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
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.

Scan a person’s genome for as little as $1000.

Fun novelty or do valuable information?

Bonetta, Cell 133: 753-756, 2008
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…. 
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.
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 bedside 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.
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

- Type 2 Diabetes: $53.2 billion
- Obesity: $51.6 billion
- Coronary Heart Disease: $38.7 billion
- Hypertension: $18.4 billion
- Stroke: $18.1 billion

*Adjusted to 1995 dollars.

Key Component of the Energy Balance System

Energy Intake

Energy Expenditure

FEEDING

Basal Metabolism
Adaptive Thermogenesis

PHYSICAL ACTIVITY
Cardiometabolic Risk Factors Promoted by Intra-abdominal Adiposity

- Inflammation
  - ↑ IL-6
  - ↑ TNFα
  - ↑ Adipsin (Complement D)
  - ↓ Adiponectin

- Lipoprotein lipase
  - ↑

- Hypertension
  - ↑ Angiotensinogen

- Atherogenic dyslipidaemia
  - ↑ FFA
  - ↑ Resistin
  - ↑ Leptin
  - ↑ RBP4

- Type 2 diabetes
  - ↑ Plasminogen activator inhibitor-1 (PAI-1)

- Atherosclerosis
  - ↑ Lipoprotein lipase

- Thrombosis
Monogenic Obesity - MC4R Mutation

9 year-old with MC4R mutation

16 year-old sibling with Normal MC4R
<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEP</td>
<td>7q</td>
<td>0.5%</td>
</tr>
<tr>
<td>LEPR</td>
<td>1p</td>
<td>0.5%</td>
</tr>
<tr>
<td>POMC</td>
<td>2p</td>
<td>0.8%</td>
</tr>
<tr>
<td>PCSK1</td>
<td>5q</td>
<td>0.4%</td>
</tr>
<tr>
<td>MC4R</td>
<td>18q</td>
<td>3%</td>
</tr>
<tr>
<td>BDNF</td>
<td>11p</td>
<td>rare</td>
</tr>
<tr>
<td>NTRK2</td>
<td>9q</td>
<td>rare</td>
</tr>
</tbody>
</table>

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
Virtual Clinical Data
Virtual Clinical Data
Virtual Clinical Data
Tissue Sample Bank
Genetic Profile
Proteomics
Imaging Data
Laboratory Data
Imaging Data
Imaging Data
Imaging Data
Drugs + side effects Toxicology
Drugs Interactions
Molecular Mechanisms
Clinical Guidelines
Patient ID
Anonymity
Our Patient = Populations

- Proteomics
- Genetic Profile
- Relevant Populations
- Epigenetics
- Target Genes
- 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?

40+

Genomics
Proteomics
Metabolomics
Pharmacogenomics
Nutrigenomics
Epigenomics
Microbiomics
Prevention of Diabetes

Table 1. Type 2 Diabetes Mellitus Prevention Trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Subjects</th>
<th>Intervention</th>
<th>Duration, yr</th>
<th>Risk Reduction Versus Control Group, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Prevention Program(^{52})</td>
<td>3234</td>
<td>Diet + exercise</td>
<td>3</td>
<td>58</td>
</tr>
<tr>
<td>Finnish Diabetes Prevention Study(^{53})</td>
<td>522</td>
<td>Diet + exercise</td>
<td>3</td>
<td>58</td>
</tr>
<tr>
<td>Da Qing IGT and Diabetes Study(^{54})</td>
<td>577</td>
<td>Diet + exercise</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td>Diabetes Prevention Program(^{52})</td>
<td>3234</td>
<td>Metformin</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>TRIPOD(^{77})</td>
<td>133</td>
<td>Troglitazone</td>
<td>2.5</td>
<td>55</td>
</tr>
<tr>
<td>DREAM(^{56})</td>
<td>2365</td>
<td>Rosiglitazone</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>STOP-NIDDM(^{78})</td>
<td>714</td>
<td>Acarbose</td>
<td>3</td>
<td>25</td>
</tr>
</tbody>
</table>

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

Can we predict who will develop Diabetes?

The DPP Research Group, NEJM 346:393-403, 2002
Can We Predict, Prevent and Treat Diabetes Tailored to the Specific Patient?
Pathways to Type 2 Diabetes Implicated by Identified Common Variant Associations

- **CDKAL1, CDKN2A, CDKN2B**
  - Reduced beta-cell mass

- **MTNR1B, TCF7L2, KCNJ11**
  - Beta-cell dysfunction

- **FTO**
  - Obesity

- **IRS1, PPARG**
  - Insulin resistance not due to obesity

- Reduced insulin secretion
- Insulin resistance
- Predisposition to type 2 diabetes

Six Functional Categories:

- Receptors;
- Transporters & Channels;
- Nuclear Receptors;
- Metabolic Enzymes;
- Secreted Factors;
- Signal Transduction Proteins;
- Transcription Factors.
That’s my diagnosis. If you want a second opinion…. I will ask my computer.
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.
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.

Prevalence of Type 2 Diabetes in Europe

Prediabetes → 55 Million T2D

Early adulthood → Late adulthood

TÜbingen Family study (TÜF): prediabetic individuals (N=2000)

TULIP Lifestyle Intervention (N=400)
Subphenotypes of Obesity

The role of ectopic fat storage

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.

Potential Defects Associated With Type 2 Diabetes

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

A. White adipose

B. Skeletal muscle

Rat (treatment)

% of control

mRNA levels

0 500 1000 1500 2000 2500 3000 3500

control STZ 4-IT 8-IT control STZ 4-IT 8-IT

GLUT4

GOI-X
CYPKO Mice Are Protected From HFD-induced Obesity

CYP2E1 Null Mice Gain Less Weight

Food Intake CYP2E1 Null Mice

Increased Energy Expenditure

- WT-HF
- Cyp2e1-HF

Gr/day vs. Age - Weeks
What About Glucose Tolerance?
IPGTT In Cyp2E1 KO Mice - 12 Weeks HF

What are Our Treatment Options?
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.

US drug safety official recommends Avandia be withdrawn

By GARDNER 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

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

US Sales declined 70%
EU – Withdrawn
Acomplia (Rimonabant) Story

Weight loss – 5-8 Kgs/year
Side effects: Anxiety & Depression

Never approved by FDA
Retracted from EU market

Methods We searched The Cochrane database and Controlled Trials Register, Medline via Pubmed, Embase via WebSirs, 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.
Subjects with preexisting cardiovascular conditions who were receiving long-term sibutramine treatment had an increased risk of nonfatal myocardial infarction and nonfatal stroke but not of cardiovascular death or death from any cause.
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
Electronic Medical Record

- Medical History
- Physical exam
- Labs

Population database analysis
- Literature Updates
- Current Clinical Guidelines

Point of Care
- Relevant Biomarkers analysis, single step biochip
- Genetic profile
- Proteomics
- Metabolomics

Virtual patients

Decision support system

Index case

Personalized diagnosis, Prediction & treatment plan

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I know an excellent Web Site that can help you with this..

Doc,
All my life is around Internet, websites, games & chats.
Please help me...

Thank You