

Risk Assessment for Complex Genetic Disease

Dietrich A. Stephan, PhD
Founder, Navigenics



Navigenics

No clinical implementation infrastructure for risk ...

- 10 years of experience with microarray platforms
- >100,000 expression profiles run
- >100,000 SNP arrays run (10k, 100k, 500k, >1M)
- Data warehousing solution
- First Affymetrix “Genomics Collaborators” in 2000
- First Affymetrix “Center of Excellence” in 2001
- First Affymetrix “TransMed” site in 2004
- NHLBI Programs in Genomic Applications (PGA)
- NEI intramural contract site
- NCI funded ALL catalog
- NIA funded Alzheimer’s disease catalog
- NIH Neuroscience Microarray Consortium
- Autism Genome Project (AGP) Genotyping Site
- Center for Cancer Nanotechnology Excellence
- NCI funded Biomarkers Program
- FIND Consortium Genotyping Site
- ADNI Genotyping Site
- GAIN Genotyping Site
- ENDGAME
- Genotyping technologies (Illumina, Affymetrix, Sequenom)
- Sequencing technologies (Solexa, ABI SOLID, 454)



Navigenics, Inc.

The private sector plays a *critical and necessary* role in disseminating research findings. This is not *de facto* at odds with quality, conscience, and responsibility.

| **Vision:**

To **improve individuals' health** across the population by educating, empowering and motivating people to take action to prevent the onset of disease or lessen its impact.

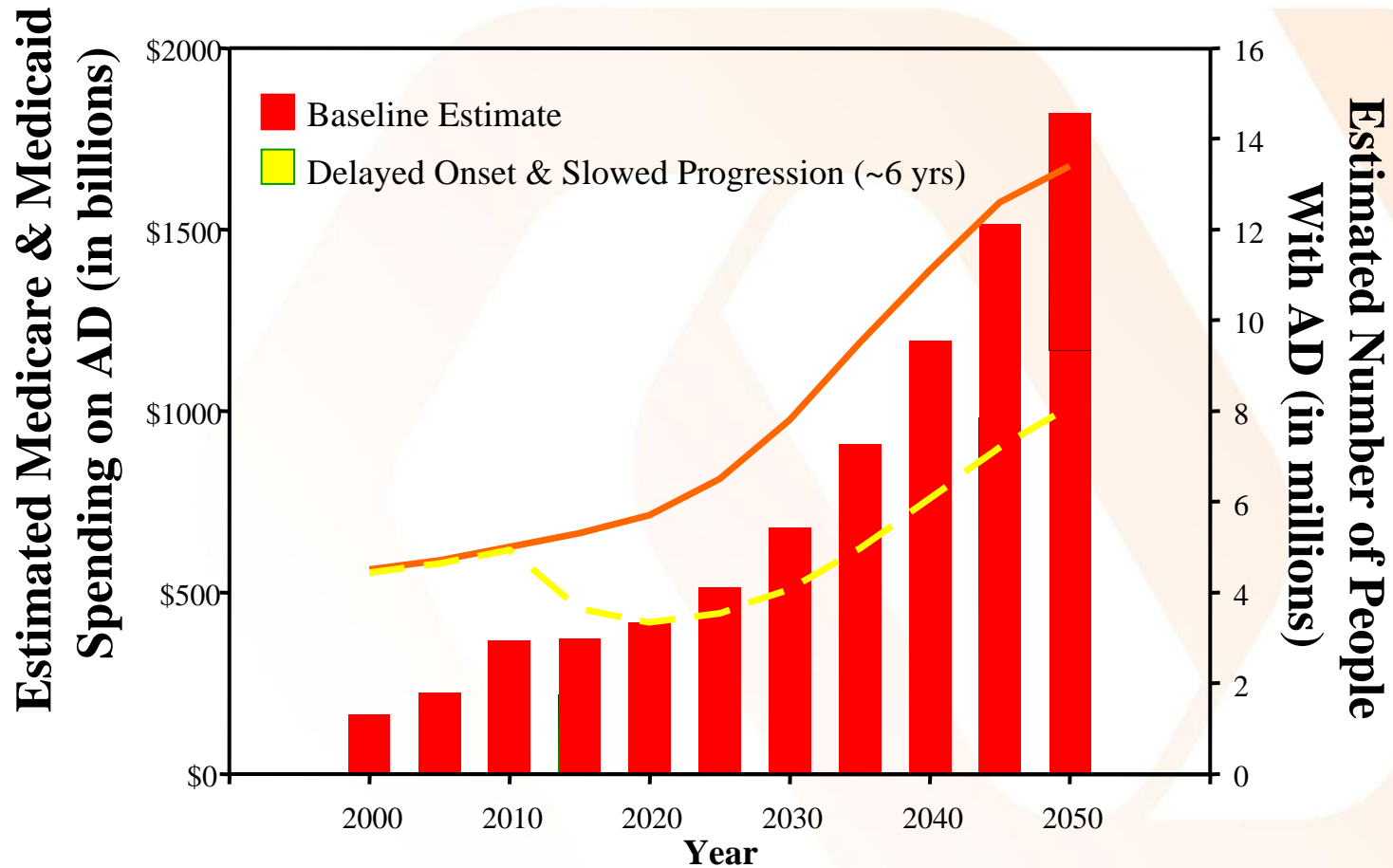
| **The Navigenics Health Compass:**

Navigenics Health Compass is an innovative service which informs individuals of their **genetic predisposition** for a variety of **common diseases**, and provides guidance and information on how to **delay** or **prevent** the onset of those diseases, to live a longer, healthier life.

I would like to convince you that ...

- | We are facing a health care crisis from CCND in this generation – and prevention is the only feasible solution
- | Validated “genetic risk factors” are not so different than validated environmental risk factors
- | Genetic risk factors can be used to refine risk and drive additional focused prevention behaviors and early detection paradigms
- | Delivery of the information in an accurate and private fashion to the public is necessary to meet timelines

Estimated Savings in Prevalence & Costs of AD with Delayed Onset/Progression



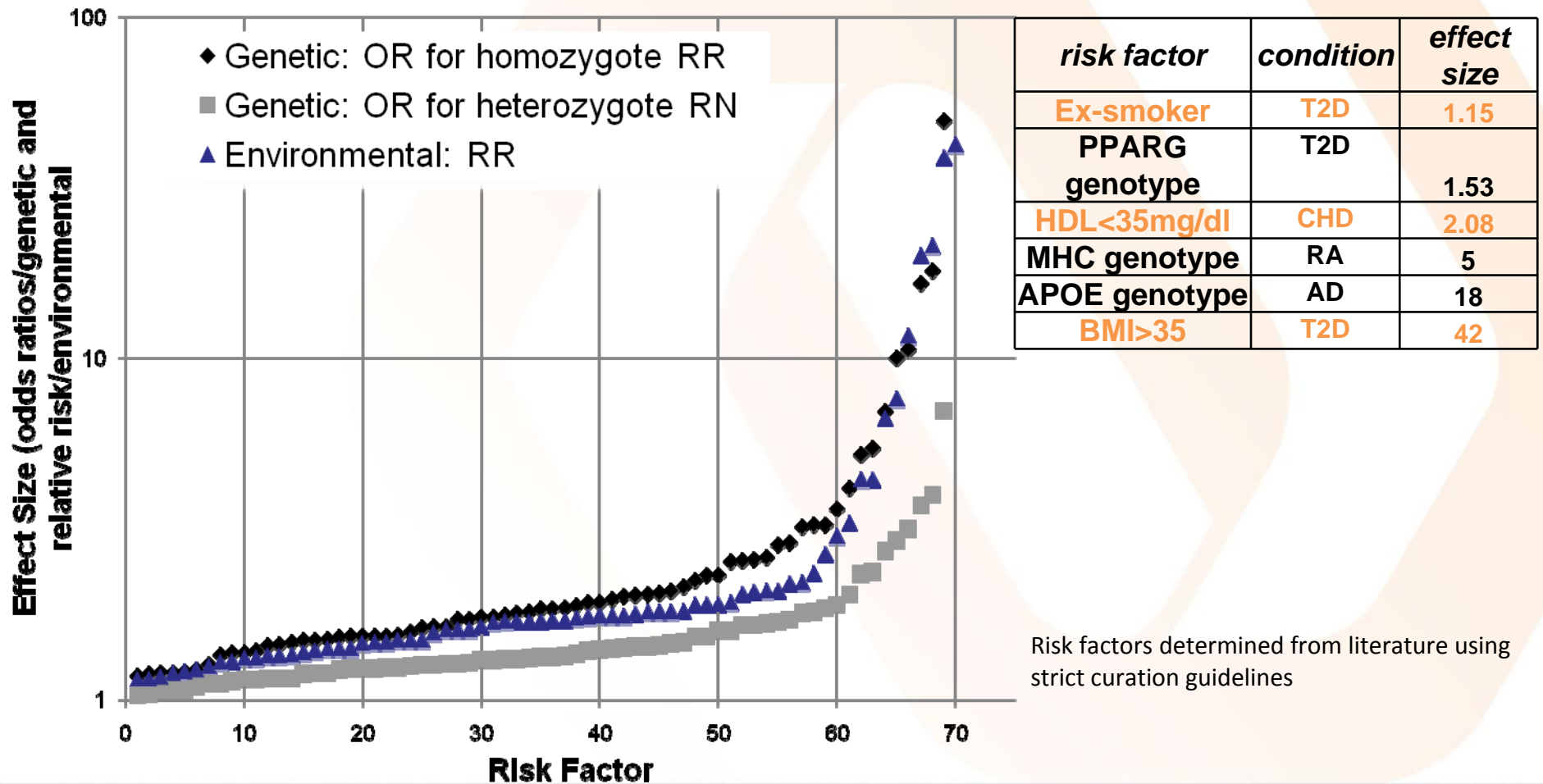
Adapted from The Lewin Group Report, June 2004, "Saving Lives. Saving Money: Dividends for Americans Investing in Alzheimer Research," The Alzheimer's Association (http://www.alz.org/Resources/FactSheets/Lewin_FullReport1.pdf)

In the USA alone...

- | CCND as a class will linearly increase in prevalence due to 1) more people, and 2) increased lifespan
- | Medicaid is on track to be depleted in ~10 years due to the baby boomer generation*
- | >40% GDP going to healthcare in the next 30 years*

*HHS Secretary Michael Levitt and Alan Greenspan, 180 Conference, 2008

Distribution of effect sizes for genetic and environmental risk factors



State-of-the-art clinical risk assessment: MI

Grade 2-4 hypertension	1.92
LDL>160	1.74
HDL<35	1.46
Smoker (last 12 mo)	1.71
T2DM	1.47
No exercise	1.39

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9p21	1.72
MTHFB1L	1.53

5-Step Service Offering

1

Customer Acquisition



2

Laboratory



3

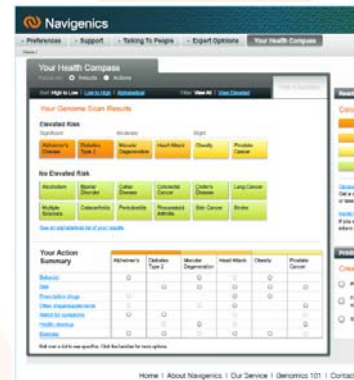
Bioinformatics

```

ATACCGCTGGCCCTT
TGGCATTACCTATGA
AGATTGCTTCAGCCA
GCGTCAGTTTCAACC
TGTACGCTAGTGTGT
TTCTACTCACGTGTC
TCAGCATTGATCGAT
ACCTGGCTATTGTTC
ACCCAATGAAGTCCC
    
```

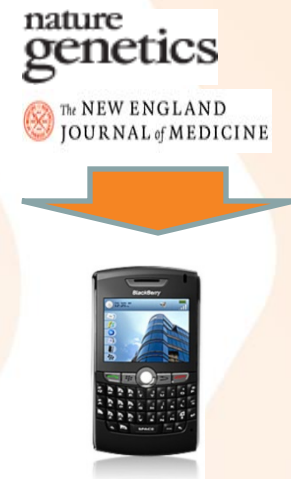
4

Personalized Web Portal



5

Ongoing Service



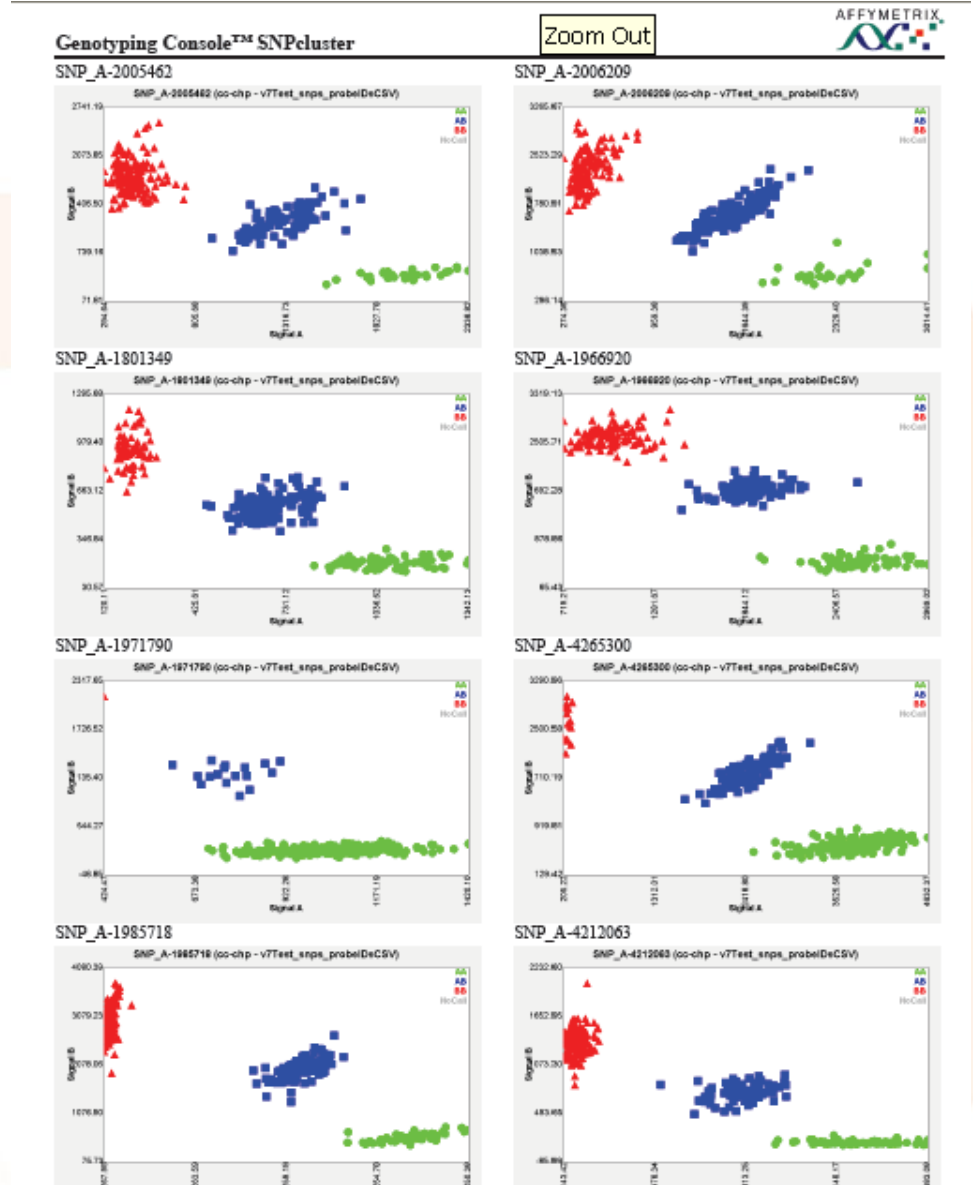
FUTURE: Full genome sequencing, copy number analysis, methylation status leading to personalized exposure mitigation strategies and biomarker monitoring programs fully integrated into the established health care system.

Common Arguments:

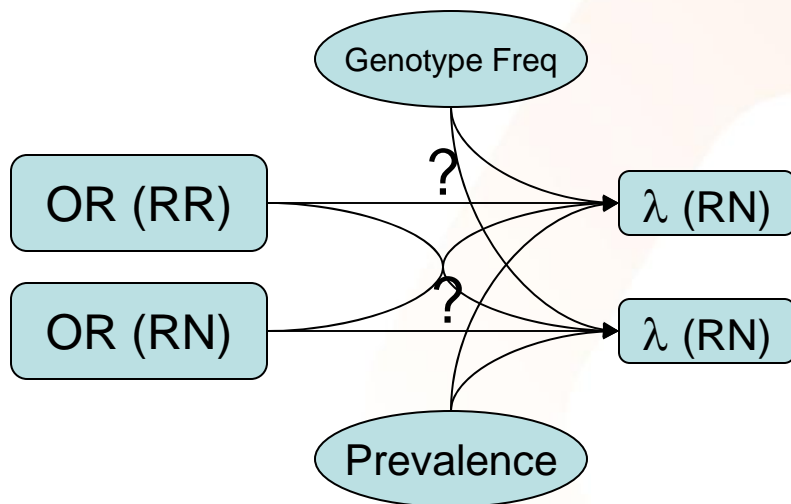
- | Analytic validity – is the genotype produced from the assay (or analytic) accurate?
- | Clinical validity – is the risk score accurate?
- | Clinical utility – is the test useful in a clinical setting?
Do individuals change their behavior?
- | Physicians are not equipped
- | Professional access
- | Regulation
- | Security/Privacy
- | Long term effect on genetic research/Commercial exploitation

QUALITY

CLIA and stringent QC lab
Captured perfectly
Per SNP algorithm checks
Per SNP concordance
H-W equilibrium checks



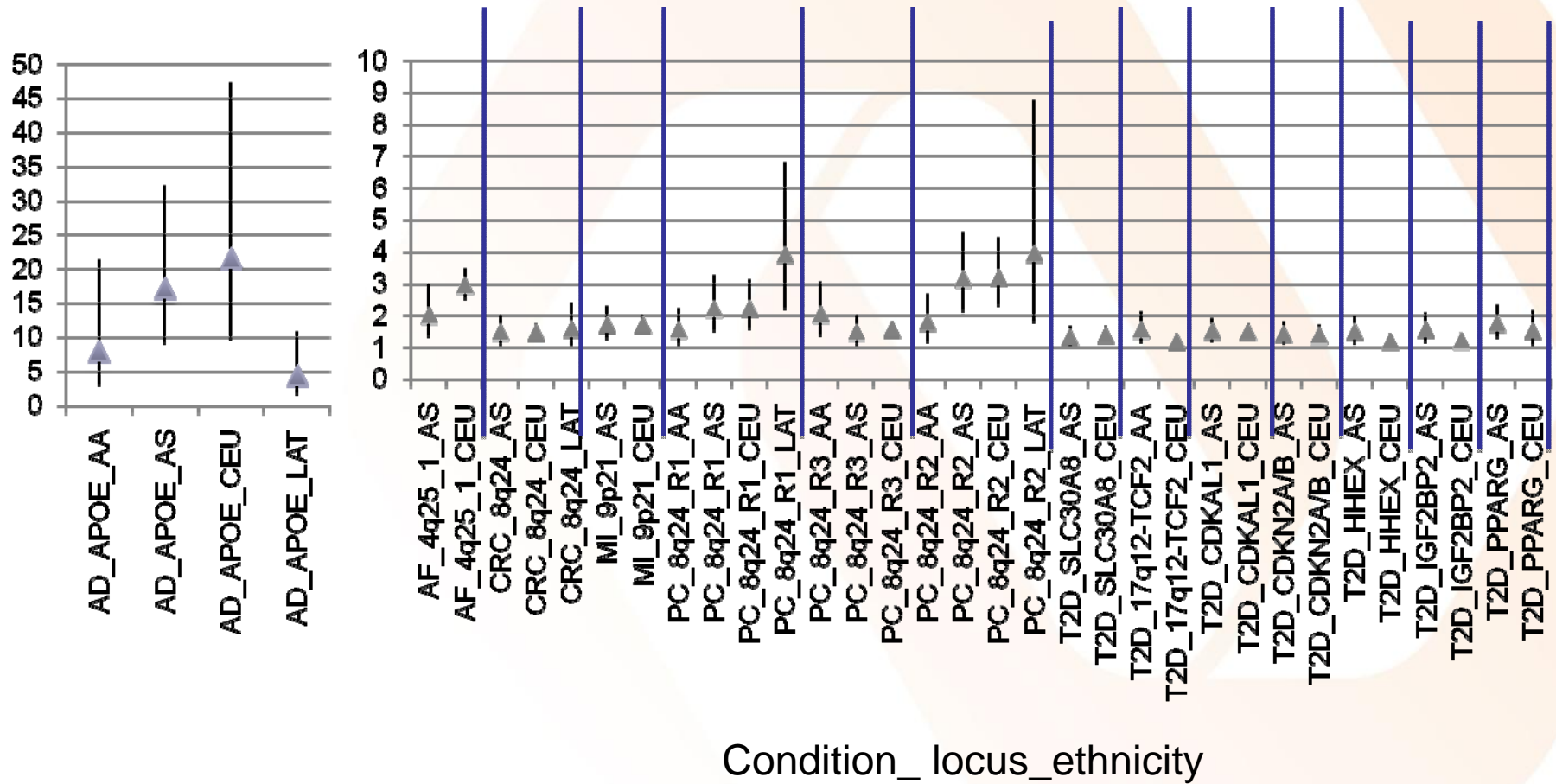
Finding the Relative Risk - see full details at navigenics.com



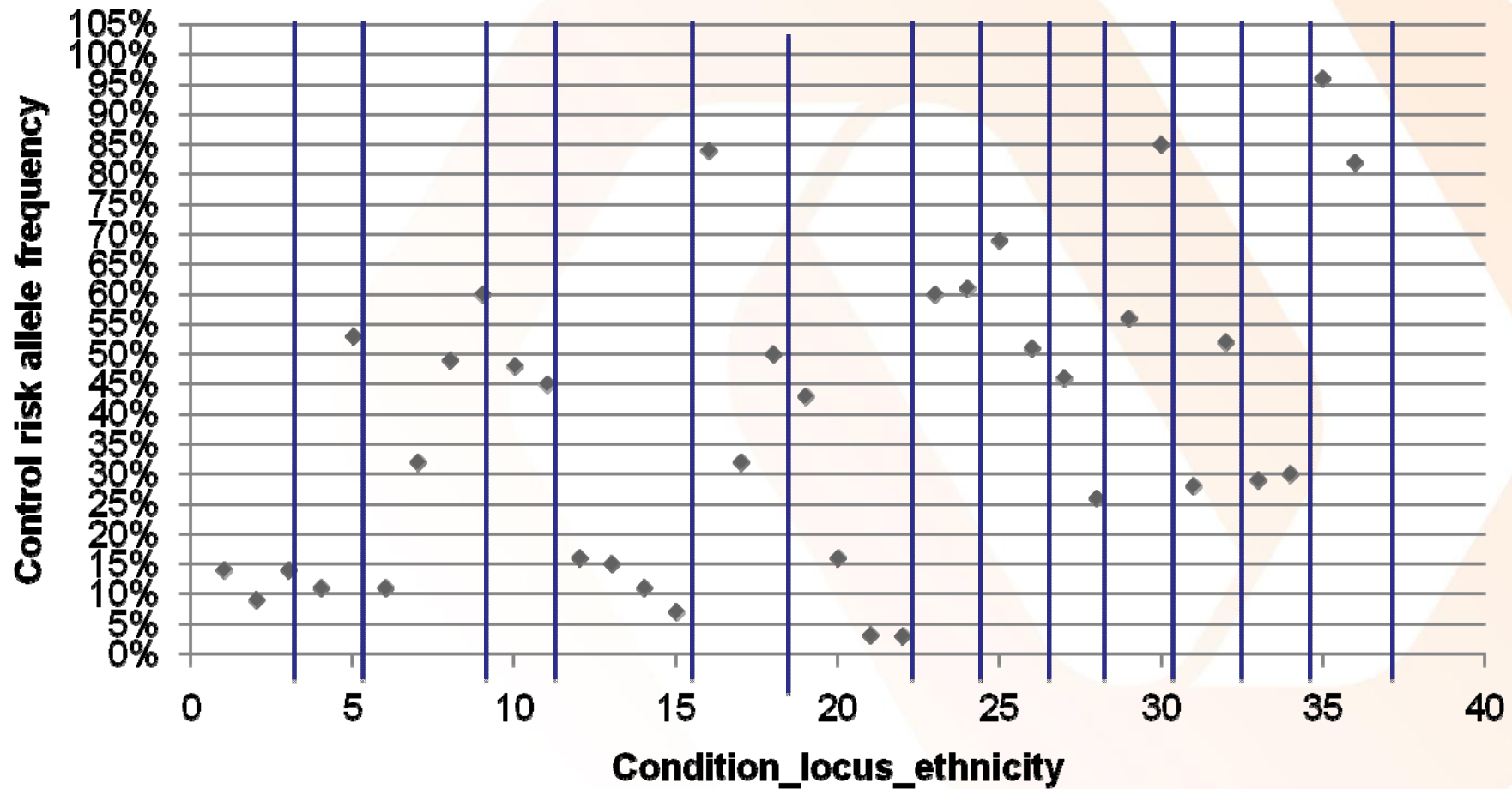
$$C = \sum_{i=0}^k f_i \lambda_i$$
$$1 = \sum_{i=0}^k \frac{OR_i f_i}{C - p + OR_i p}$$

- We normally get genotypic odds ratios RR/NN, RN/NN
- Using genotype frequencies and prevalence, we derive a set of quadratic equations – the solution provides the relative risks.

Odds-ratios for different ethnicities are usually similar

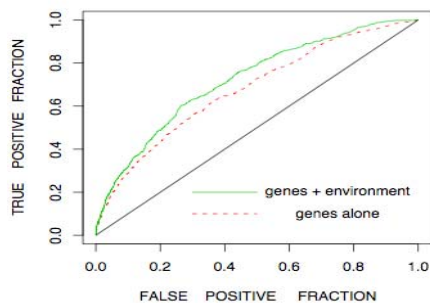
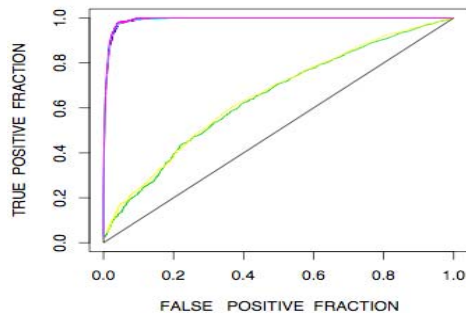
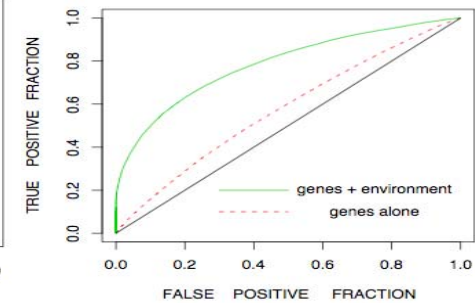
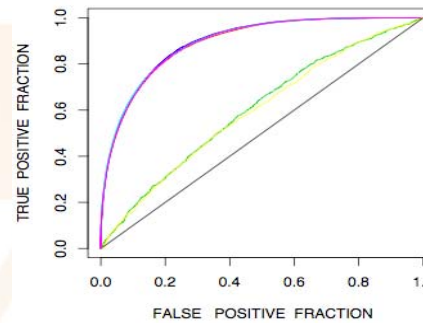


Risk allele frequencies in controls for different ethnicities are usually different



Estimated Genetic Variance we have Today

- Large effect sizes have been found
- No GxE



Disease	Relative risk of homozygous risk	Relative risk of heterozygous	Estimated number of unknown variants	Fraction of genetic variation explained by known variants out of the entire GENETIC variation
Type 2 Diabetes	1.10	1.05	1600	7%
Crohn's Disease	1.10	1.05	13958	4.4%
Rheumatoid Arthritis	1.10	1.05	6237	14.4%

Navigenics' competencies & partnerships

Core competencies

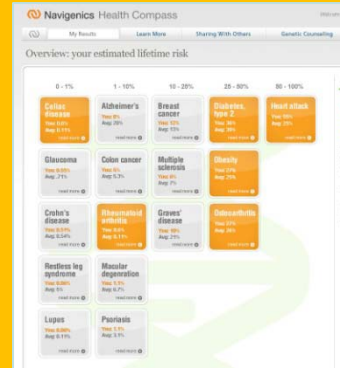
Platforms and assays



Scientific and Clinical Curation



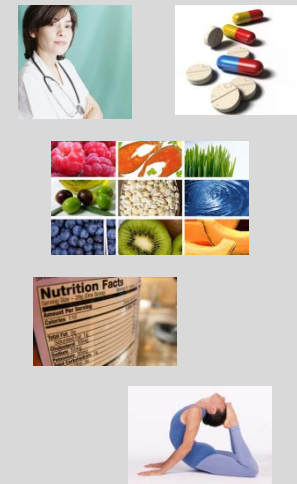
Personalized Web Portal



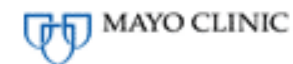
Customer Experience



Lifestyle and Behavior



Partnerships



Partnerships

Physicians Are Not Equipped – Education:

- | **TOP DOWN:** Ongoing education of the “physician’s physician” at leading clinical centers in the country such as the Mayo Clinic, Scripps, Harvard, Duke, and the Cleveland Clinic.
- | **DIRECT ENGAGEMENT:** Navigenics sponsored Genomic Medicine CME training program with Medscape. This course generated >5,000 readers within the first two months, with 99.6% of readers completing the entire course
- | **BOTTOM UP:** A physician portal to the Navigenics product is provided. This site explains additional scientific details that the physician can use to learn about the product and how it can help their patients.

Health Compass: Results Overview

People want to know what this means for them

Navigenics Health Compass Welcome Jane098 | [Manage Profile](#) | [Log Out](#)

My Results | Learn More | Sharing With Others | Genetic Counseling | Member Services

Overview: your estimated lifetime risk last updated on 1/22/08

0 - 1%	1 - 10%	10 - 25%	25 - 50%	50 - 100%
Celiac disease You: 0.6% Avg: 0.11% read more	Alzheimer's You: 8% Avg: 20% read more	Breast cancer You: 12% Avg: 13% read more	Diabetes, type 2 You: 36% Avg: 39% read more	Heart attack You: 55% Avg: 25% read more
Glaucoma You: 0.55% Avg: .71% read more	Colon cancer You: 5% Avg: 5.3% read more	Multiple sclerosis You: 6% Avg: 7% read more	Obesity You: 27% Avg: 25% read more	
Crohn's disease You: 0.51% Avg: 0.54% read more	Rheumatoid arthritis You: 0.6% Avg: 0.11% read more	Graves' disease You: 10% Avg: 21% read more	Osteoarthritis You: 27% Avg: 26% read more	
Restless leg syndrome You: 0.06% Avg: 5% read more	Macular degeneration You: 1.1% Avg: 6.7% read more			
Lupus You: 0.06% Avg: 0.11% read more	Psoriasis You: 1.1% Avg: 3.1% read more			

Key to your results

Condition name

Your results

Population average

Each box gives your estimated lifetime risk of that condition, compared with the average risk for your gender. Orange boxes indicate either:

- Your overall risk is greater than 25 percent or
- Your risk is more than 20 percent above average for that condition.

We will e-mail you as new scientific research refines your results.

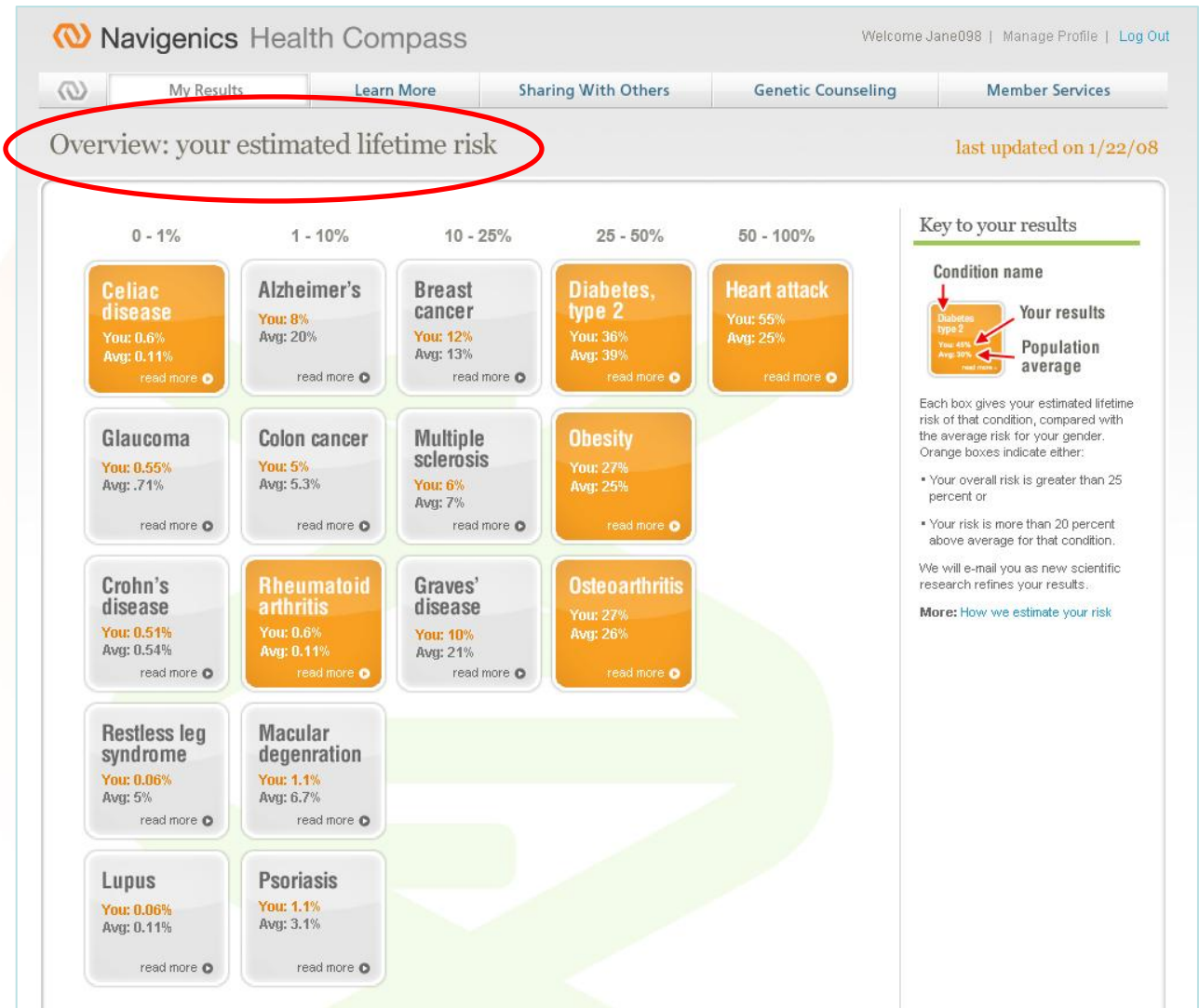
More: [How we estimate your risk](#)

Health Compass: Results Overview

People want to know what this means *for them*

Estimated Lifetime Risk

Take the general population LTR and refine based on the individual's genotypes



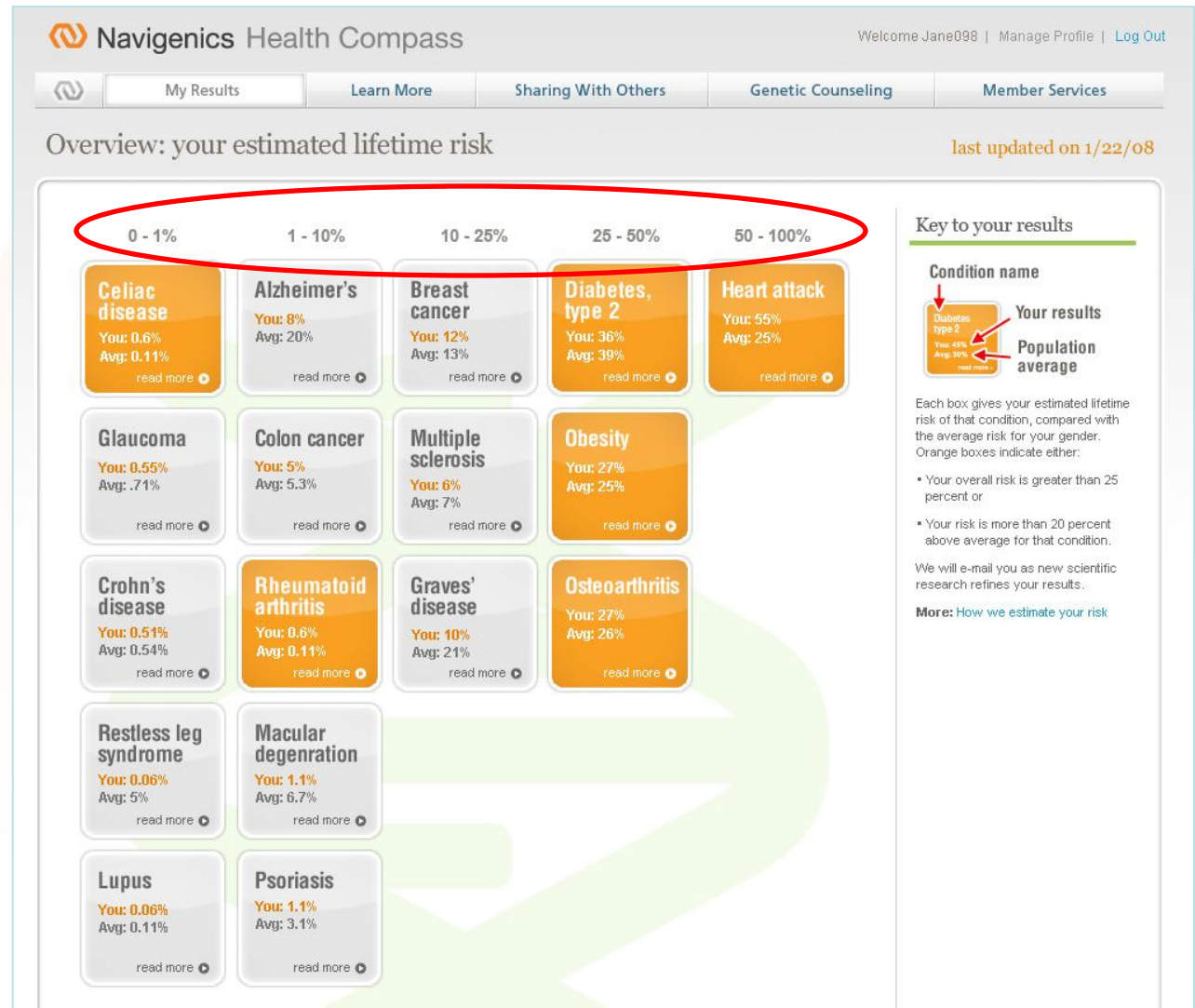
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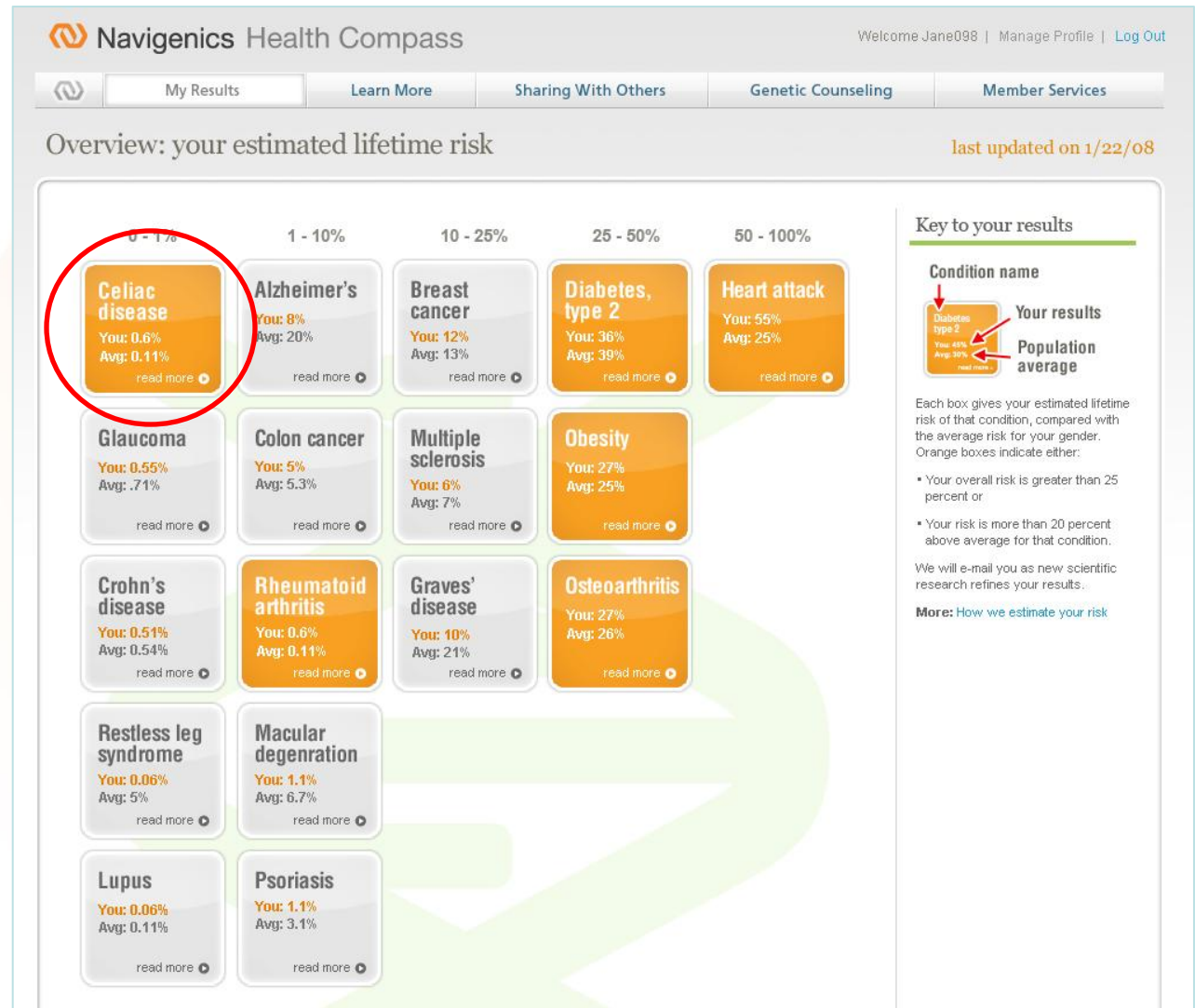
Place the conditions into "buckets" to highlight the overall LTR estimate



Health Compass: Results Overview

Orange Box

Estimated LTR is 20% or more than the general population

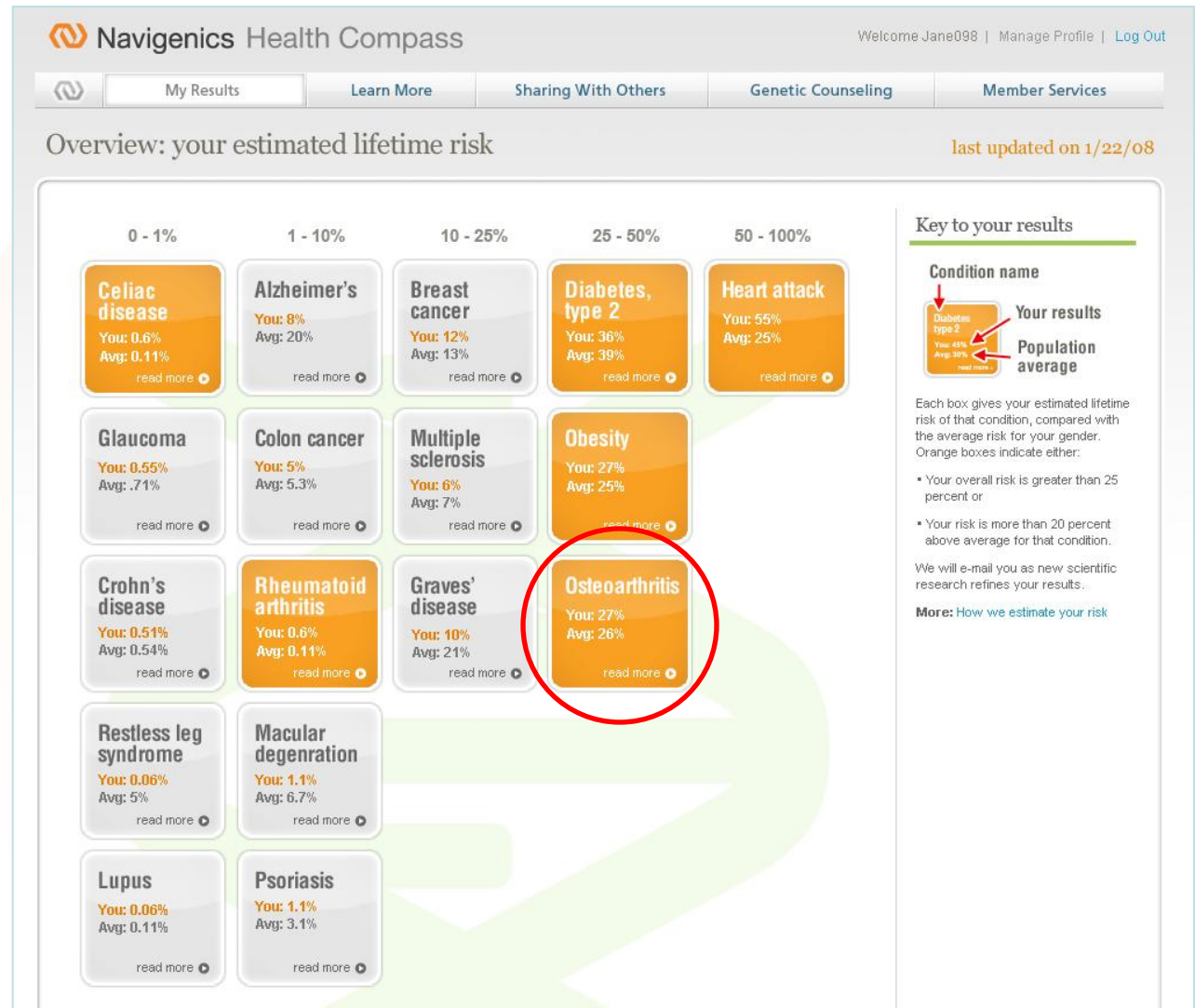


Health Compass: Results Overview

Orange Box

Estimated LTR is 20% or more than the general population

Estimated LTR is more than 25% total



Health Compass: Results Overview

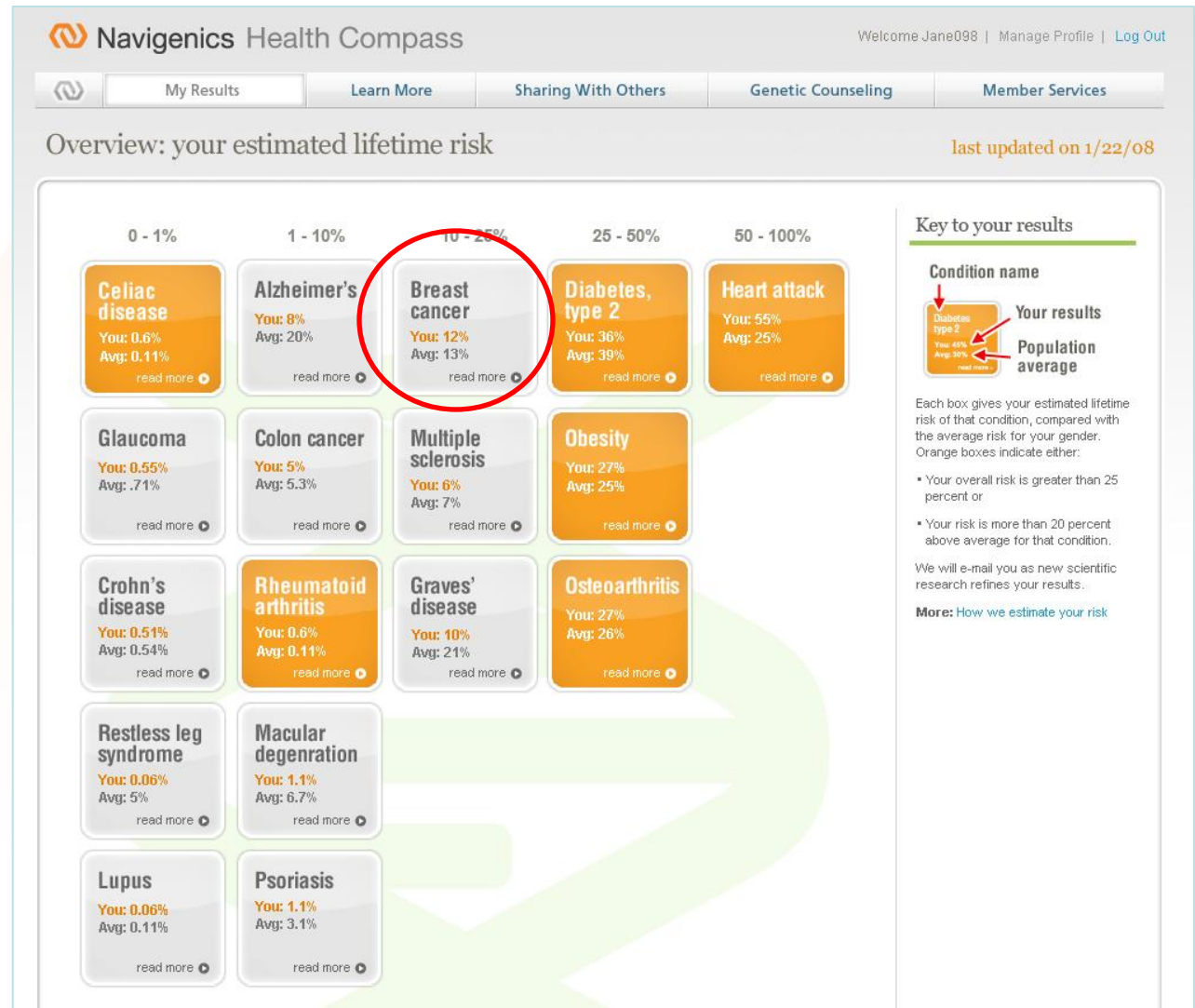
Orange Box

Estimated LTR is 20% or more than the general population

Estimated LTR is more than 25% total

Gray Box

Estimated LTR is at or below the population average



Condition-Specific Summary

- | In-depth report for each condition
- | Highlight genetic vs. environmental contribution to disease

The screenshot displays the Navigenics Health Compass interface for a user named Jane098. The main content area is titled "Summary" for "Diabetes, type 2". It provides a relative risk of "high", a lifetime risk of 36%, and notes that the user has 12 of 20 risk markers. A pie chart highlights the contribution of environment (36%) and genetics (64%) to the condition. A "What's next?" section offers lifestyle advice, such as losing weight and exercising, to reduce risk. The page also features a "Your DNA" section and related content links.

Diabetes, type 2
Your relative risk: **high** | Your lifetime risk: 36% | You have 12 of the 20 risk markers

Your estimated risk
We took the average risk for women and used your genetic markers to estimate your lifetime risk for type 2 diabetes: 36 percent, or 360 out of 1,000.

Causes: type 2 diabetes
Genes are only part of the story. Environment and behavior play a role too.

36% Environment
64% Genetic

What's next?
If you're overweight, try to lose weight.

- If you don't exercise, consider starting. Exercise lowers weight and blood sugar.
- Talk to your doctor about how often your blood sugar levels should be tested. Be ready to share any family history or symptoms you have.

More: What you can do

What does it mean?
You're at high risk for type 2 diabetes, which affects 7 percent of Americans. If you want to reduce your risk even more, lifestyle changes can have a powerful preventive effect.

In type 2 diabetes, high blood sugar affects the internal organs. There is no cure, but it can be controlled with diet, exercise, weight control and, for some people, oral medication or insulin injections.

More: About type 2 diabetes

Your DNA
To calculate your estimated lifetime risk, we looked at 20 markers in your genome that are associated with type 2 diabetes. You have 12 of the 20

Related content

- Fish oil prevents type 2 diabetes plaques
- Sugar & type 2 diabetes: are they linked?
- Hypertension, type 2 diabetes linked
- Protein may treat type 1 diabetes
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- Diabetes drug may up elderly deaths
- Smoking linked to type 2 diabetes
- Diabetes and your sex life
- Are you in diabetes denial?
- How to lose weight when you have diabetes

Condition-Specific Summary

- | In-depth report for each condition
- | What's next?

Navigenics Health Compass | Welcome Jane098 | Manage Profile | Log Out

My Results | Learn More | Sharing With Others | Genetic Counseling | Member Services

Overview
Diabetes, type 2
What you can do
About
Your DNA
More information

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Condition-Specific Summary

- | In-depth report for each condition
- | What's next?
- | What does it mean?
- | Your DNA
- | Total risk markers identified
- | SNPs included in analysis
- | Effect of genotype
- | Primary resources

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- Overview
- Diabetes, type 2**
- What you can do
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- More information

What you can do

“Diabetes can be delayed or prevented with careful attention to your health habits. You and your physician can construct a health plan to minimize the chance of your developing diabetes.”

— Dr. Michael Nierenberg, medical director

Prevention measures

Clinically proven

If you are overweight, lose a few pounds. Body Mass Index less than 25. People with a modest weight loss of 5 to 7 percent.

Eat a healthy diet. Aim for a reduced-calorie diet with a low amount of fat in foods. Avoid foods that are high in sugar. Eat small portions when you do eat. Eat fruits and vegetables, whole-grain foods, and low-fat dairy. Limit intake of simple sugars. Fiber has been shown to help.

Get moving. Aim for 30 minutes of moderate-intensity activity each week. Brisk walking, swimming, and cycling are especially easy to fit into a busy schedule. If you are blocked from your stop, park at a distance from your destination.

Lower cholesterol and blood pressure. If your cholesterol is 140/90 or higher, talk with your doctor about treatment. Suggestions for diet and exercise may help.

Early detection

Symptoms

Many people with diabetes have very mild symptoms, or none at all. Often, diabetes is diagnosed only after the onset of severe complications.

Diabetes, type 2
You: 36%

Related content

- Fish oil prevents type 2 diabetes plaques

More Information...

Early detection

Symptoms

Many people with diabetes have very mild symptoms, or none at all. Often, diabetes is diagnosed only after the onset of severe complications. Early diagnosis and treatment can help prevent complications.

Watch for

- unexplained fatigue
- frequent urination
- unexplained weight loss
- increased thirst and hunger
- blurred vision
- wounds that won't heal

Testing

Talk with your doctor about the best testing method. Simple blood tests:

- The fasting glucose test. A blood sample is taken after you have not eaten for at least 8 hours. Results are reported in milligrams/deciliter or in moles per liter.
- Other tests that may be used include the hemoglobin A1c test, which is based on a sample of your blood that with one sample and the oral glucose tolerance test, which involves drinking a sugary liquid following the ingestion of a glucose solution.
- Aim for 30 minutes of moderate-intensity activity each week. Brisk walking, swimming, and cycling are especially easy to fit into a busy schedule. If you are blocked from your stop, park at a distance from your destination.



Talking to your doctor

What should I tell my doctor?

- Do you have a family history of diabetes?
- Has anyone ever mentioned that you had a high or borderline blood sugar?
- If you have been pregnant, did you have gestational diabetes?
- Are you taking any medication that can raise your blood sugar, such as corticosteroids like prednisone?
- Are you under extreme stress, which can elevate your blood sugar?
- What is your current weight in comparison to what it has been in the past? Obesity promotes diabetes.
- Do you have any symptoms of possible diabetes, such as increased thirst, increased appetite, weight loss despite increased appetite, increased urination, blurred vision or fatigue?

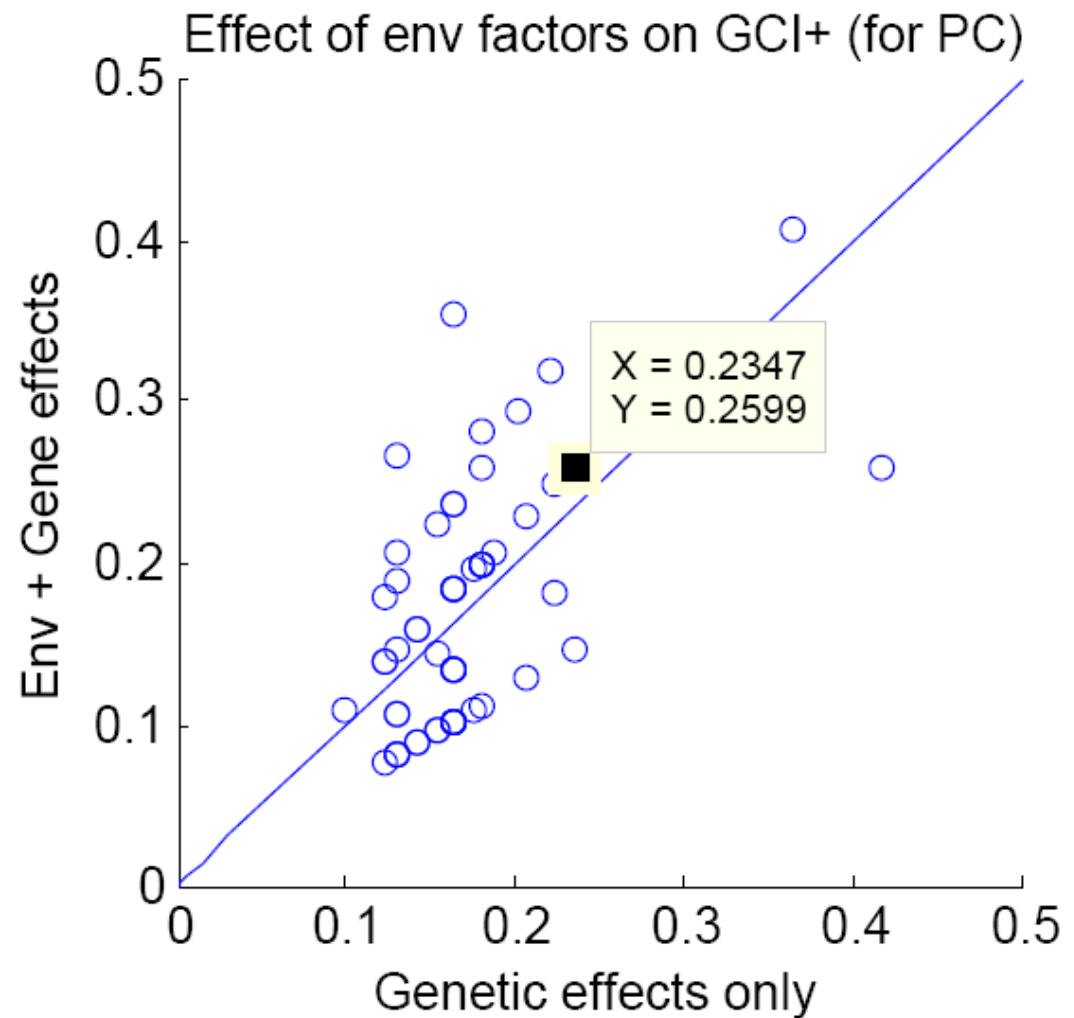
What can my doctor do?

- Order blood tests to get a baseline of your blood sugar, probably including a fasting blood glucose test and possibly an oral glucose tolerance test.
- Advise you about starting a weight loss and exercise program.
- Perform a baseline exam and lab tests to check organs that can be affected by diabetes: heart, eyes and kidneys.
- Be attentive to even modest elevations in blood pressure or cholesterol, as these are affected adversely by diabetes.
- Advise you to get a glucometer so you can periodically check your blood sugar on your own.

Next: About

Cohort Exposure Data On Genetic Subclasses?

It is not a reasonable assumption that the established environmental risk factors act equally on the multitude of genetic subclasses



Take-home points

- | We are facing a health care crisis from CCND in this generation – and prevention is the only feasible solution
- | Validated “genetic risk factors” are no different than validated environmental risk factors
- | Genetic risk factors can be used to refine risk and drive additional focused prevention behaviors and early detection paradigms
- | Delivery of the information in an accurate and private fashion to the public is necessary to meet timelines

Navigenics Industry Standards Setting Conference

- | Announced April 8th, in partnership with the Personalized Medicine Coalition (www.personalizedmedicinecoalition.org)
- | Public conference event in Dec 2008, Washington D.C. venue TBD
- | Broad participation of key stakeholders
- | Potential Areas of focus for dialogue and recommendations:
 - Implementation of Privacy Protections for Online data
 - Operational/Lab Processing Standards
 - Diffusion of Communication Methods for Risk-based Information
 - Ensuring Consumers Understand and Adopt Genetic Risk-based information
 - Assessing Clinical Validity of Association Studies
 - Defining Actionable Health Information
 - Educating the Provider and Public



Genetic and Epidemiology Team

David Botstein, MD, PhD

***Michele Cargill, PhD**

***Eran Halperin, PhD**

Shannon Kieren, MS, CGC

Isaac Kohane, MD, PhD

Elissa Levin, MS, CGC

Michael Nirenberg, MD

Badri Pakhukasahasram, PhD

Nik Schork, PhD

Elana Silver, MPH

***Daryl Thomas, PhD**

Heather Trumblower, MS

Jeffrey Trent, PhD

Vance Vanier, MD

Jennifer Wessel, PhD, MPH

Stringent Curation Criteria

- **Replication in the same ethnic group**
 - Once for GWAS, twice for candidate gene studies
 - >60% independent sample sets show same statistically significant effect with same allele (after trimming underpowered samples)
- **Study design** - An effort was made to sample controls from the same source population as the cases, e.g. ethnicity, gender, age, or other risk factors.
- **Reasonable sample size to detect weak effects.** OR <1.5 needs 250 cases/250 controls at least.
- **Significance level** - Exact value depends on magnitude of the study (e.g. GWAS or candidate gene)
 - **Sound statistical design** - correction for multiple testing, population stratification, confounding
 - **Sound laboratory practice** - independent genotyping platforms, replicated samples
 - **Functional data and magnitude of effect** are also taken into account, but studies are not automatically excluded if functional data is unavailable or the effect estimate is small.

Professional Access

- | Genetic counselors at any time included in the Navigenics service
- | Tools to talk to your doctor
- | Website was built with input from physicians, genetic counselors, medical journalists to make it consumer friendly and understandable for a non-expert individual.

Regulation

- | We are in discussions with relevant regulatory agencies to develop appropriate regulatory standards for the industry.
- | We operate in a manner consistent with currently applicable regulatory guidelines.
- | We supported **GINA!**
- | Informed consent is required and we do not test minors.
- | We are completely transparent as to our scientific and clinical criteria, our calculations, and our primary references.
- | We adhere to testing guidelines and position statements of professional organizations including the National Society of Genetic Counselors, the American College of Medical Genetics, and the American Society of Human Genetics.

Security / Privacy

- | We operate in a HIPAA consistent manner
- | We require opt-in for internal research and/or third party research
- | Privacy and security policies ensure that our members can feel comfortable and confident receiving genetic information and analyses, and that they alone control how that information is to be used and distributed.
- | We use the most advanced data protection systems; we safeguard, maintain and update your genetic profile in a highly secure environment. All customer profiles are anonymous to assure data security.
- | Although there is concern about insurance companies misusing genetic information, there are currently no cases on record of this happening. We are very diligent about communicating how to avoid this problem to our members.

Long-term effect on genetic research / Commercial exploitation

- | Transparency in what we are testing for, assumptions in our risk score calculations, statements about the state of the science
- | Informed consent is required
- | We are taking a responsible approach – providing information about medically relevant conditions that are socially responsible (excluding HIV resistance, for example)
- | We will not sell our member's genetic information in any way
- | Individuals can opt-in to donate their genotype information to our product refinement efforts and our prospective outcomes trials research.