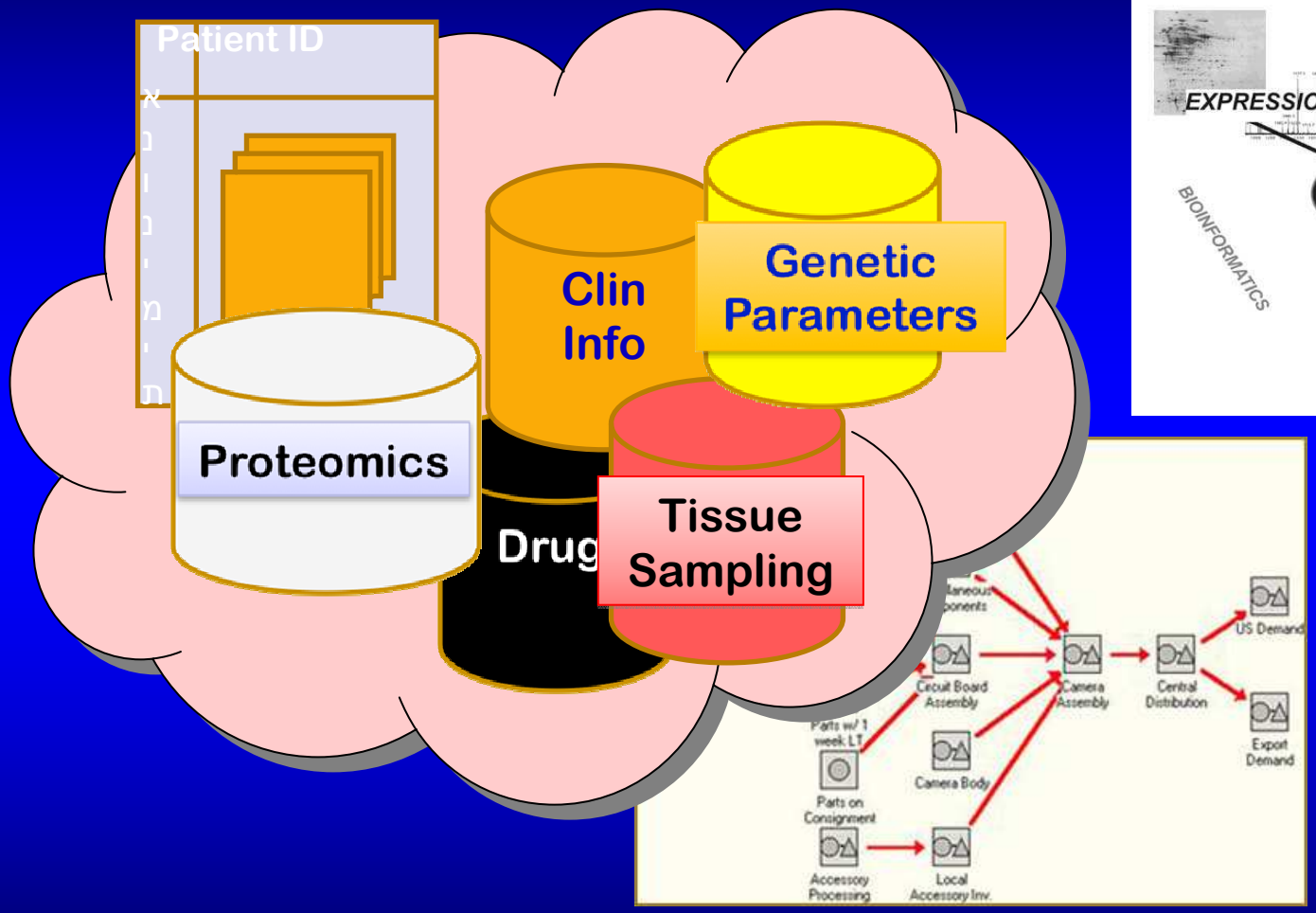
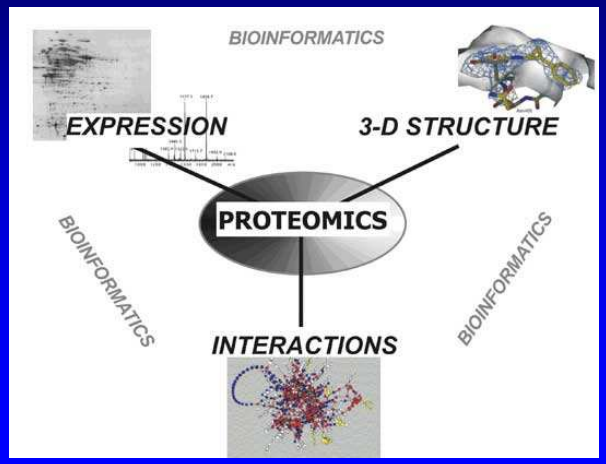
Why Good Medications Aiming at Treating Obesity And Diabetes Fail ?

Future Directions

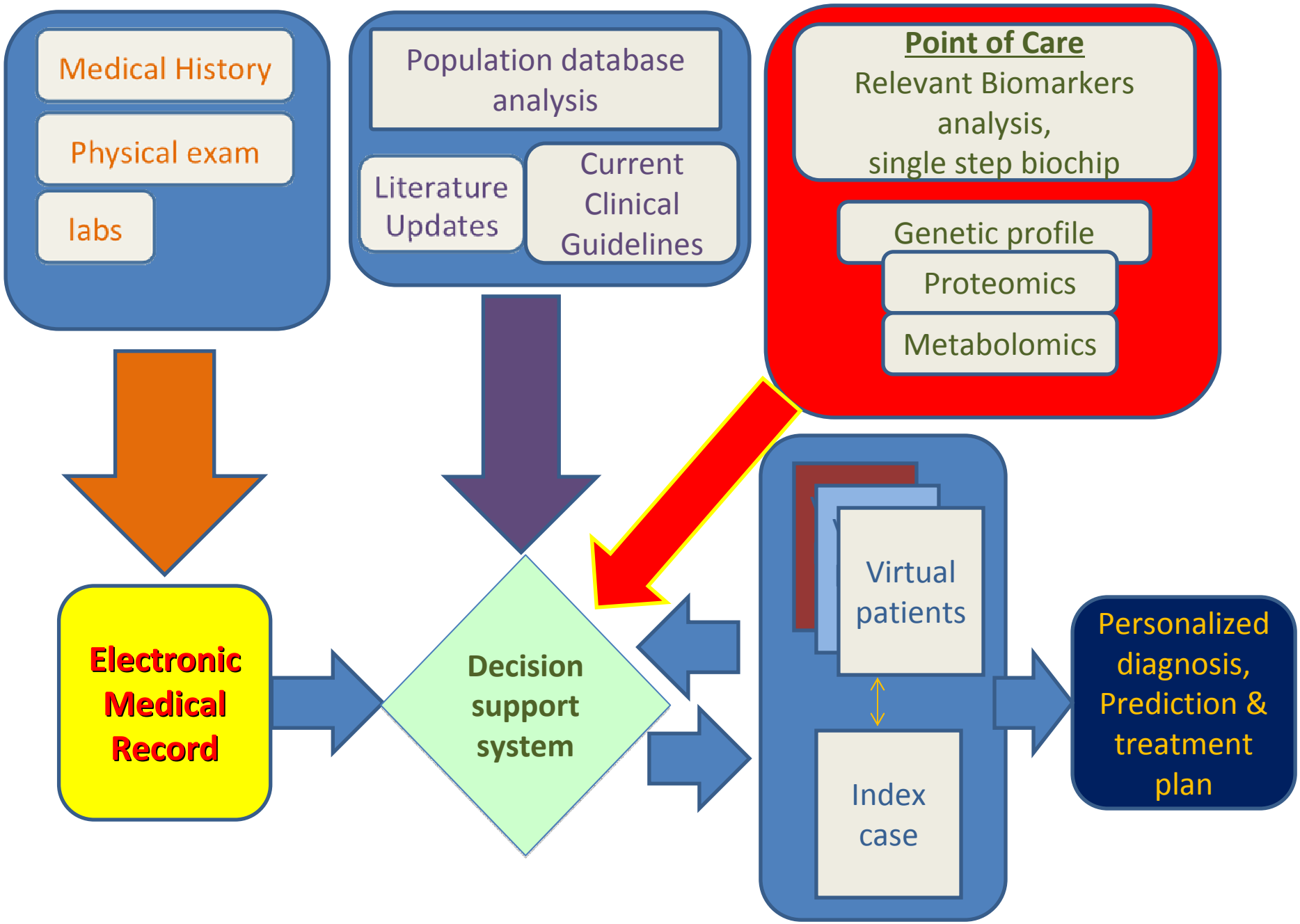
- To analyze and define the essential clinical and laboratory data in order to develop reliable algorithms for predicting clinical outcome.
- Examine the specificity and sensitivity of these algorithms in subset of patients by checking their molecular profile.
- Apply and integrate the algorithms into updated decision support systems
- Test the applicability of the new platform in selected clinics.

To Narrow the Gap Between Knowledge and Clinical Practice





Personalized Medicine – Predict Prevent & Treat



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