

# **Personal Genomics: The Impact on Obesity Interventions**

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# All Disease is a Result of Genes Interacting with the Environment...



Exercise



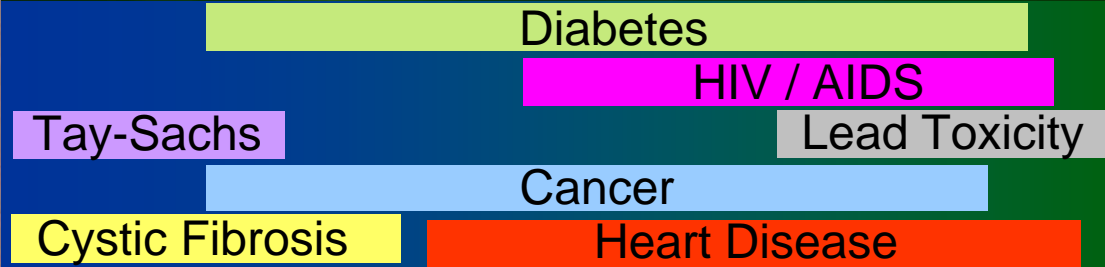
Diet



Drugs

Genetics

Environment



Infectious Disease

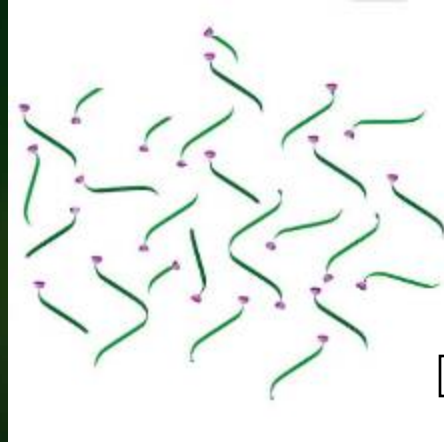
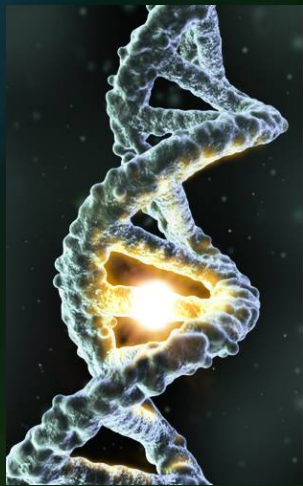
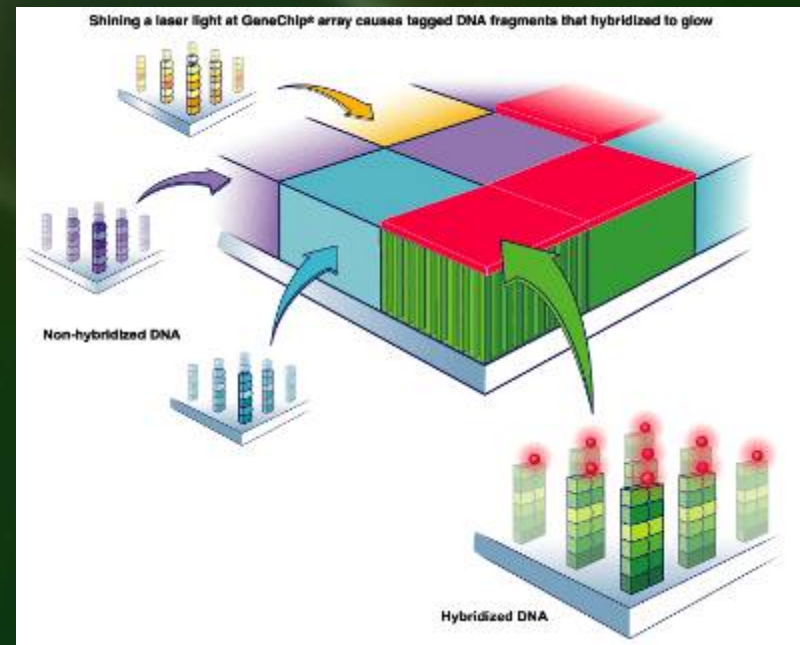
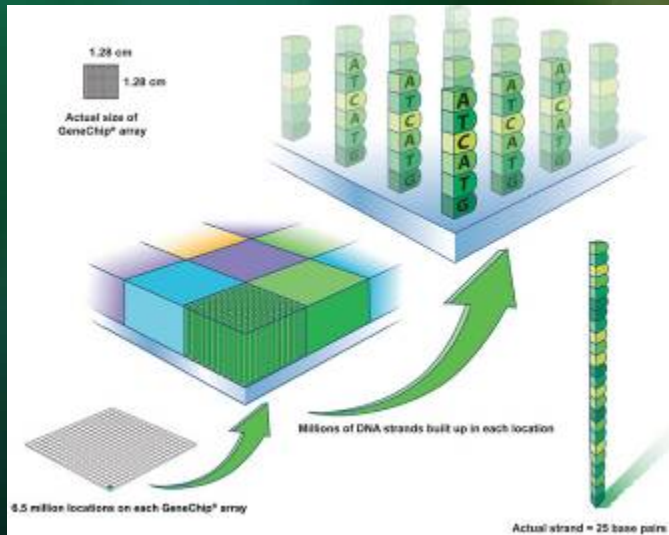


Lifestyle Choices

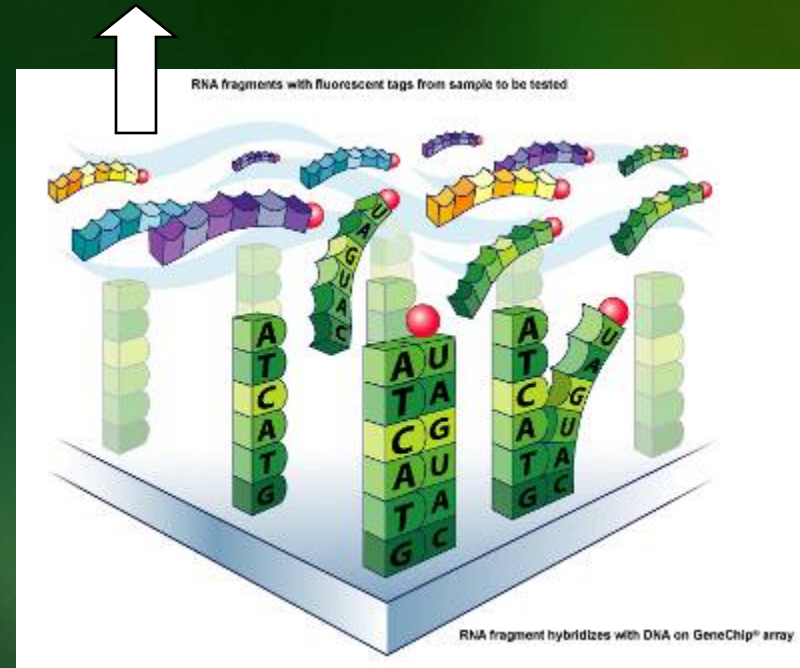


Exposures

# How to find a SNP...



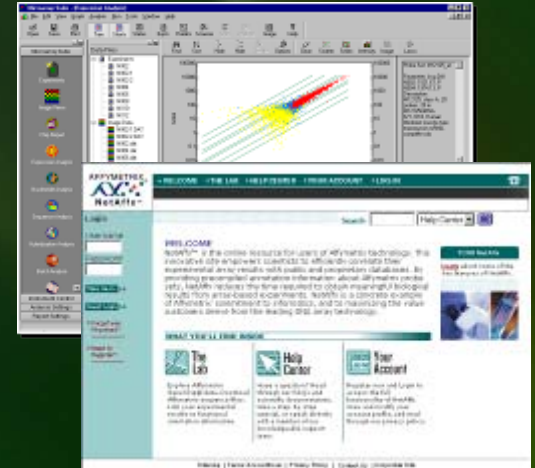
Fragmented,  
Replicated, Labeled  
RNA



# GeneChip System



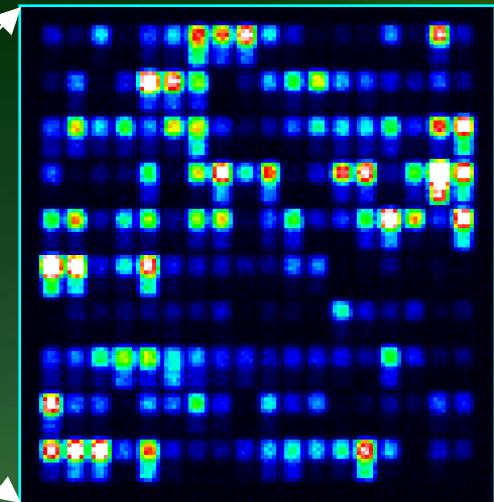
Fluidics Station



Software Data Analysis



Probe Arrays (chips)



# Genetic Array Technology

- **Exponential increase in genes scanned:**  
From a single gene (Tay Sachs, Cystic Fibrosis)...  
To 1,000's of genes & 100,000's genetic variants
- **Exponential reduction in Cost:**  
From a single gene for \$10,000...  
Dozens of genes for \$3,000...  
Thousands of genes for \$1,000...  
To Millions of genetic variants for \$300
- **Complete individual genome sequence**  
From \$100,000 to \$5,000 next year?  
To \$1,000 within 5 years?

*Cost of screening a single genetic variant:  
From \$10,000 to 1/100<sup>th</sup> of a penny*



**A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants**

Laura J. Scott, *et al.*

*Science* **316**, 1341 (2007);

DOI: 10.1126/science.1142382

- **T2D is “the geneticist’s nightmare”**
- **Identify genetic variants that increase the risk of Type 2 Diabetes in Finnish glucose-tolerant and type 2 diabetic participants**
- **Constructed 10 robust and replicated T2D associated genetic loci**
- **Each gene discovery leads to a pathway that contributes to pathogenesis**
- **All resultant proteins and pathways are potential drug targets for prevention and treatment**



**Replication of Genome-Wide Association Signals in UK Samples Reveals Risk Loci for Type 2 Diabetes**

Eleftheria Zeggini, *et al.*

*Science* **316**, 1336 (2007);

DOI: 10.1126/science.1142364

- **Diabetic and normal populations in the UK**
- **Identified the genetic architecture of T2D**
- **Complex interaction by multiple genetic variants working together to cause T2D**
- **Validates genome wide association mapping and benefits of aggressive data-sharing efforts**
- **The T2D loci identified emphasize the importance of pathways influencing pancreatic beta cell development, regeneration, and function**

# Variation in *FTO* contributes to childhood obesity and severe adult obesity

- **Fat Mass and Obesity Associated Gene (FTO)**
- **Consistently & strongly associated with early-onset and severe obesity (adults & children)**
- **At-risk haplo-type yields a proportion of attributable risk of 22%**
- **Target for further study and intervention**
- **Does not provide an excuse, but rather a reason for some of obesity...thus can help with guiding therapy**

## Frequency of the C34T mutation of the *AMPD1* gene in world-class endurance athletes: does this mutation impair performance?

Juan C. Rubio,<sup>1</sup> Miguel A. Martín,<sup>1</sup> Manuel Rabadán,<sup>2</sup> Félix Gómez-Gallego,<sup>3</sup> Alejandro F. San Juan,<sup>3</sup> Juan M. Alonso,<sup>4</sup> José L. Chicharro,<sup>5</sup> Margarita Pérez,<sup>3</sup> Joaquín Arenas,<sup>1</sup> and Alejandro Lucia<sup>3</sup>

<sup>1</sup>Research Centre, University Hospital 12 de Octubre; <sup>2</sup>Department of Physiology, Sport Medicine Center, Higher Sports Council; <sup>3</sup>European University of Madrid; <sup>4</sup>Medical Department, Spanish Track and Field Federation; and <sup>5</sup>Complutense University, Madrid, Spain

- Intense exercise causes Adenosine Monophosphate (AMP) accumulation
- AMP deaminase regulates muscle energy metabolism and has a highly regulated expression (genetically influenced activation)
- The mutation of AMPD1 limits endurance performance & impairs exercise capacity, (maximal oxygen uptake or ventilatory thresholds)
- Examined male Caucasian (Spanish) elite athletes and non-athletes
- Frequency of mutation was 50% lower in elite athletes than non-athletes
- Endurance performance did not differ within elite athlete carriers or non-carriers (Once elite athlete status is achieved, the mutation does not appear to limit endurance)
- This mutation will make it harder to get to elite-athletic status, however once you get there it's effect on muscle metabolism is negated

Research

Open Access

## Physiogenomic comparison of human fat loss in response to diets restrictive of carbohydrate or fat

Richard L Seip<sup>\*1,2</sup>, Jeff S Volek<sup>3</sup>, Andreas Windemuth<sup>1</sup>, Mohan Kocherla<sup>1</sup>, Maria Luz Fernandez<sup>4</sup>, William J Kraemer<sup>3</sup> and Gualberto Rúaño<sup>1</sup>

- Examined 53 SNPs involved in food intake, energy homeostasis, and fat cell regulation
- Related to % body-fat loss with low fat and low carbohydrate diets
- Fat loss with LF and LC regimes have distinct mechanisms and different pathways....thereby different success rates
- Successful treatment (LF or LC diets) depends in part upon genetically inherited metabolic responses
- Genetic factors predict dietary success
- DNA guided dietary recommendations

# Predictive Medicine

- **New Specialty of Medicine (Genetics plus Preventive Medicine)**
- **Paradigm shift from generalized (population) guidelines in Medicine (Age, Ethnicity, and Gender) to the individual**
- **Like a Radiologist for DNA**
  - **Provides comprehensive genetic testing and analysis, report, guidance, and consultation for the generalist**
- **Predictive Medicine Specialist**
  - **Trained to understand all the intricacies of the technology, interpretation of the data, based on current published and reliable data**
- **Summarize the data so that the primary care giver doesn't have to become the expert in the field**



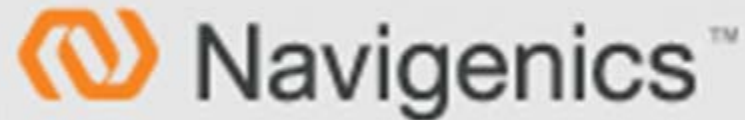
**Technology- Internet Play**  
**Silicon Valley, California**  
**As Google is to the internet...**  
**...23andme is to genetic testing**  
**Accessible and affordable to everyone**  
**Social networking---not sure I want to**  
**share my Spit (DNA) with others?!**



**Physician – Clinical Play**  
**Los Angeles, California**  
**Extensive database**  
**All services include genetic**  
**Counselor & physician consultation**  
**Cost and availability??**



**Iceland**  
**Research Play**  
**Downsizing**



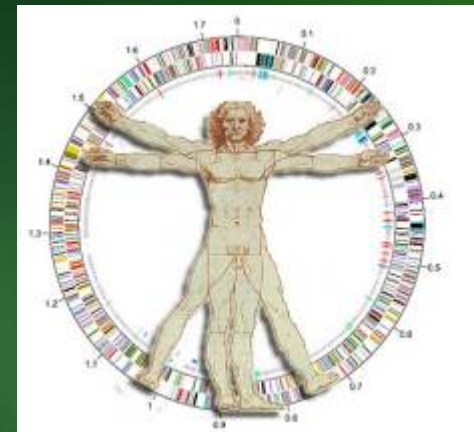
**Venture Capital Play**  
**Redwood Shores, California**  
**CLIA certified**  
**Comprehensive disclaimer**  
**Planning Genetic Counseling service**  
**Partnering with Mayo Clinic**

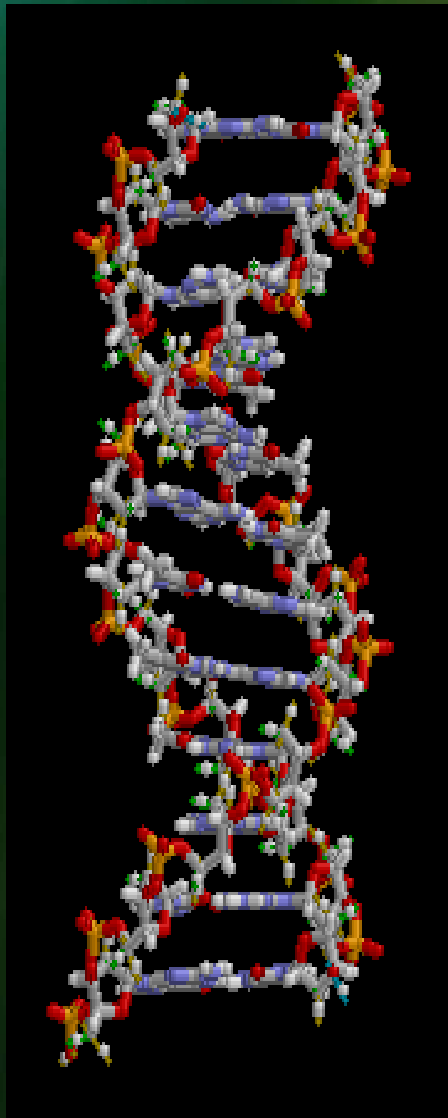
# **High-Resolution Personalized (DNA Directed) Obesity Interventions**

- **Dietary plans (LF or LC)**
- **Exercise regimens (Muscle metabolism)**
- **Drugs**  
(Target genetically influenced pathways)
- **Individualized counseling**  
Hyperphagia syndromes, Leptin receptor
- **Match the diet, exercise, and pharmacologic therapies to the patient's genetic "contour"**

# Goal of DNA Guided Obesity Intervention

The most individualized (genetically optimized) diet, exercise, and pharmacologic program for Obesity Intervention





# Action on Obesity Intervention Model

(Adapted from Dr. Abby King, Stanford)

- AOO task force represents all levels of **bidirectional model**

