Risk Assessment for Complex Genetic Disease

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Founder, Navigenics
No clinical implementation infrastructure for risk ...
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

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

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Condition</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex-smoker</td>
<td>T2D</td>
<td>1.15</td>
</tr>
<tr>
<td>PPAR genotypes</td>
<td>T2D</td>
<td>1.53</td>
</tr>
<tr>
<td>HDL&lt;35mg/dl</td>
<td>CHD</td>
<td>2.08</td>
</tr>
<tr>
<td>MHC genotype</td>
<td>RA</td>
<td>5</td>
</tr>
<tr>
<td>APOE genotype</td>
<td>AD</td>
<td>18</td>
</tr>
<tr>
<td>BMI&gt;35</td>
<td>T2D</td>
<td>42</td>
</tr>
</tbody>
</table>

Risk factors determined from literature using strict curation guidelines
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2-4 hypertension</td>
<td>1.92</td>
</tr>
<tr>
<td>LDL &gt; 160</td>
<td>1.74</td>
</tr>
<tr>
<td>HDL &lt; 35</td>
<td>1.46</td>
</tr>
<tr>
<td>Smoker (last 12 mo)</td>
<td>1.71</td>
</tr>
<tr>
<td>T2DM</td>
<td>1.47</td>
</tr>
<tr>
<td>No exercise</td>
<td>1.39</td>
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# State-of-the-art clinical risk assessment: MI

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<tr>
<td>9p21</td>
<td>1.72</td>
</tr>
<tr>
<td>MTHFB1L</td>
<td>1.53</td>
</tr>
</tbody>
</table>
5-Step Service Offering

1. Customer Acquisition
2. Laboratory
3. Bioinformatics
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
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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Relative risk of homozygous risk</th>
<th>Relative risk of heterozygous</th>
<th>Estimated number of unknown variants</th>
<th>Fraction of genetic variation explained by known variants out of the entire GENETIC variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes</td>
<td>1.10</td>
<td>1.05</td>
<td>1600</td>
<td>7%</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>1.10</td>
<td>1.05</td>
<td>13958</td>
<td>4.4%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>1.10</td>
<td>1.05</td>
<td>6237</td>
<td>14.4%</td>
</tr>
</tbody>
</table>
Navigenics’ competencies & partnerships

Core competencies

Platforms and assays

Scientific and Clinical Curation

Personalized Web Portal

Customer Experience

Lifestyle and Behavior

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.
People want to know what this means for them.
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?

[Image of a Navigenics Health Compass webpage showing a summary of diabetes type 2 risk, with sections on causes, what's next, and related content.]
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
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.

Diabetes

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 symptoms have appeared.

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 simple blood tests:

- Fasting glucose test: Measure blood glucose 75 milligrams per deciliter or higher.
- Other tests that may be done: that with one sample every six months, glucose tolerance test (GTT) following the ingestion of a glucose drink.
- Aim for 30 minutes of brisk walking, swimming, or a bus ride to keep your weight at a distance.

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 also 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, eye 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.
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.
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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.