Risk Assessment for Complex Genetic Disease

Navigenics

Dietrich A. Stephan, PhD
Founder, 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.

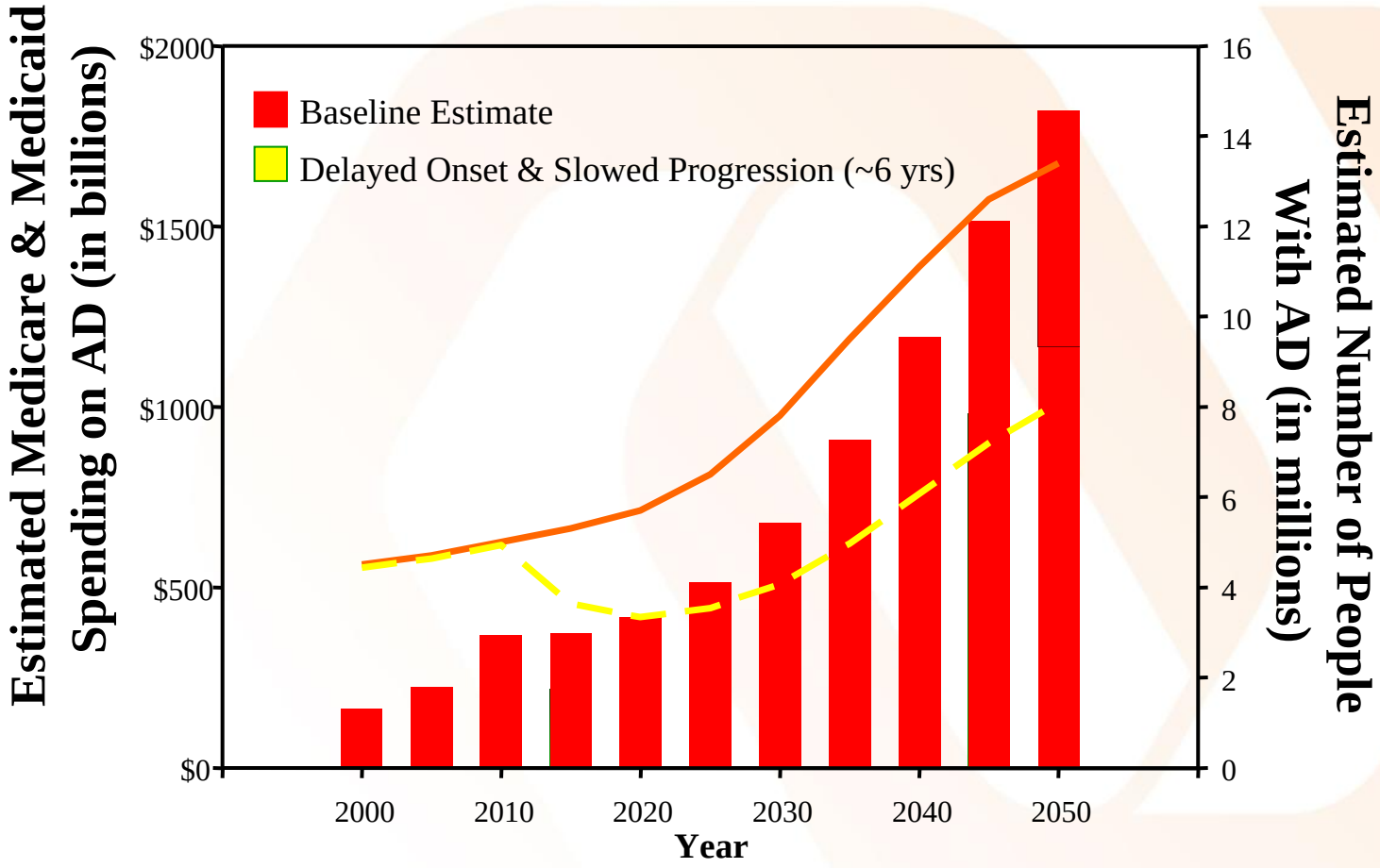
- **The Navigenics Health Compass:**

  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



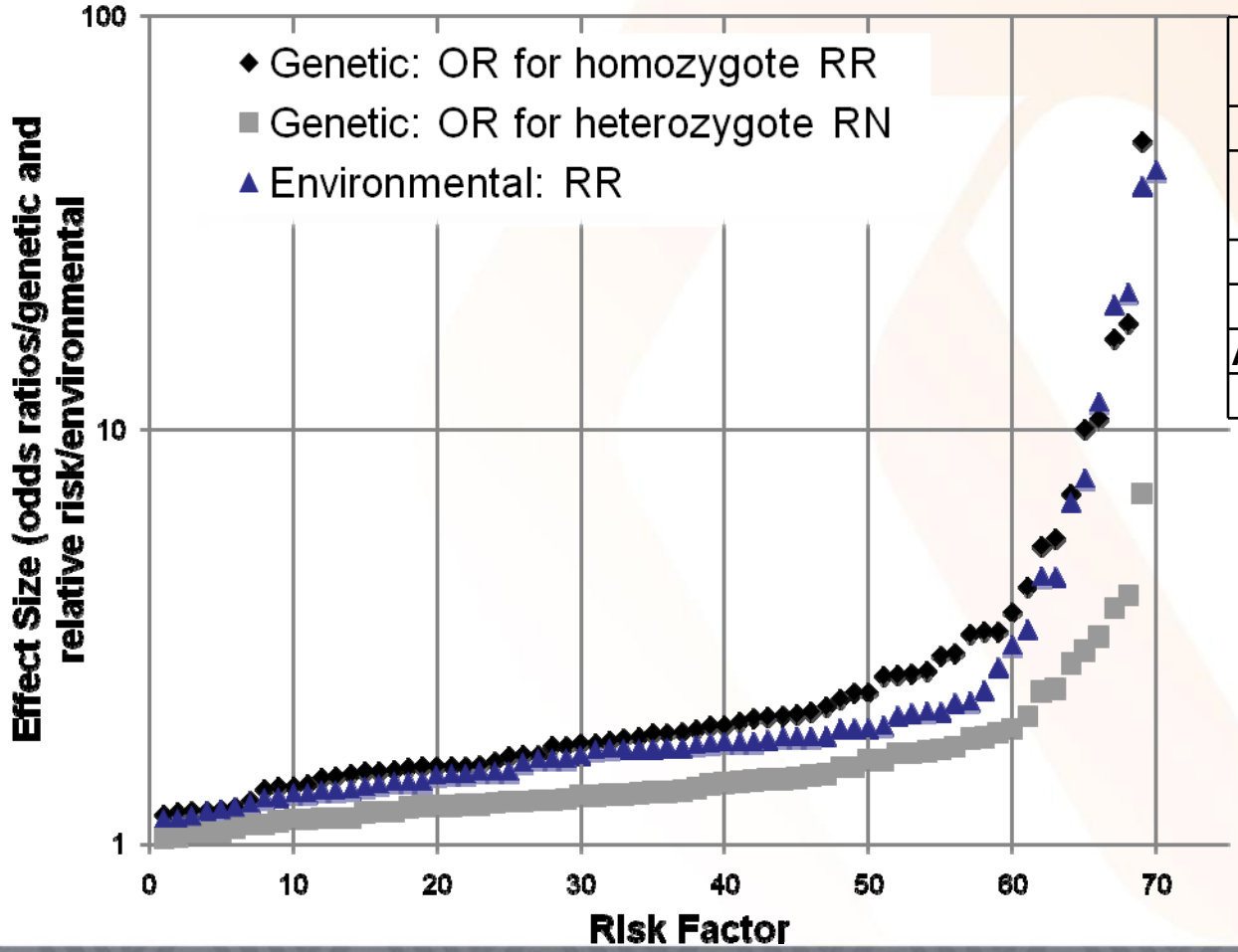
Adapted from The Lewin Group Report, June 2004, "Saving Lives. Saving Money: Dividends for Americans Investing in Alzheimer Research," The Alzheimer's Association (http://www.alz.org/Resources/FactSheets/Lewin_FullReport1.pdf)

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



risk factor	*condition*	*effect size*
Ex-smoker	T2D	1.15
PPARG genotype	T2D	1.53
HDL<35mg/dl	CHD	2.08
MHC genotype	RA	5
APOE genotype	AD	18
BMI>35	T2D	42

Risk factors determined from literature using strict curation guidelines

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	2	3	4	5
Customer Acquisition	Laboratory	Bioinformatics	Personalized Web Portal	Ongoing Service


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ATACCGCTGGCCCTT
TGGCATTACCTATGA
AGATTGCTTCAGCCA
GCGTCAGTTTCAACC
TGTACGCTAGTGTGT
TTCTACTCACGTGTC
TCAGCATTGATCGAT
ACCTGGCTATTGTTC
ACCCAATGAAGTCCC
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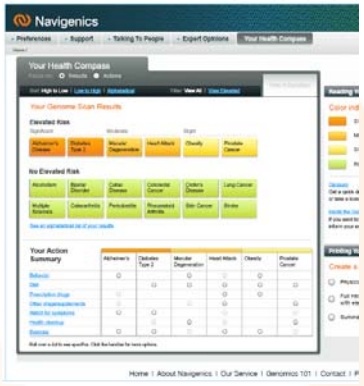


nature genetics

The NEW ENGLAND JOURNAL of MEDICINE

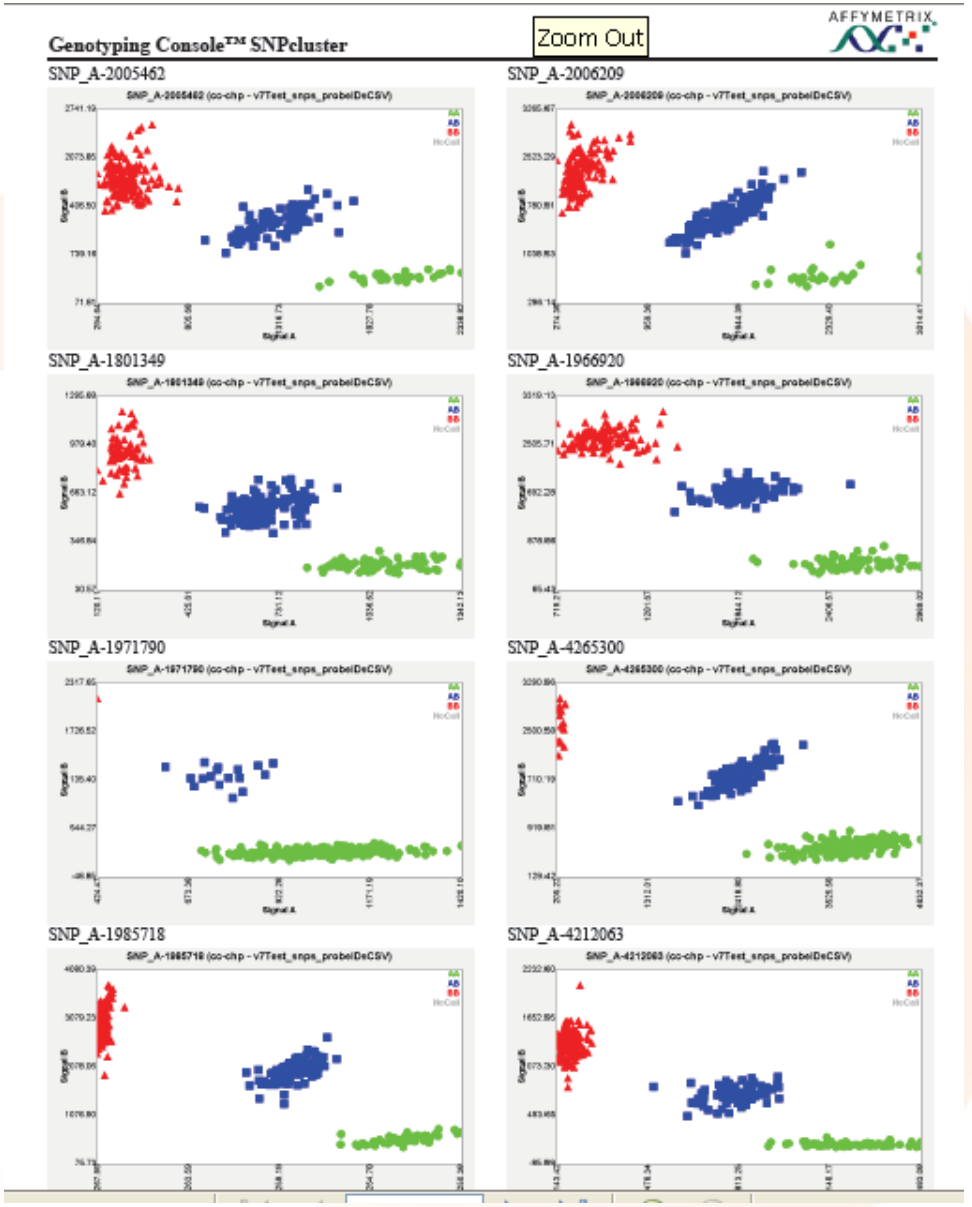
FUTURE: Full genome sequencing, copy number analysis, methylation status leading to personalized exposure mitigation strategies and biomarker monitoring programs fully integrated into the established health care system.

Common Arguments:

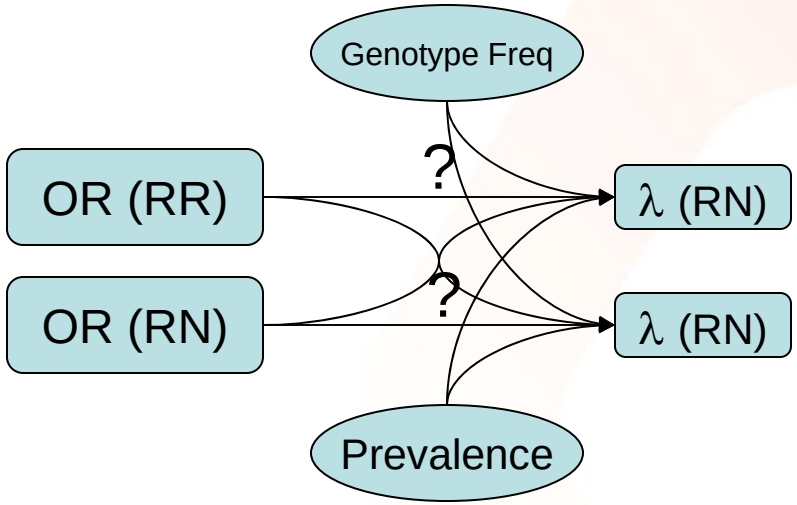
- Analytic validity – is the genotype produced from the assay (or analytic) accurate?
- Clinical validity – is the risk score accurate?
- Clinical utility – is the test useful in a clinical setting? Do individuals change their behavior?
- Physicians are not equipped
- Professional access
- Regulation
- 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

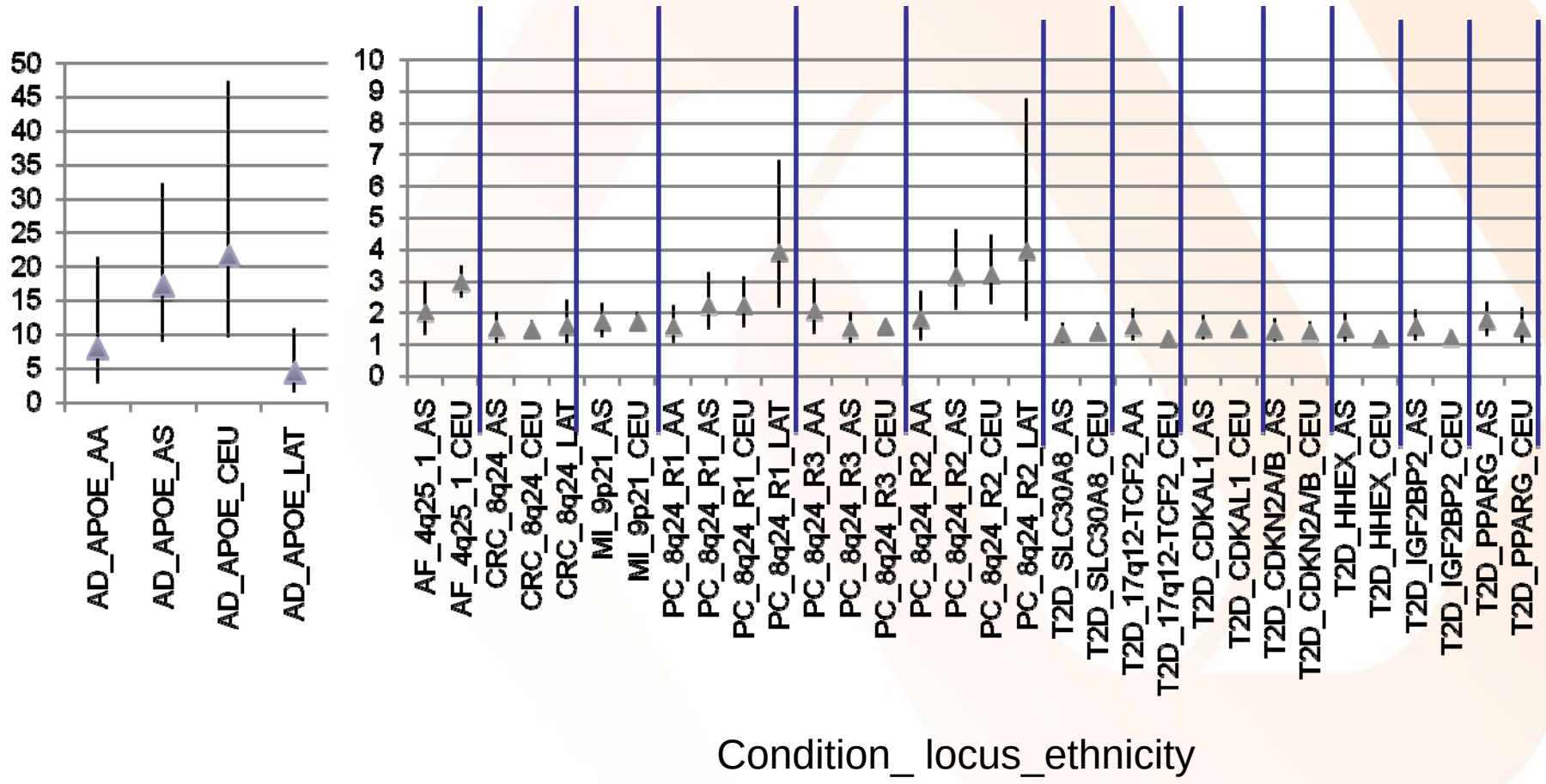


$$C = \sum_{i=0}^{k} f_i \lambda_i$$

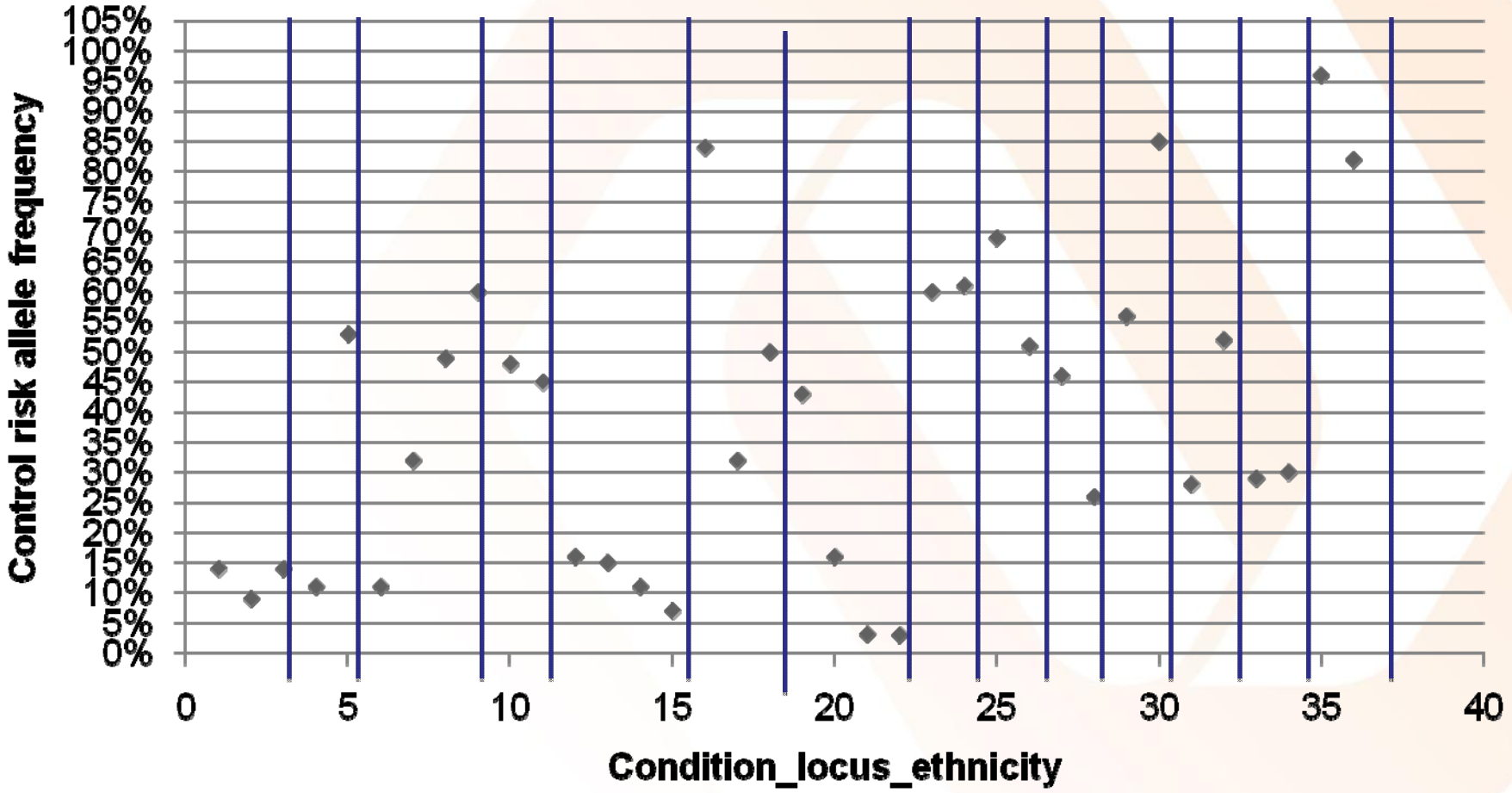
$$1 = \sum_{i=0}^{k} \frac{OR_i f_i}{C - p + OR_i p}$$

- 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

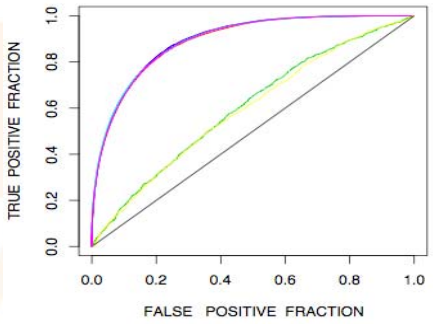


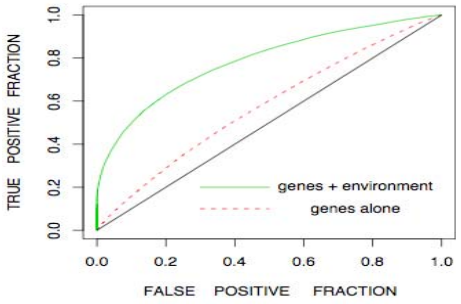
Risk allele frequencies in controls for different ethnicities are usually different

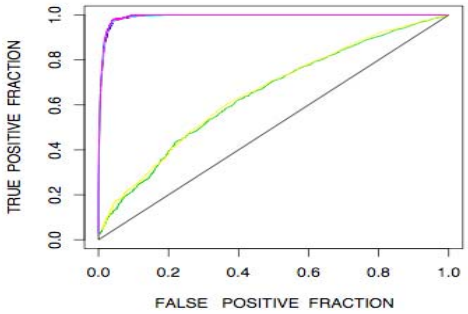


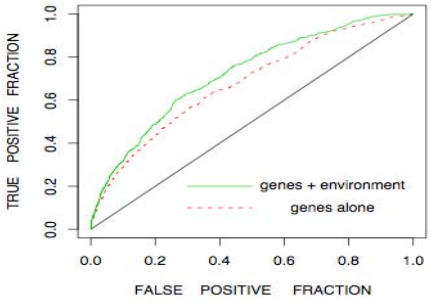
Estimated Genetic Variance we have Today

- Large effect sizes have been found
- No GxE









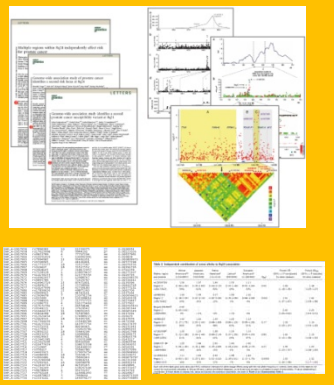
Disease	Relative risk of homozygous risk	Relative risk of heterozygous	Estimated number of unknown variants	Fraction of genetic variation explained by known variants out of the entire GENETIC variation
Type 2 Diabetes	1.10	1.05	1600	7%
Crohn's Disease	1.10	1.05	13958	4.4%
Rheumatoid Arthritis	1.10	1.05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

Navigenics' competencies & partnerships

Core competencies

Platforms and assays

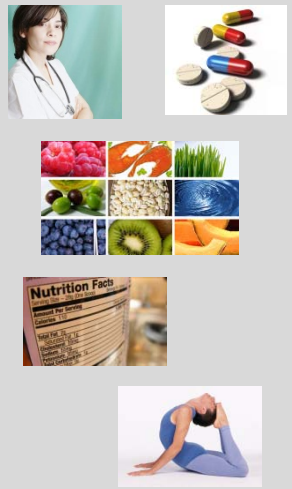
Scientific and Clinical Curation



Personalized Web Portal

Customer Experience

Lifestyle and Behavior



Partnerships

Correlagen

DNAdirect

DukeMedicine

AFFYMETRIX

Medscape from WebMD

Partnerships

MAYO CLINIC

PARTNERS HEALTHCARE

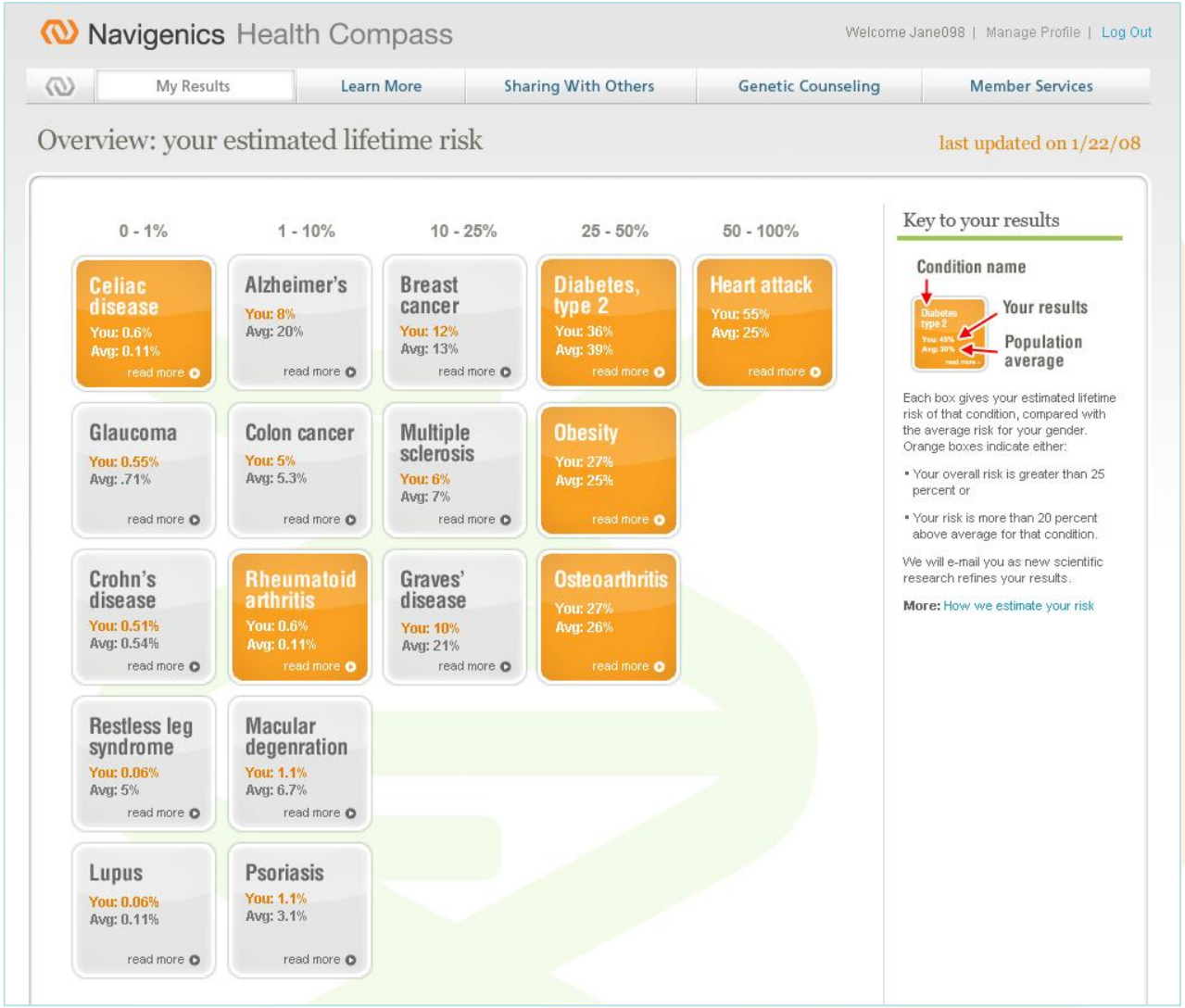
Scripps

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*

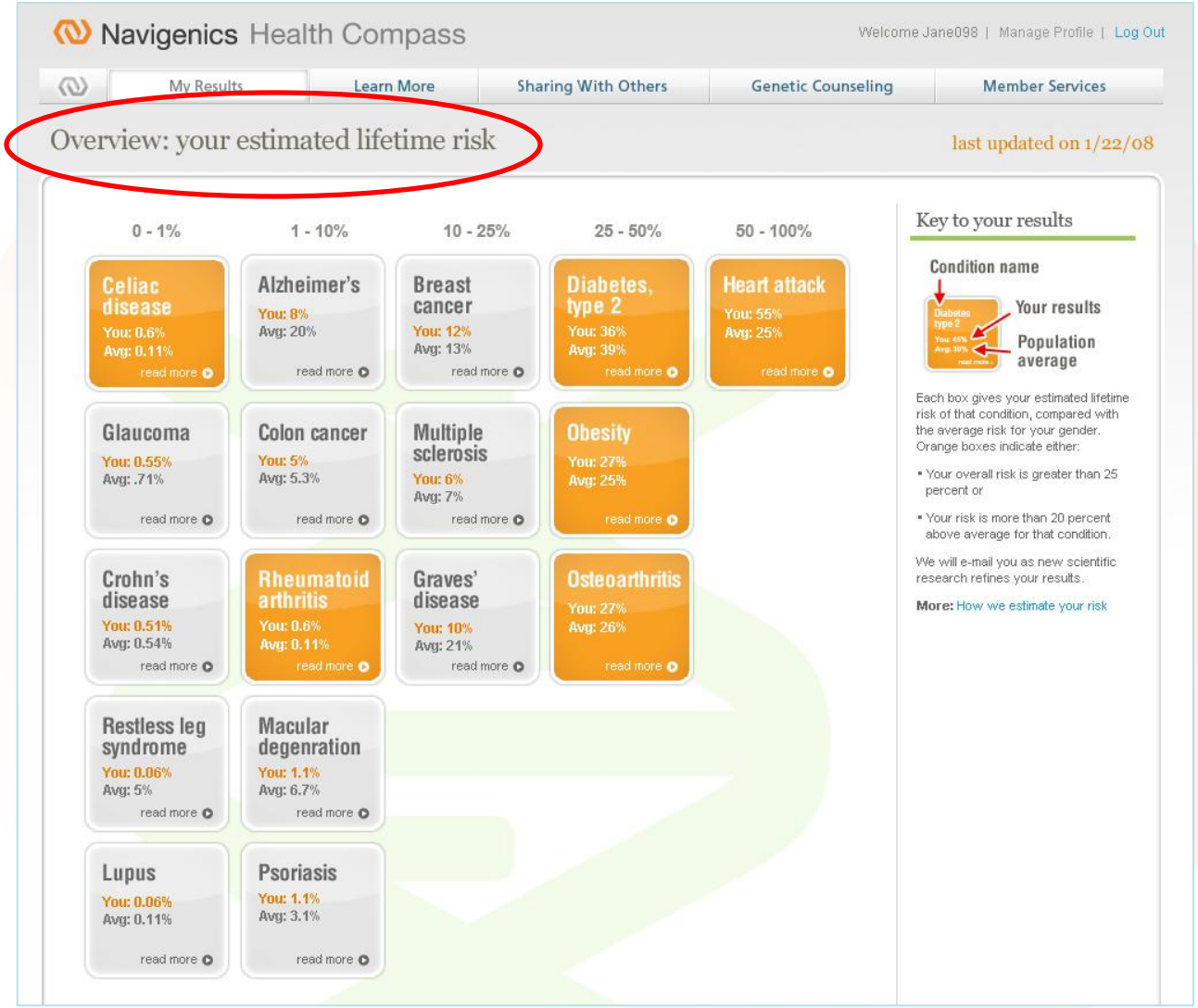


Health Compass: Results Overview

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



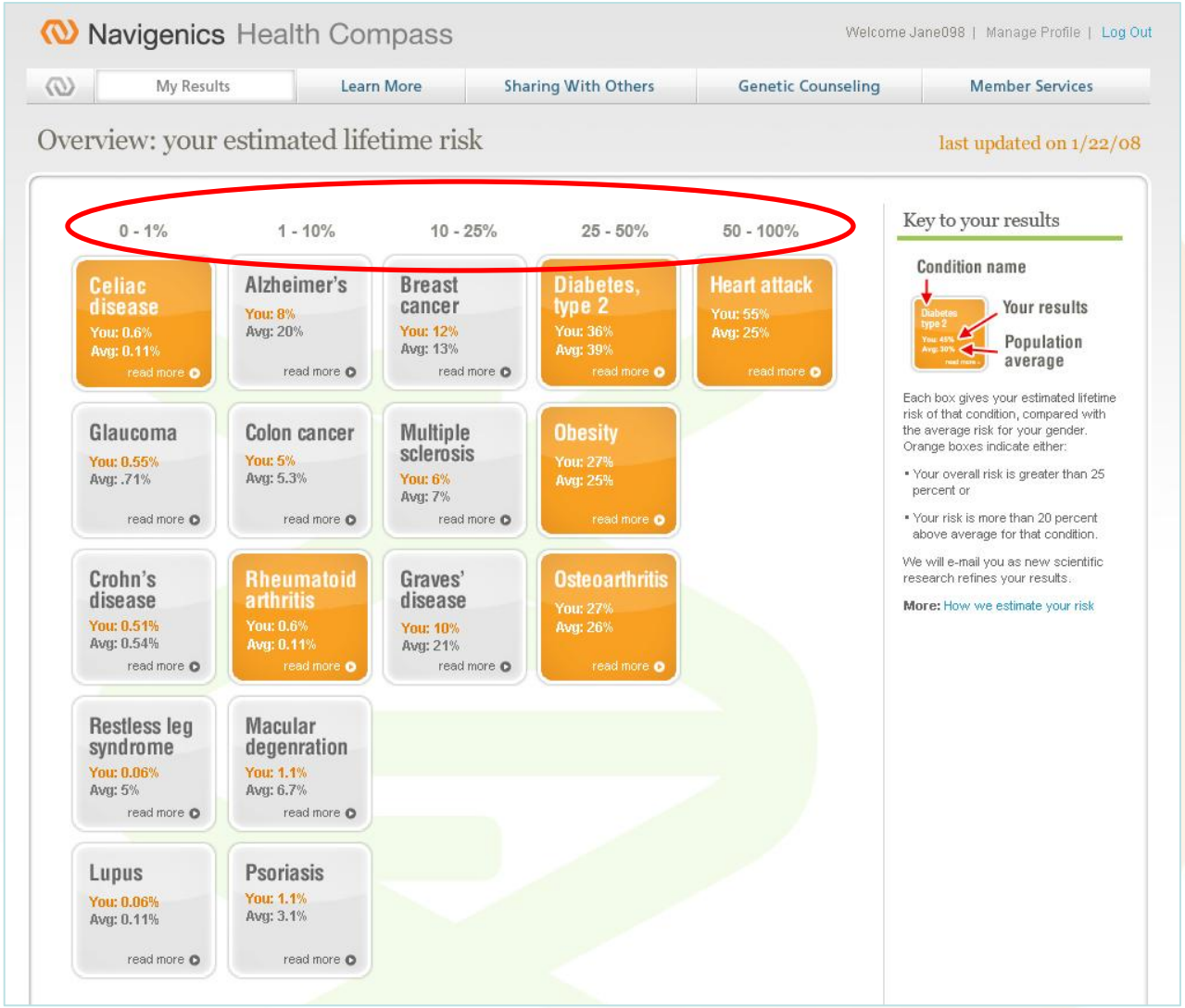
Health Compass: Results Overview

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

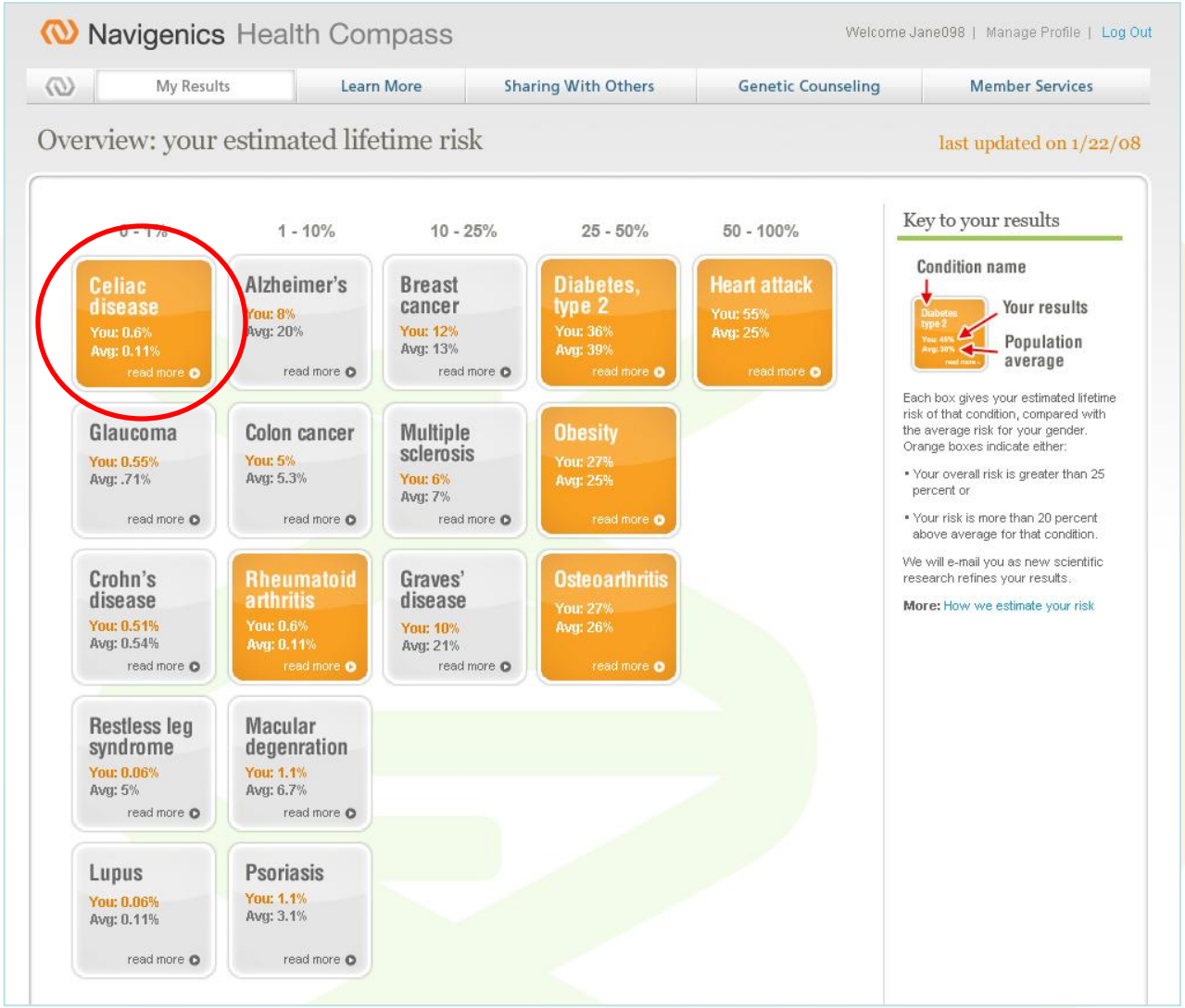
Place the conditions into "buckets" to highlight the overall LTR estimate



Health Compass: Results Overview

Orange Box

Estimated LTR is 20% or more than the general population

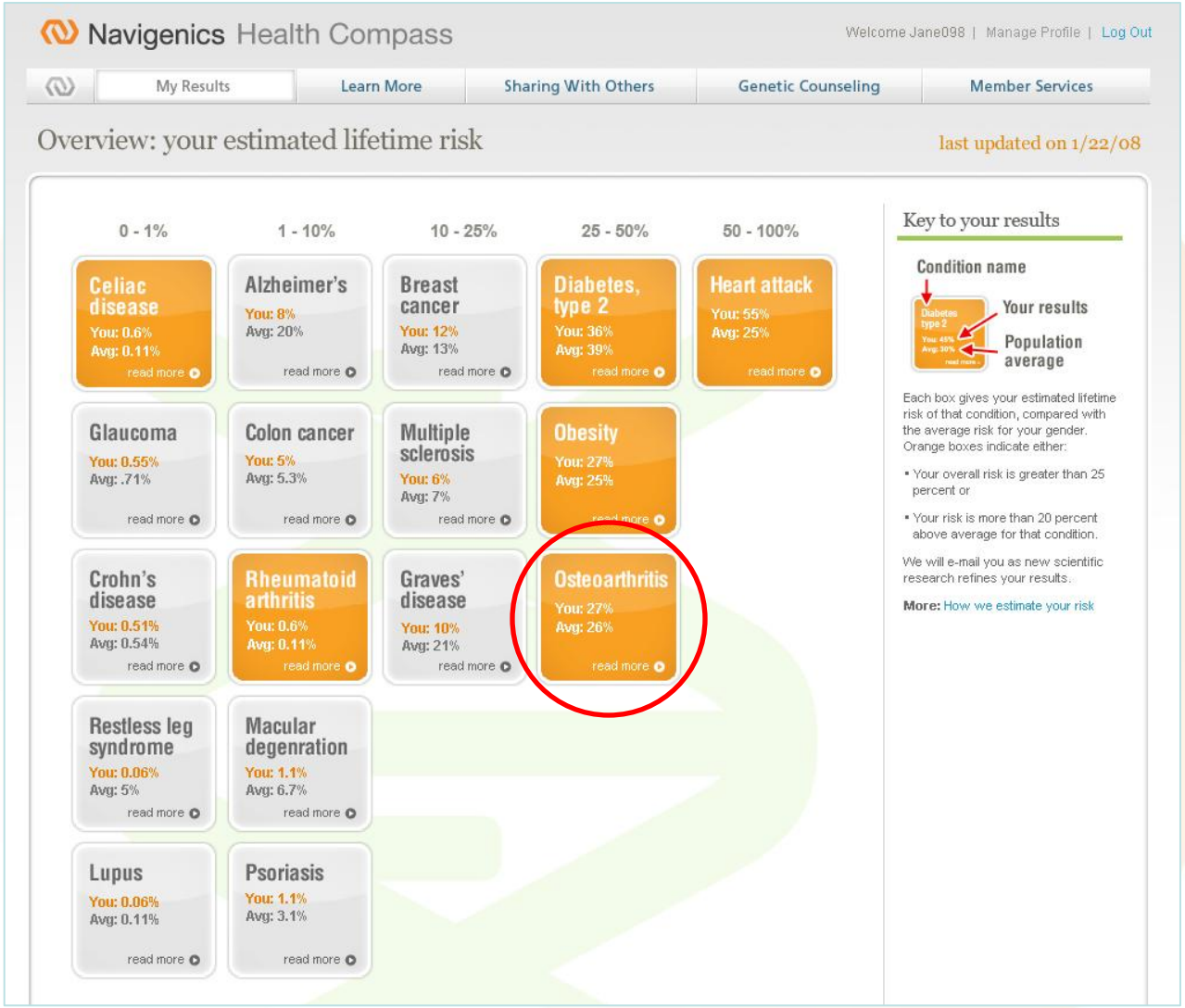


Health Compass: Results Overview

Orange Box

Estimated LTR is 20% or more than the general population

Estimated LTR is more than 25% total



Health Compass: Results Overview

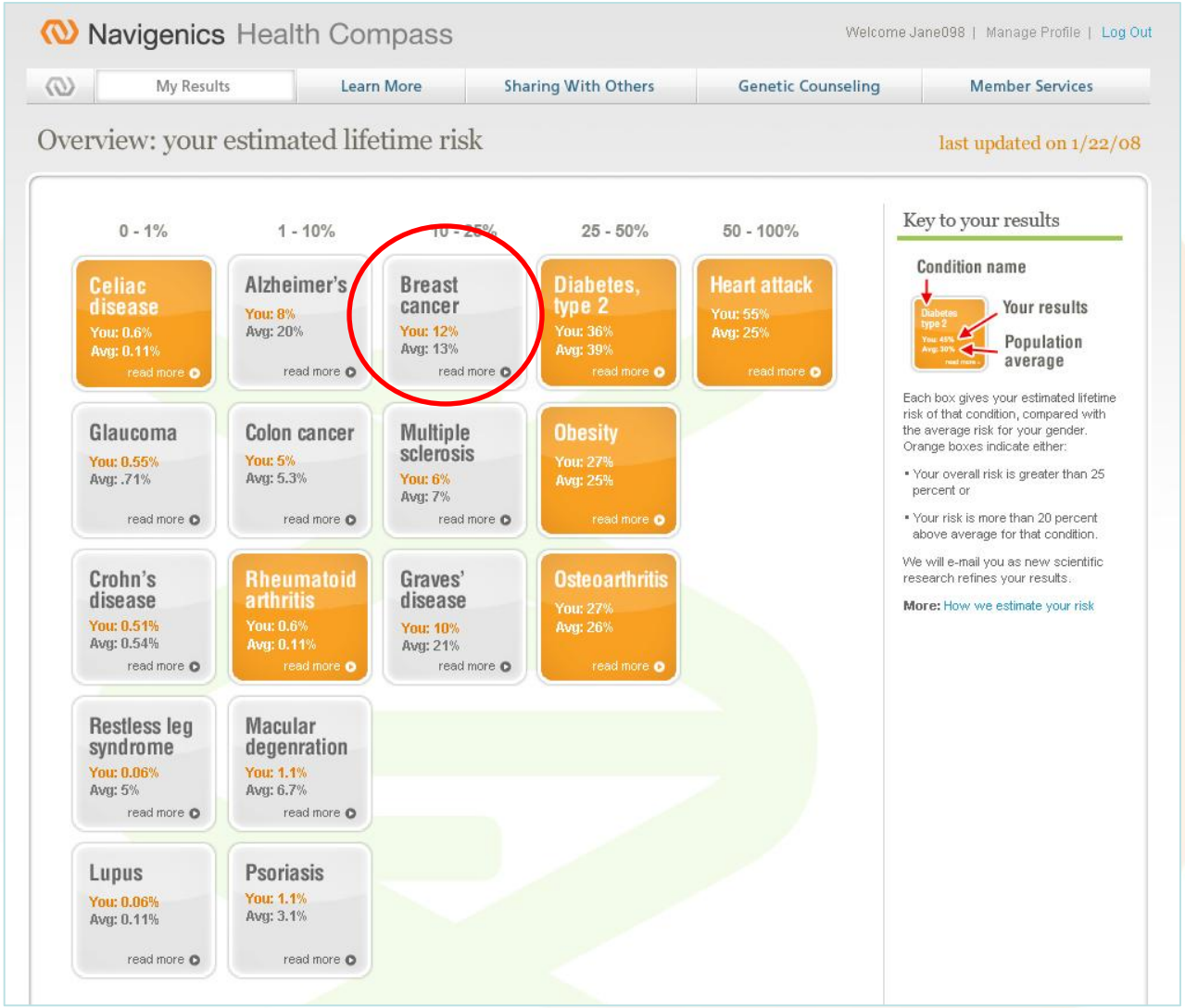
Orange Box

Estimated LTR is 20% or more than the general population

Estimated LTR is more than 25% total

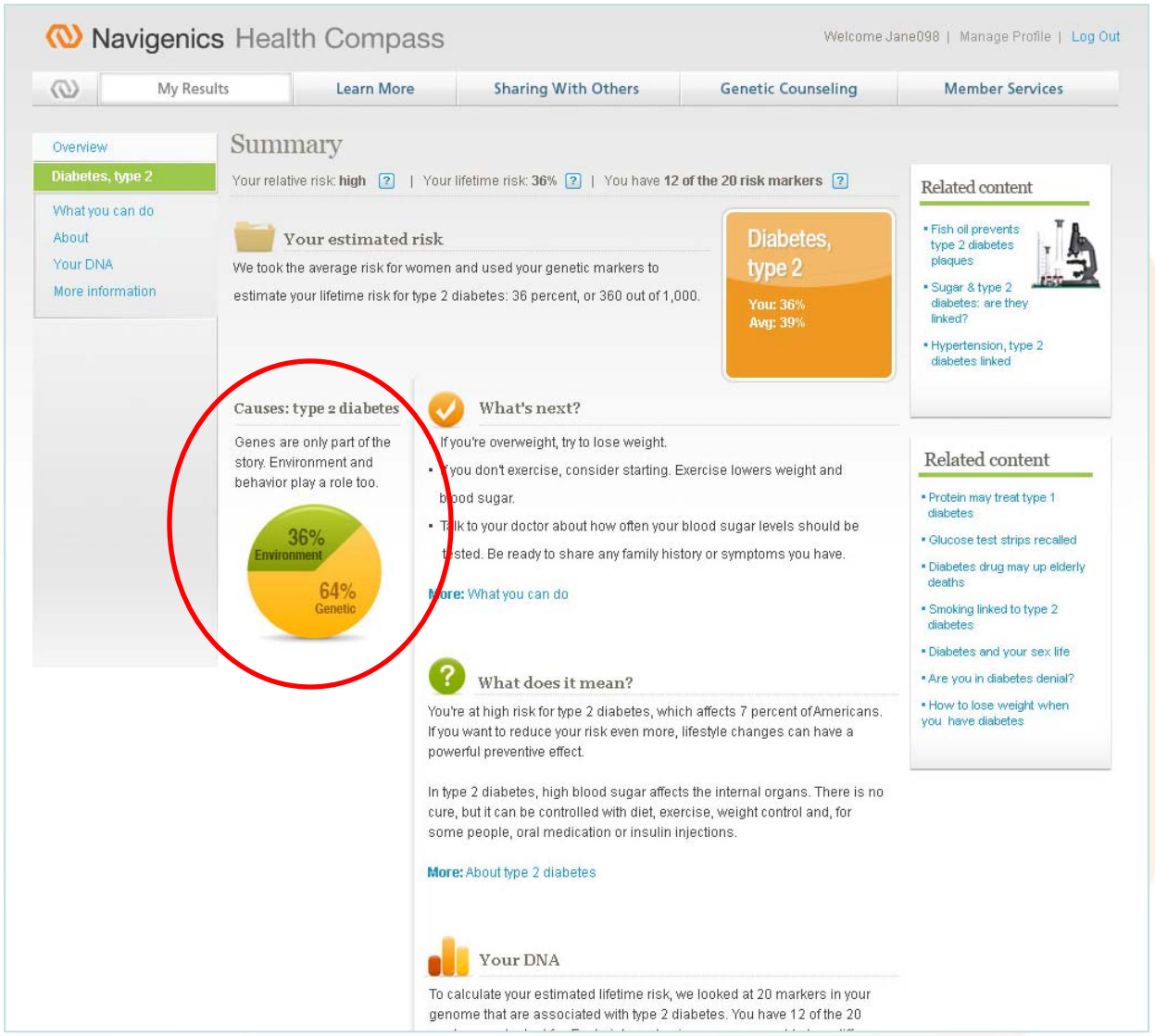
Gray Box

Estimated LTR is at or below the population average



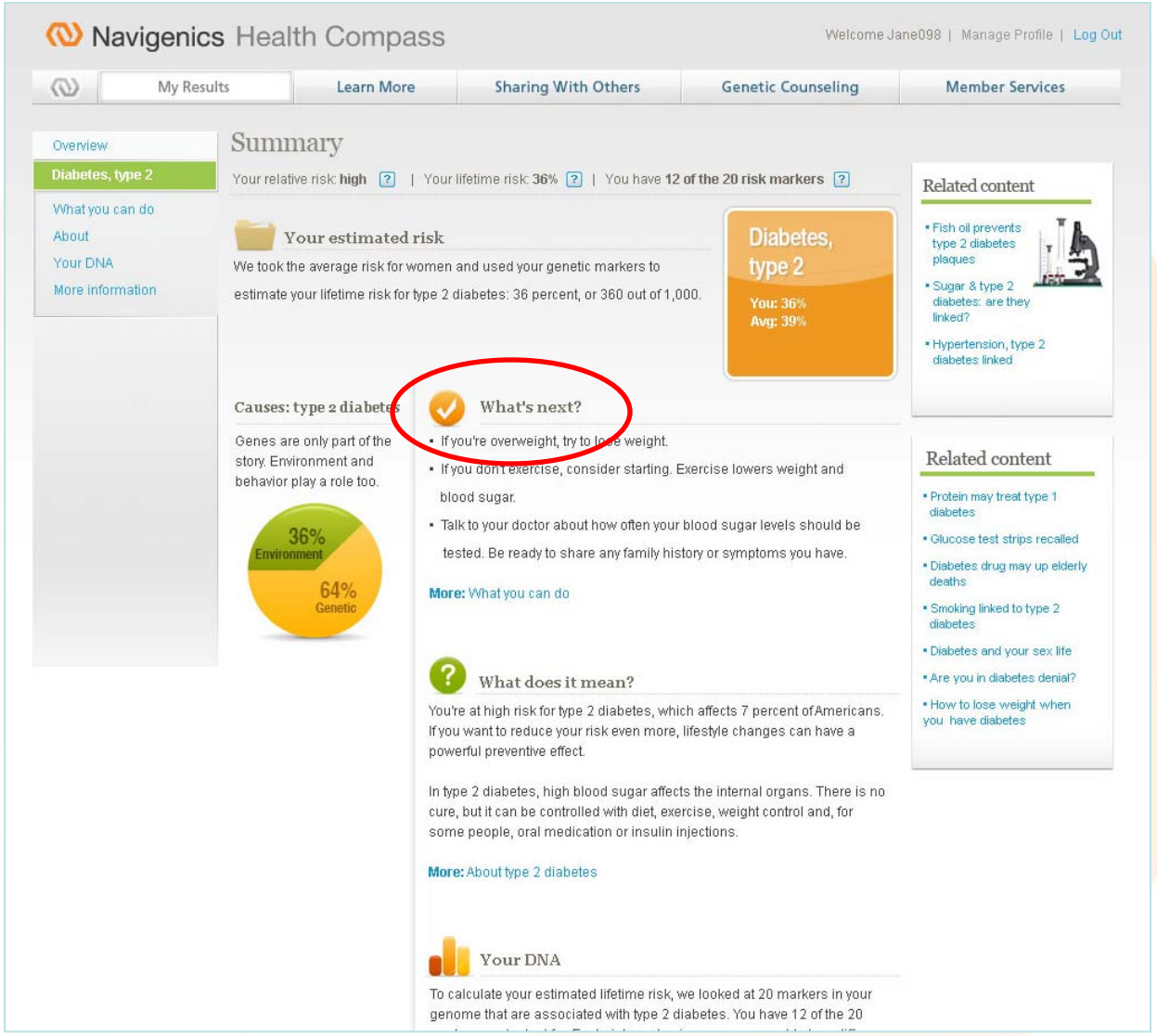
Condition-Specific Summary

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



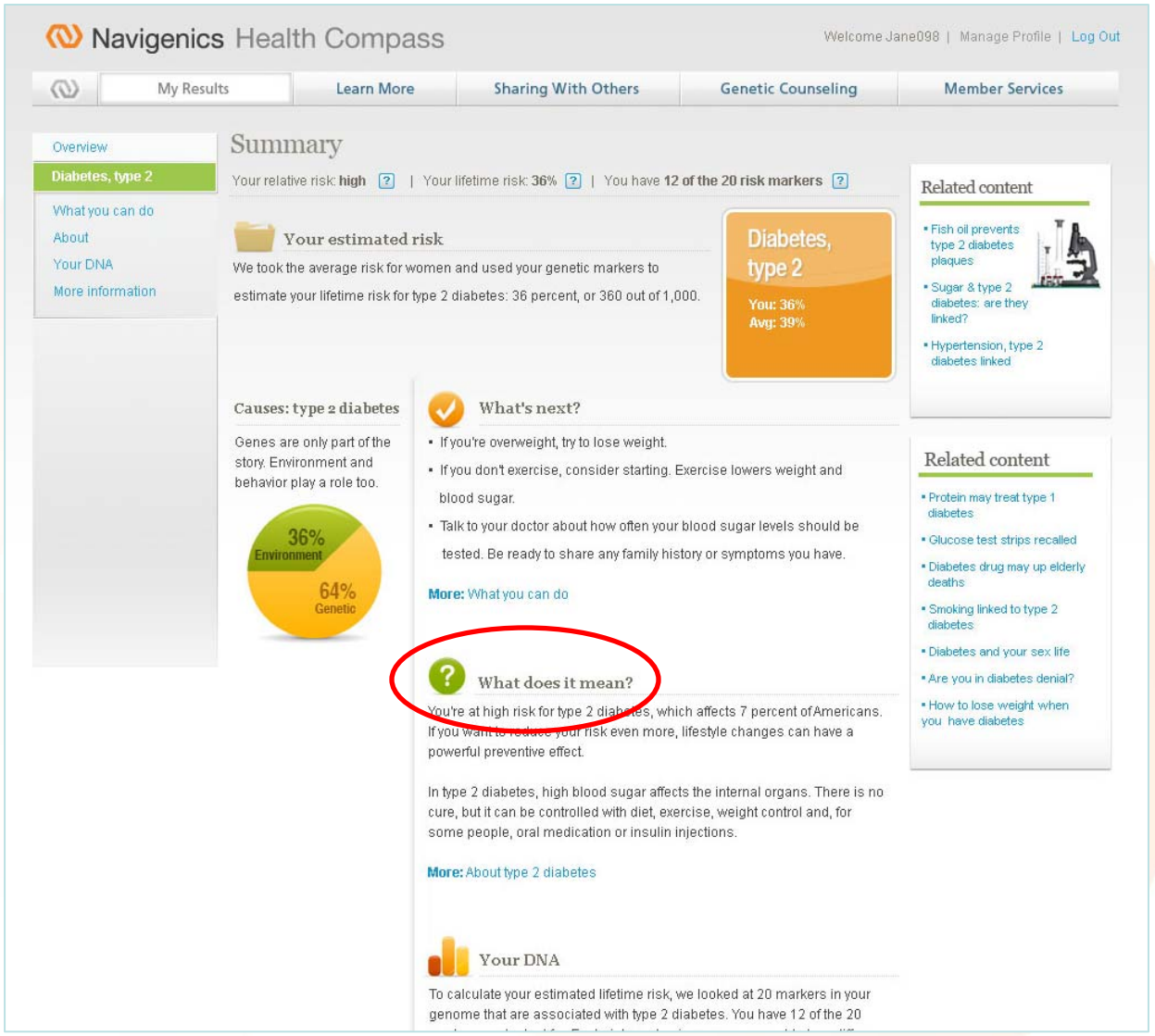
Condition-Specific Summary

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



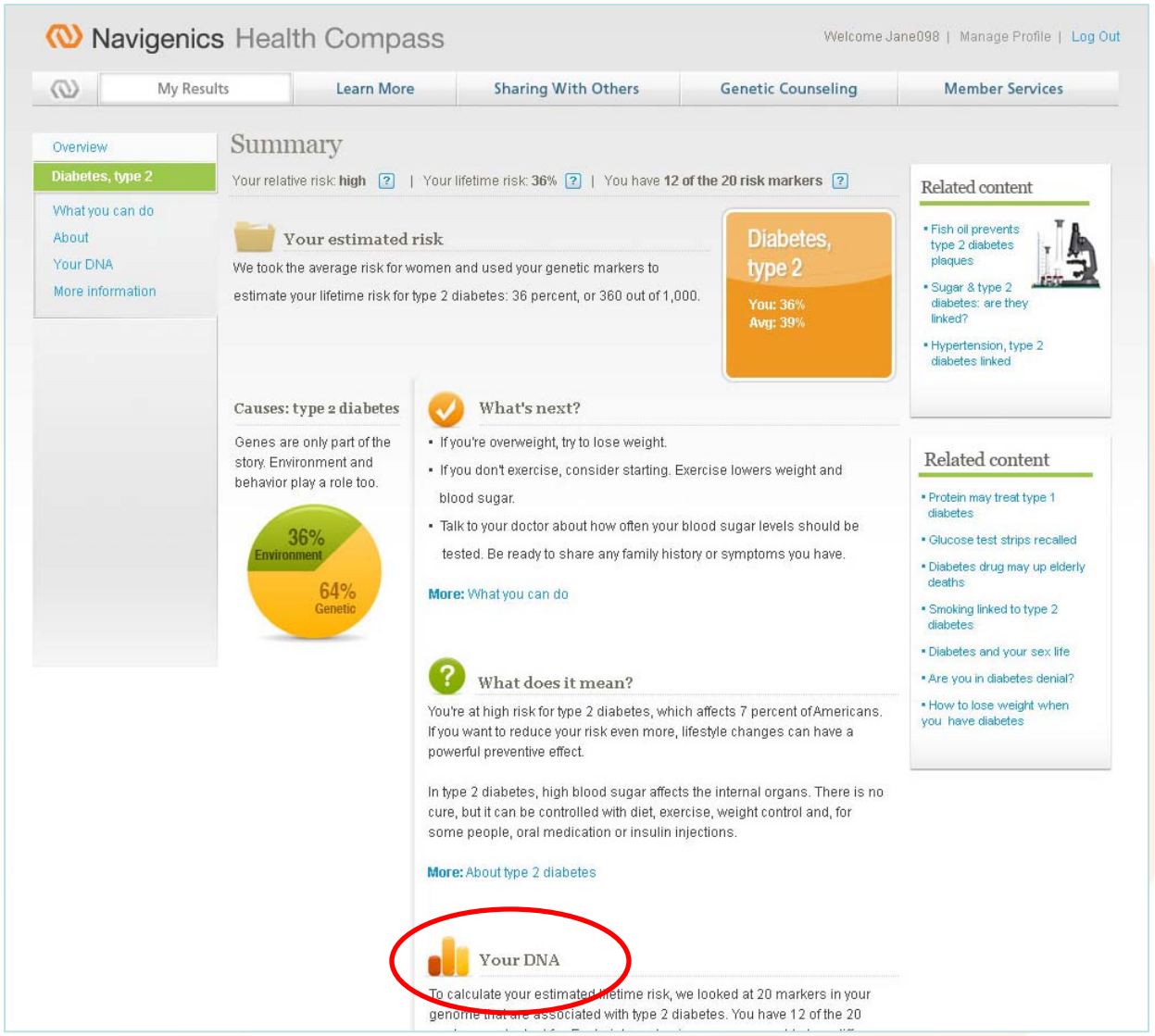
Condition-Specific Summary

- In-depth report for each condition
- What's next?
- What does it mean?

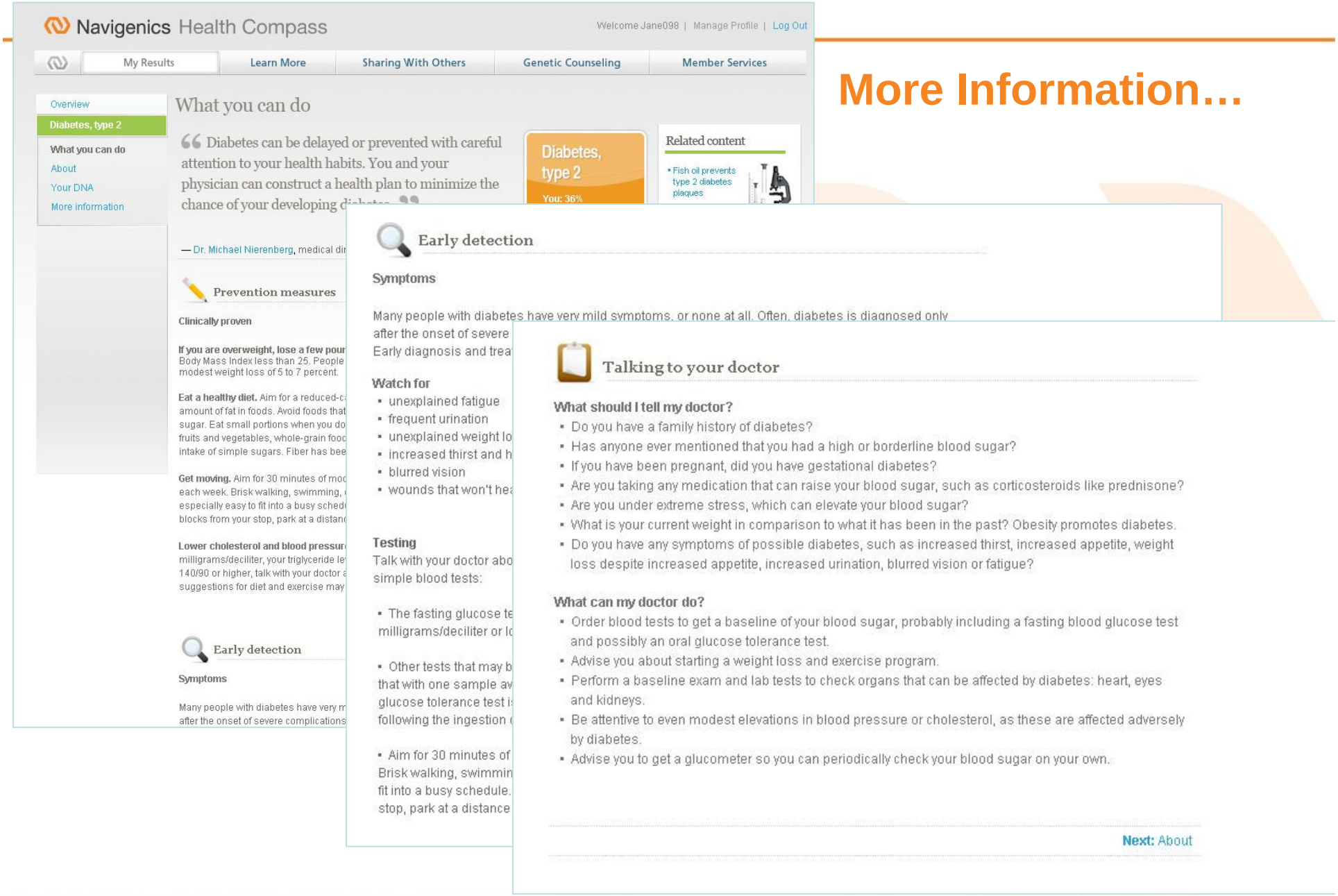


Condition-Specific Summary

- 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

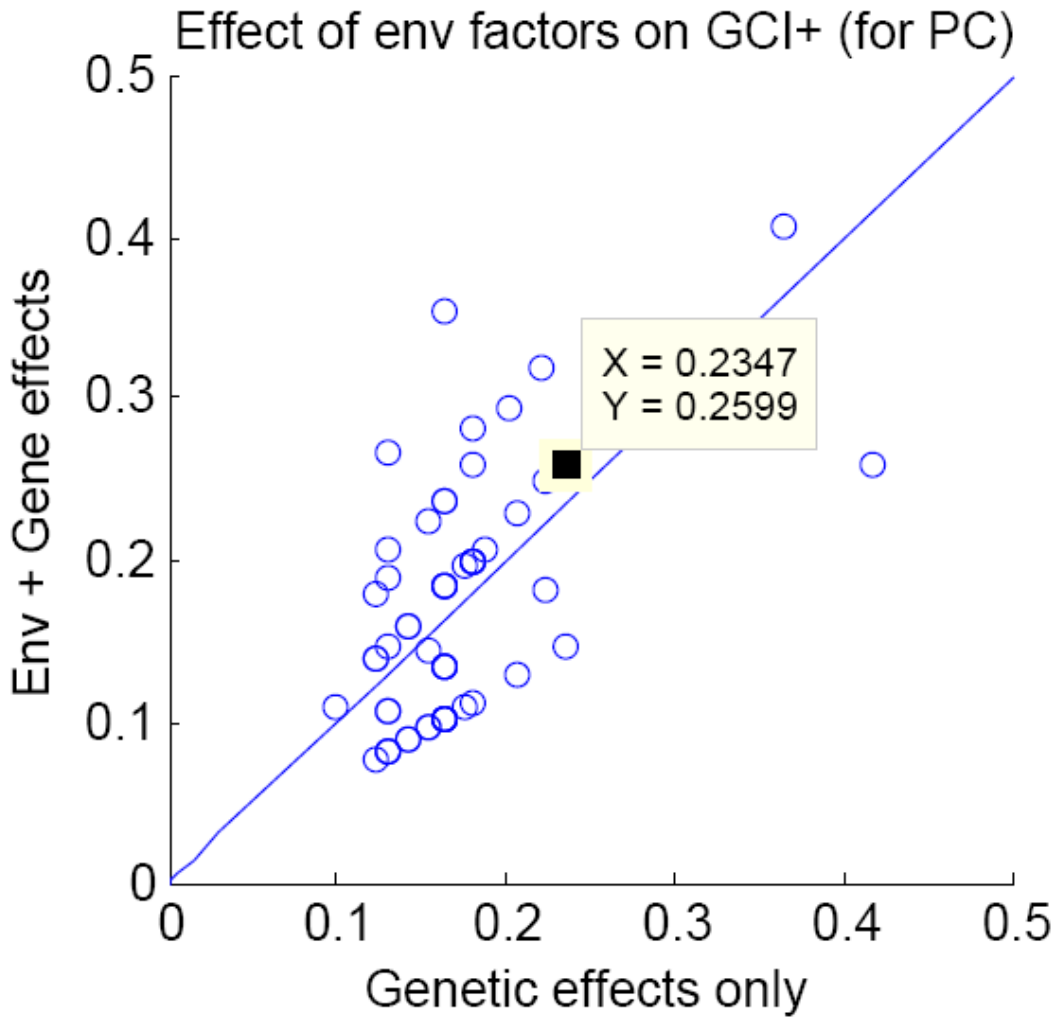


More Information…



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 support**ed** 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.