Personalized Medicine Approaches in RA*

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Abstracted from: Fritzler MJ. Personalized Medicine Approaches in Rheumatoid Arthritis and Other Systemic Autoimmune Rheumatic Diseases. From Prediction to Prevention of Autoimmune Diseases, Autoantigens, Autoantibodies, Autoimmunity, Conrad K, Chan EKL, Fritzler MJ, Humbel RL, Meroni PL, Shoenfeld, Eds. Pabst Science Publishers, Lengerich. pp 127-137, 2011.

Disclosure

Dr. Marvin Fritzler does not hold shares in and is not a paid consultant to 23andme, Google, Luminex Corporation, imaGenes, Yonder Biology or any of their distributors.

He is a consultant to or received honoraria from ImmunoConcepts, INOVA Diagnostics, Euroimmun, BioRad, Mikrogen GmbH, Dr. Fooke Laboratorien and GSK Canada.

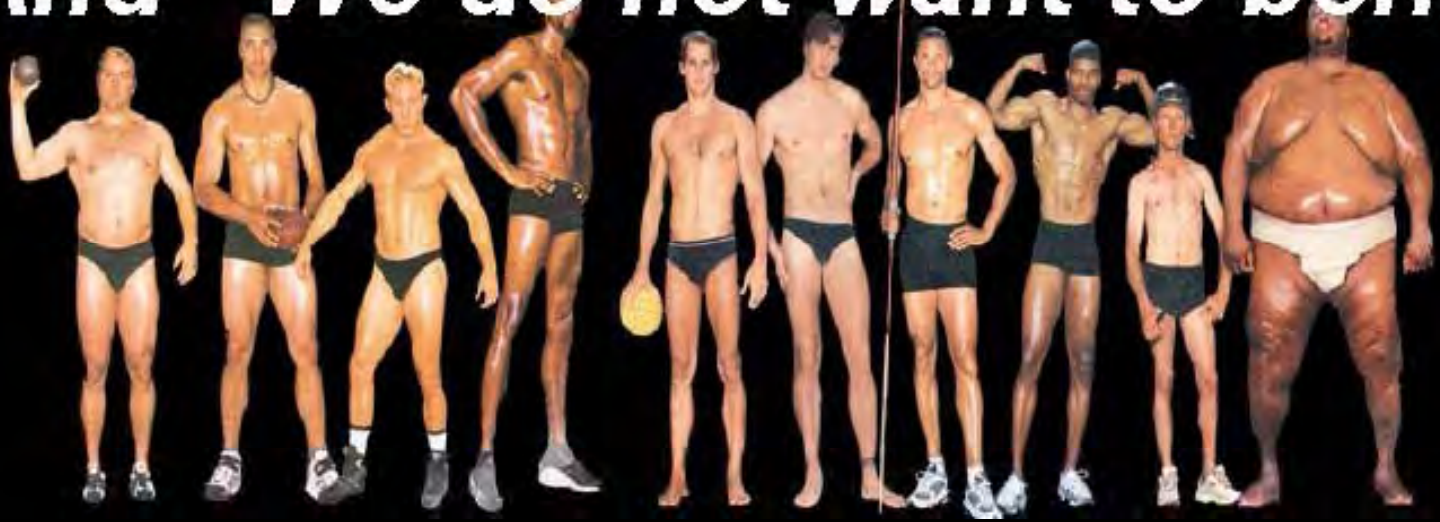
OUTLINE:
THREE CONSIDERATIONS

1. What is Personalized Medicine?
2. Is there a compelling case for PM?
3. What resources are needed?
4. Supporting evidence?

The Basis of Personalized Medicine

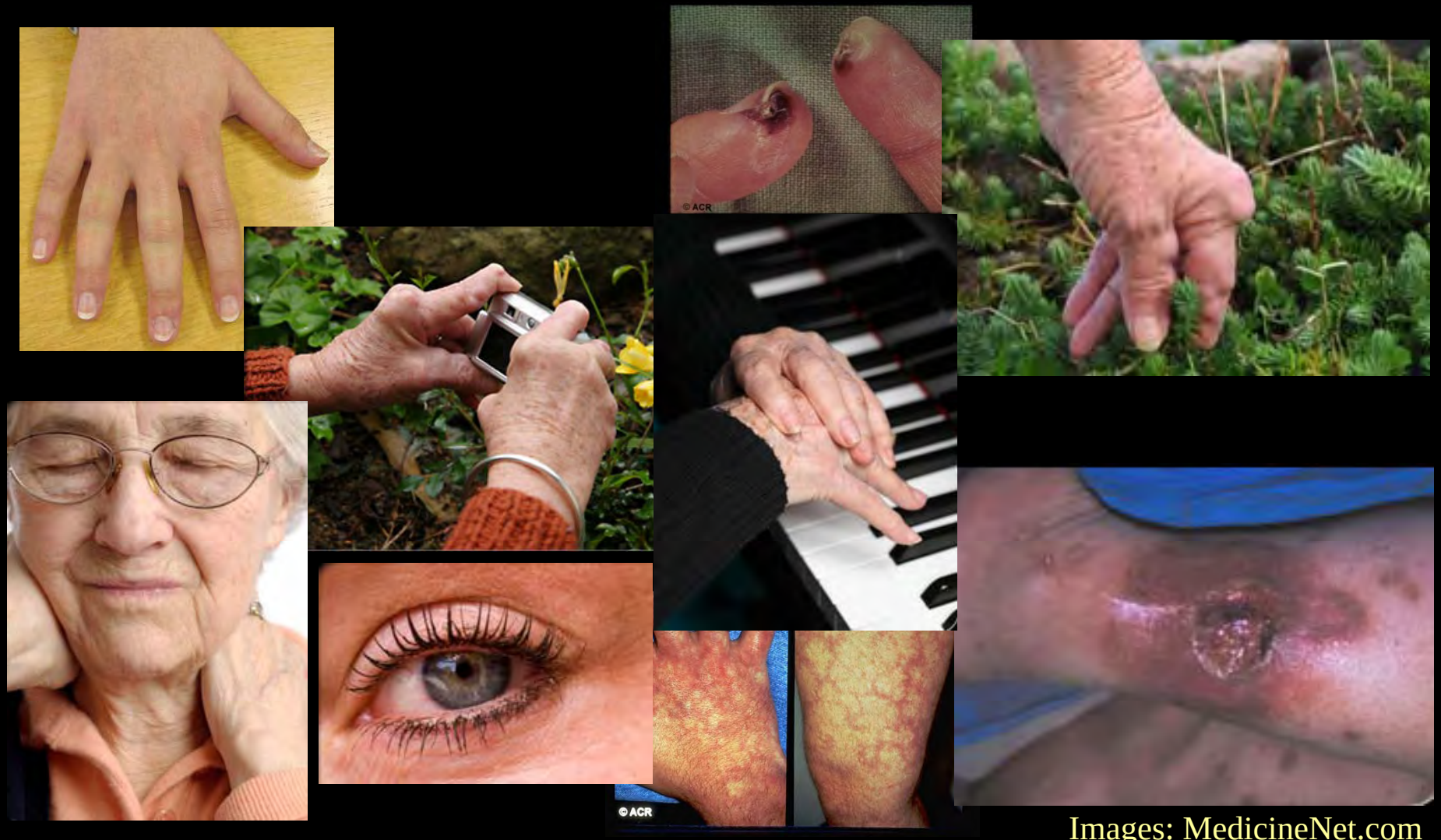
AND We are not all the same!

And We do not want to be!!!!



From Sports Illustrated

And neither are all RA patients the same... multiple clinical phenotypes…



Images: MedicineNet.com

Personalized Medicine aka

- Theranostics
  - Diagnostics/Therapeutics Partnering
- Individualized Medicine (Mayo)
- Designer Medicine
- Molecular Medicine
- Companion Medicine
- Prospective Medicine
- Translational Genomics
- Pharmacogenomics

PM is already alive and well

- Predictive — Preventative
  - BRCA1/BRCA2 — mastectomy/ovarectomy??
  - SNP for CytP450/VKORC1 — warfarin dosing
  - CYPs — neuroleptic medications
- Targeted
  - HER2 and HER2 receptor — Herceptin
  - BCR-ABL — Gleevec (95% of CML)
- MRD (minimal residual disease): detect disease with molecular markers before it clinically returns.

COMPELLING CASES for Personalized Medicine in RA?

Key References:

Centola et al. Scand J Immunol 64: 236, 2006

Goldknopf IL Expert Rev. Mol. Diagn. 7: 339, 2007.

Merril JT Current Rheumatol Rep 10: 257, 2008

Rhodes & Vise. Nat Rev Rheumatol 6: 373, 2010

Compelling Case #1: Cost of Lives

- **News Item: "A 747 crashes every 2-3 days and all on board are killed. If this continues ~100,000 people will die in 747 air crashes this year."**
- **Sept 20, 2011: More people die from drug related deaths than motor vehicle accidents.**
- **Iatrogenic drug reactions = 2 million/year: 100,000 die***

*Sources: Denis Cortese former CEO Mayo Clinic
Corus News Network 20/09/11

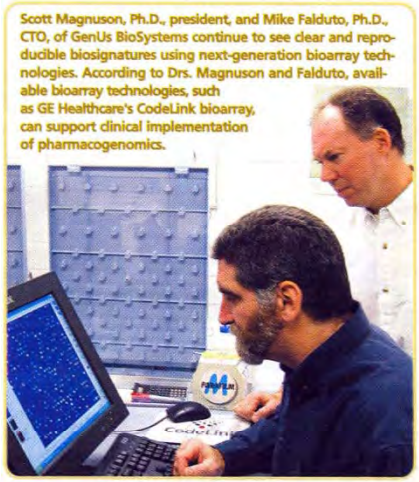
Personalized Arthritis Therapy

With Blockbuster Drugs in Jeopardy Firms Look To Pharmacogenetics

Catherine Shaffer

Recent reports of an increased risk of heart attack with the Cox-2 inhibiting drugs Vioxx® and Celebrex® have resulted in a huge setback for arthritis therapeutics. These drugs had become staples for the treatment of osteoarthritis (OA) and rheumatoid arthritis, both debilitating inflammatory diseases.

It seems that the only hope of keeping these drugs available would be to find some way to identify patients who are susceptible to the cardiovascular effects, possibly by nature of a genetic difference. The FDA has recently begun to solicit data, on a voluntary basis, from pharmaceutical companies, and some time this year will issue a final set of standards for pharmacogenetic data.



Scott Magnuson, Ph.D., president, and Mike Falduto, Ph.D., CTO, of GenUs BioSystems continue to see clear and reproducible biosignatures using next-generation bioarray technologies. According to Drs. Magnuson and Falduto, available bioarray technologies, such as GE Healthcare's CodeLink bioarray, can support clinical implementation of pharmacogenomics.

At the same time, technology such as **GE Healthcare's** (Little Chalfont, U.K.) Codelink has overcome some key hurdles in terms of data accuracy and reproducibility. Now, experts across the industry are waiting and wondering whether Vioxx and Celebrex will be the first blockbuster drugs to be rescued by pharmacogenetics.

Meanwhile, the science of personalized medi-

See Pharmacogenetics on page 13

COMPELLING CASE #2:

FAILURE TO ACHIEVE TAGETS

One size does not fit all…..

Compelling Case #3

Class action law suits.

$4.85 billion *settlement* fund made payments to the families of 2878 *Vioxx* users

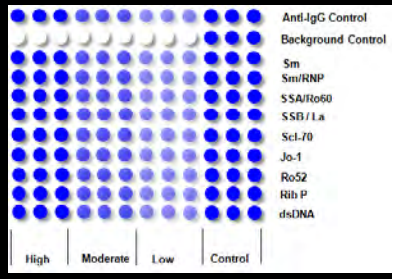
PM: Is technology up to the challenge?

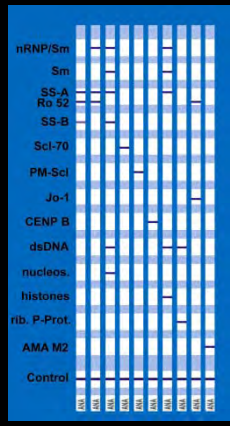
Technologies/Platforms/'OMICS
Patient Profiling

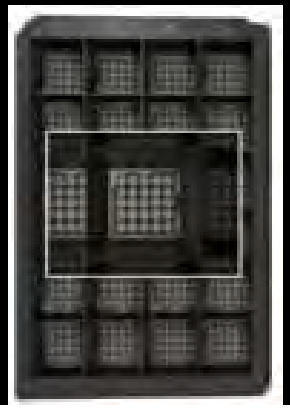
- **Autoantibody profiles**
- **T and B cell subsets profile**
- **Cytokine subsets**
- **Genomics and Epigenomics advancing rapidly**
- **Proteomics**
- **Ribonomics: rapidly emerging especially miRNA**
- **Metabolomics**
- **Metalomics**
- **BIOINFORMATICS is the major challenge!**
- **Integrated SYSTEMS BIOLOGY: mandatory**

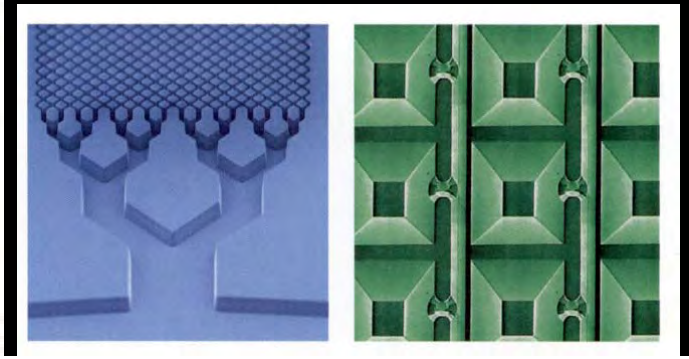
Contemporary & Emerging Technologies

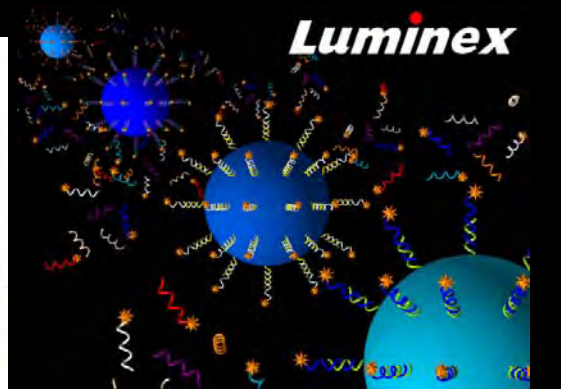
- **Line Immunoassays: Euroline, InnoLIA, Mikrogen**
- **Addressable Laser Bead Assays: INOVA, Zeuss, BMD**
- **Antigen Arrays on Planar Surfaces: ImmunoConcepts, others**
- **Bioflash: Werfen Group**
- **Multiplexed Lateral Flow: Point of Care Diagnostics**
- **Microfluidics or *'Lab on a chip'***
- **Electrochemiluminescence Arrays**: MesoScale Discovery
- **Mass & NMR Spectroscopy**
- **Nanotechnology — nanobarcodes: Pronostics**











OPINION

Using genetics to deliver personalized SLE therapy—a realistic prospect?

Benjamin Rhodes and Timothy J. Vyse

Nat. Rev. Rheumatol. 6, 373–377 (2010)

- Potential of Genomics in SLE
- SLE is attended "by strong underlying genetic predisposition, mediated by multiple gene variants.... the disease risk imparted by many of these variants is strong.... this particular combination of genetic effects means that the personalized prediction of disease onset or manifestation is certainly a realistic possibility"
  - On its own: LOW Odds Ratios
  - Predict onset
  - Predict disease course

See also: Centola et al. Scand J Immunol 64: 236, 2006.

Genomic Markers in RA

- rs17301249, mapping to the EYA4 gene: improved response to treatment
- rs1532269, mapping to the PDZD2 gene: a reduced treatment response
- SNPs mapped to intergenic regions on chromosomes 1, 4, 11, and 12
- IL-6 promoter SNPs
- T allele of TNFα -857C/T SNP

Need Combinations of 2 or more SNPs

*** Reviewed in: Isaacs JD, Ferraccioli G. The need for personalised medicine for rheumatoid arthritis. Ann Rheum Dis 2011;70:4-7.**

Kang CP, Lee KW, Yoo DH, Kang C, Bae SC

The influence of a polymorphism at position -857 of the tumour necrosis factor-α gene on clinical response to etanercept therapy in rheumatoid arthritis.

Rheumatology 44:547-52, 2005

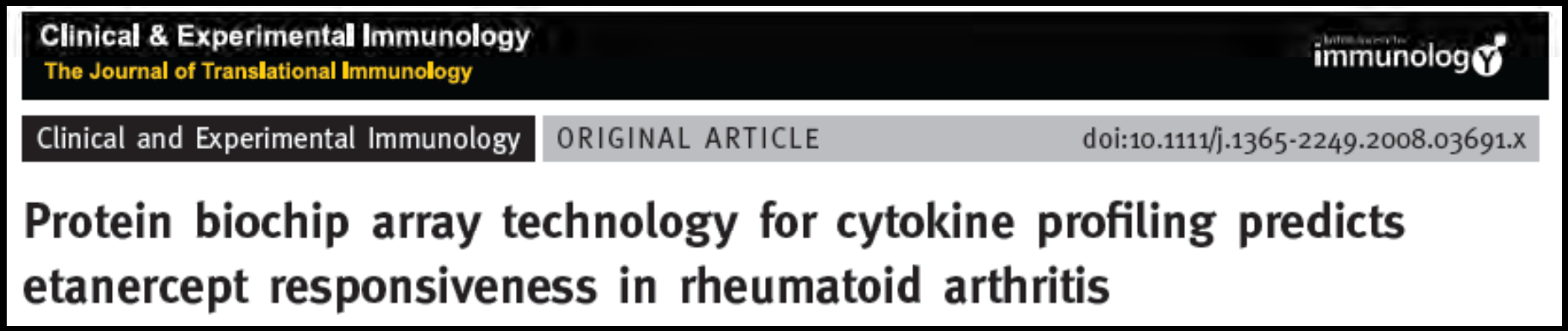
CONCLUSION:

RA patients with the T allele of TNFα -857C/T SNP respond better to etanercept therapy than homozygotes for the C allele, indicating that … this SNP could become a useful genetic marker for predicting responses.

Clinical , Proteomic and Cellular Markers Associated With Therapeutic Outcomes in RA

- Clinical Status and Demographic Features*
  - Baseline diseases activity and disability
  - Smoking status
  - Monotherapy
  - Rheumatoid factor and ACPA status
- Cytokine profiles
- Interleukin-7 receptor (IL-7R) pathway
- T cell receptor (TCR) signalling
- Memory T cells

*** Reviewed in: Isaacs JD, Ferraccioli G. The need for personalised medicine for rheumatoid arthritis. Ann Rheum Dis 2011;70:4-7.**



Fabre S, Dupuy AM, Dossat N, et al. Clin Exp Immunol 153: 188, 2008.

Fabre S, Guisset C, Tatem L, et al. Clin Exp Immunol 155: 395, 2009.

LETTERS

Ribonomics

nature medicine

A CD8$^+$ T cell transcription signature predicts prognosis in autoimmune disease

Eoin F McKinney[1,2], Paul A Lyons[1,2], Edward J Carr[1,2], Jane L Hollis[2], David R W Jayne[2], Lisa C Willcocks[1,2], Maria Koukoulaki[1,2], Alvis Brazma[3], Vojislav Jovanovic[4], D Michael Kemeny[4], Andrew J Pollard[5], Paul A MacAry[4], Afzal N Chaudhry[2] & Kenneth G C Smith[1,2]

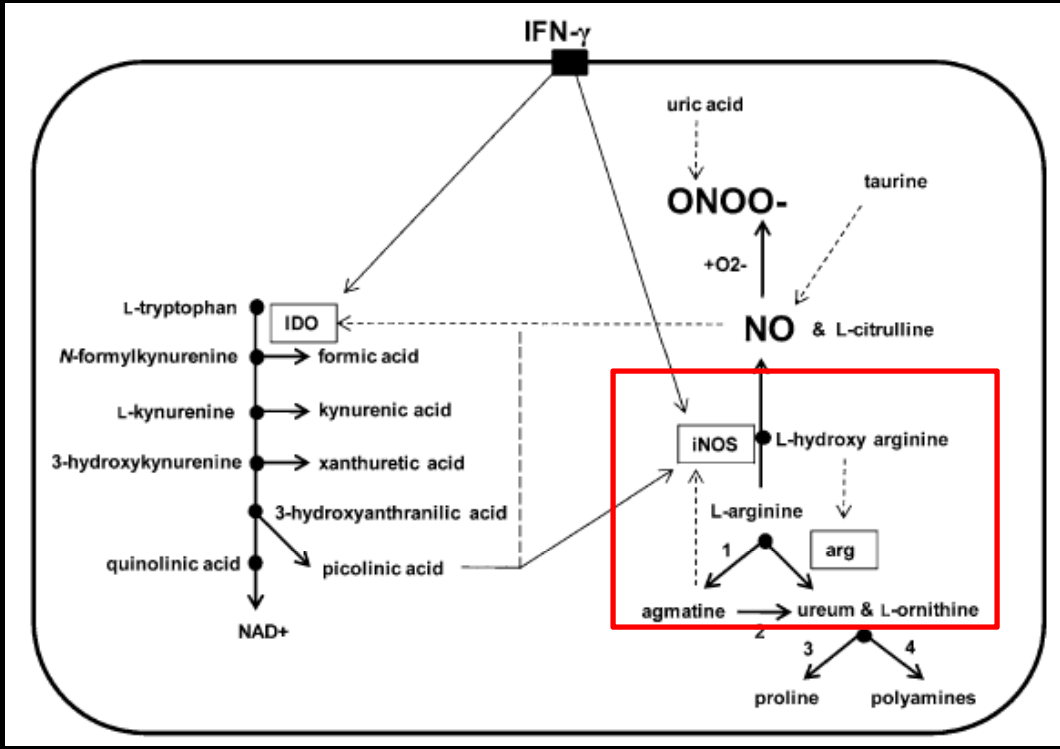
Nature Medicine 16: 586, 2010.

- **"... the subset of genes defining the poor prognostic group is enriched for genes involved in the interleukin-7 receptor (IL-7R) pathway and T cell receptor (TCR) signalling and those expressed by memory T cells."**

- **' (the poor prognosis group) can be identified by measuring expression of only three genes, raise the prospect of individualized therapy and suggest new potential therapeutic targets in autoimmunity.'**

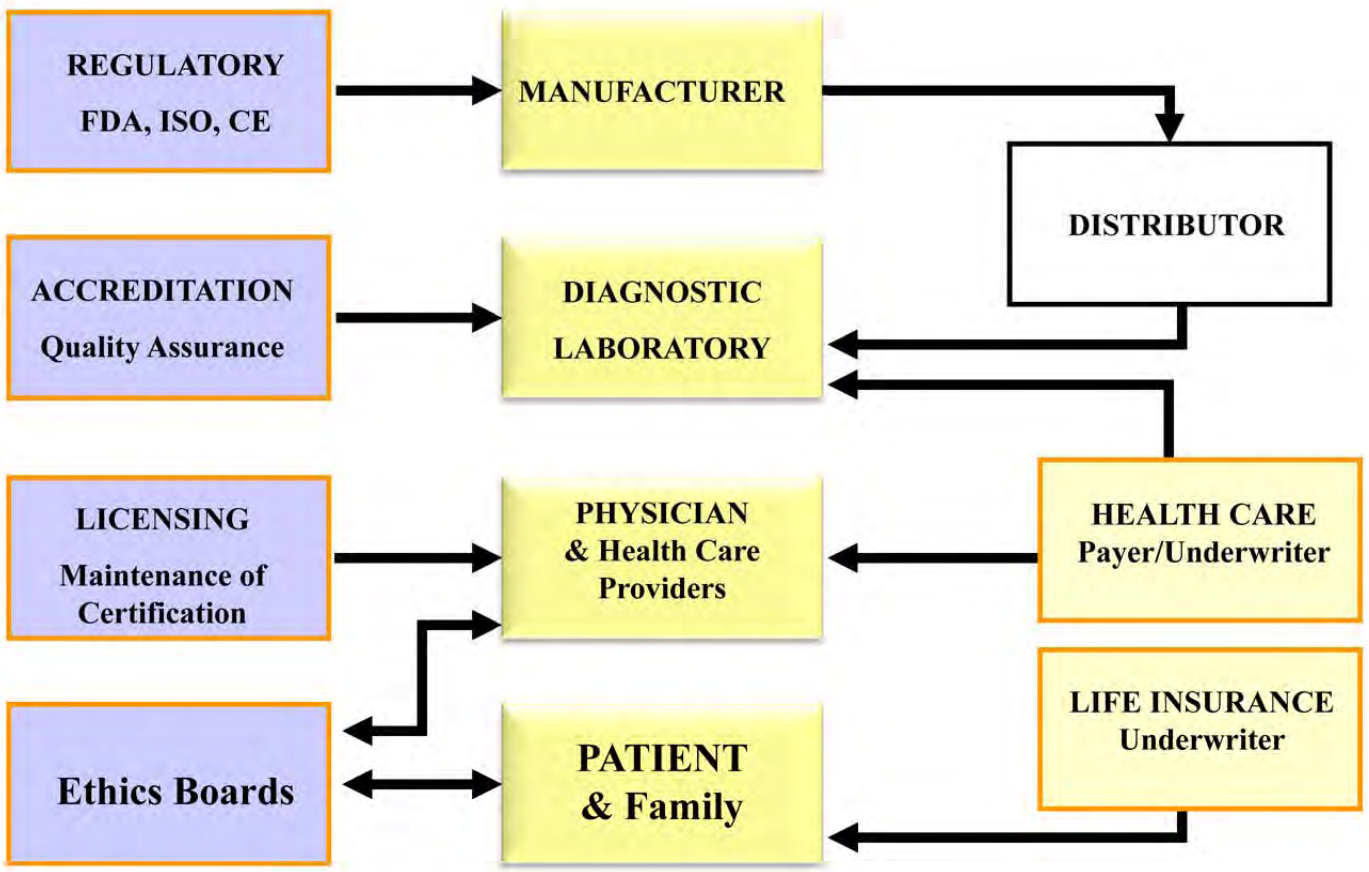
Metabolomics and the Immune Response

- + correlation > acetylglycoprotein signature > IFNγ
- – correlation > glucose signature
- NO > L-arginine/L-kynurenine > IFNγ

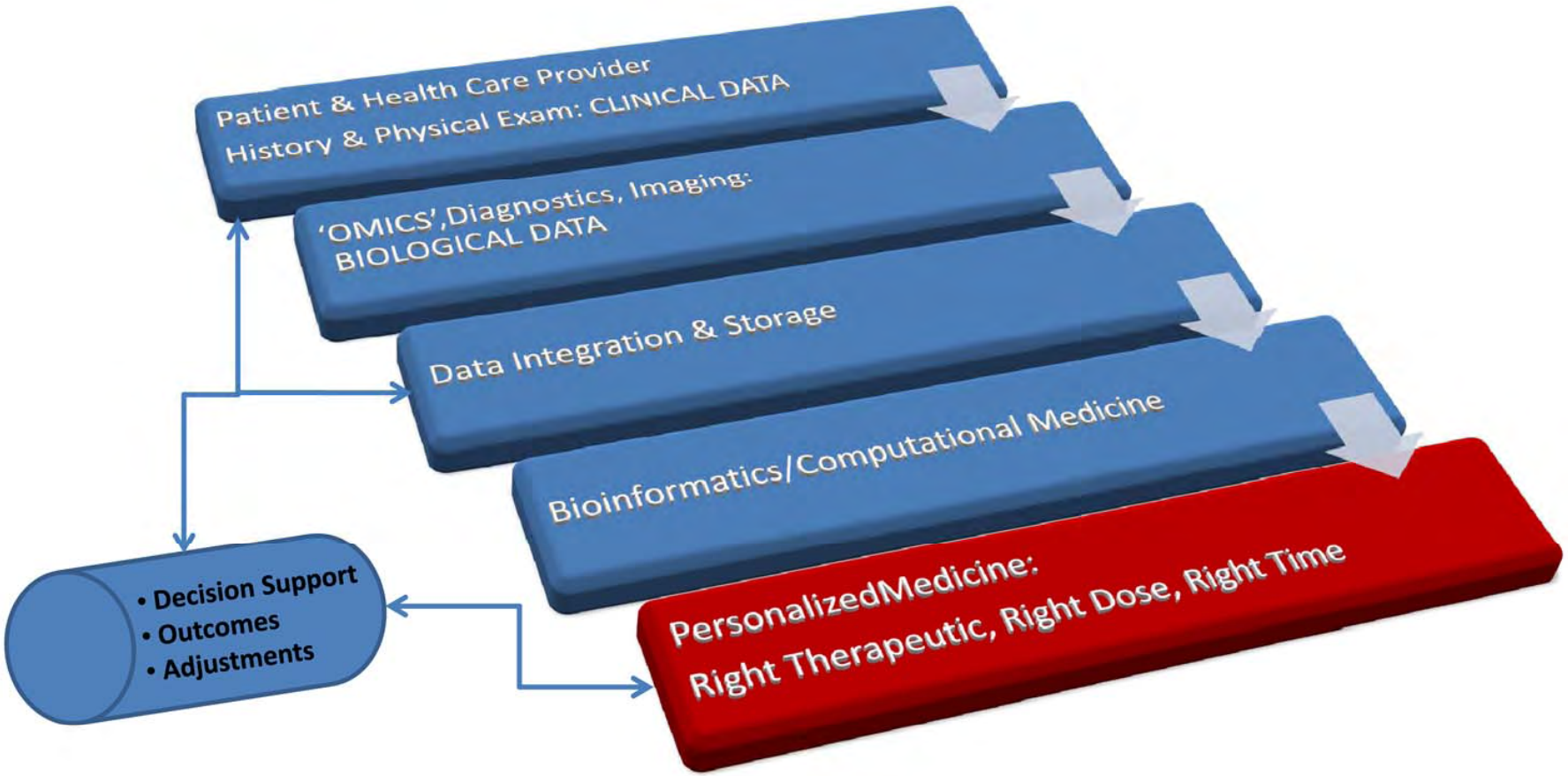


from: Saric J. Interactions between immunity and metabolism: contributions from the metabolic profiling of parasite-rodent models. Parastiology137: 1451, 2010

Complexity: The "Players" in PM



PM: Integrated Multidisciplinary Approach



The PM Bandwagon

- **Harvard: Center for Personalized Medicine**
- **Mayo Clinic**

http://healthpolicyblog.mayoclinic.org/2009/03/16/personalized-medicine-important-to-delivering-value-in-health-care/

- **Stanford University**
- **2007 'Senator' Barack Obama: Proposed The Genomics & Personalized Medicine Act**
- **British House of Lords Science & Technology Committee**

http://www.parliament.uk/business/committees/committees-archive/lords-s-t-select/genomic/

- **In Canada: Ontario, British Columbia and Alberta**
- **EPEMED**: European **PE**rsonalised **MED**icine Association
- **BioM/M4 (Munich)**

Sceptics abound…

RHEUMINATIONS | THOUGHTS FROM THE PHYSICIAN EDITOR

Let's Get Personal

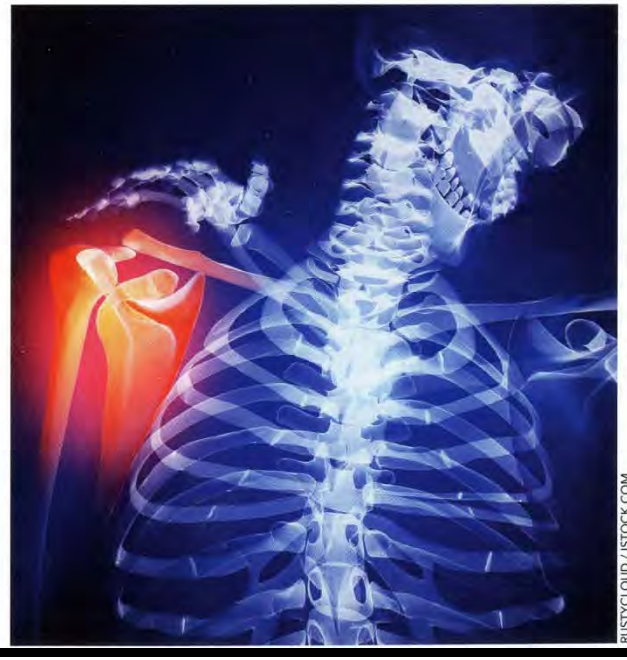
"The Rheumatologist", May 2009, page 6

Finding cost-effective solutions in the quest for personalized medicine

>> By David S. Pisetsky, MD, PhD

As recent history shows, research advances are not cheap, and focusing on the individual can be very expensive and, indeed, can skew healthcare funding and detract from outcomes for the population as a whole. As is well documented, despite healthcare expenditures that, on a per capita basis, dwarf those of other Western countries, American life expectancy is lagging, and childbirth mortality is shockingly high. In the absence of a comprehensive vision for allocation of healthcare resources, focusing on the individual can be very, very expensive, as reflected in the relentless growth of healthcare expenditures that outstrip inflation.

Except for vaccines, most new therapies or interventions to improve health outcomes increase, not decrease, costs. Often, it takes a bunch of smart pharmacoeconomists to develop models and juggle the math of quality-adjusted life years to demonstrate that certain treatments are worth the costs in a dollars-and-cents way. For new oncology



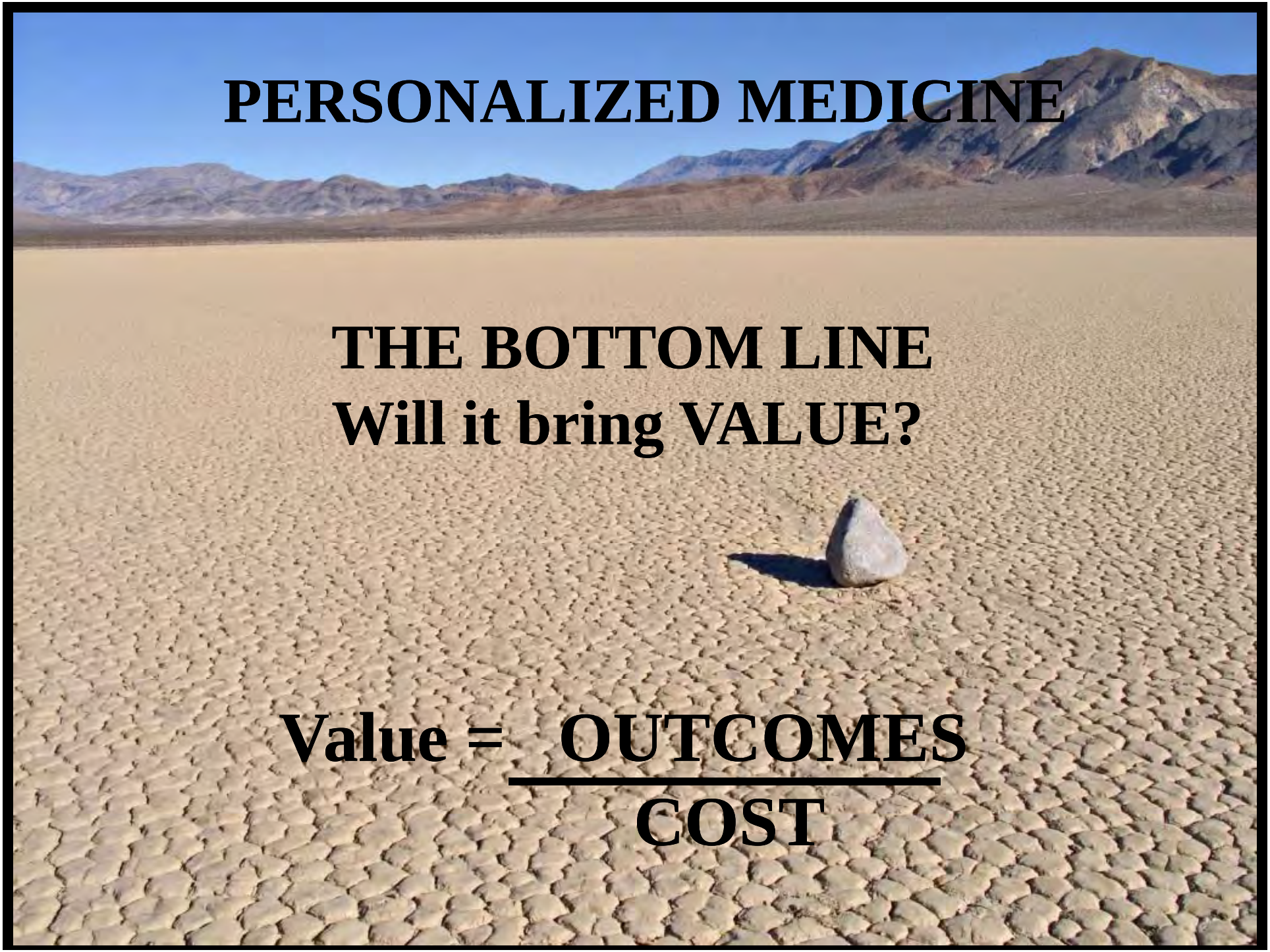
RUSTYCLOUD / ISTOCK.COM

Making Personalized Medicine Personal

Imagine now that Joe the Plumber has decided to move from cold and cloudy Ohio to the sunny, verdant, and congenial state of North Carolina. Joe has heard that homes are still going up in Holly Springs and Fuquay Varina and that plumbers are needed to install showers (times are tough here, too—no more Jacuzzis). Joe has also seen the light in sports and will forsake the Buckeyes for the Blue Devils or Wolfpack.

In his newfound home in the South, Joe works like a demon and, in a hurry one day, he yanks hard on his wrench and suddenly his shoulder erupts with pain. Joe comes to see me, and my exam shows limited range of motion and signs of impingement. Joe says that he wants an MRI because one of his buddies on the job with similar complaint had one and got better.

What should I do to provide the most cost-effective care to soothe the pain in Joe's throbbing shoulder? Do I think only about Joe? What is the place of systems-based prac-


PERSONALIZED MEDICINE
THE BOTTOM LINE
Will it bring VALUE?
Value = OUTCOMES / COST

Personalized Medicine: Cautionary Tale

Duke University misadventure

http://www.nytimes.com/2011/07/08/health/research/08genes.html

"I didn't say it was good for you,
I merely said there is nothing like it"

Through the Looking Glass