

Considerations when undergoing personal genotyping

Kelly Ormond, MS, CGC
Louanne Hudgins, MD, FACMG

June 23, 2010
GENE 210


Disclosures and introductions

- Professor Ormond provided paid consultation for Navigenics GC Task Force (an advisory board) from 7/07-7/09
- Professor Hudgins has no disclosures

The “old” genetics

- Most genetic conditions were seen as rare and serious
- Medical Genetics was mostly practiced in pediatrics or obstetrics
- Testing was usually not available for inherited conditions
- Risk information was often limited
- Newborn screening and carrier testing based on ethnicity were as “population based” as genetics got...

Genetics of Today

- Testing available for several thousand conditions ()
 - Still mostly rare, mendelian,
 - based on family history or other risk factors (age, ethnicity)
- Family history is recognized as a key “genetic test”
- Focus shifting from mendelian to complex disease
- Approximately 3,000 genetic counselors and 1,100 medical geneticists in pediatrics, obstetrics, cancer genetics, neurogenetics, cardiogenetics...

Testing strategies: Mendelian conditions

- **Test a relative who is known to be affected first, so that results are most informative**
- Positive results (e.g. identify a pathogenic mutation)
 - Medical management, planning ahead
 - Consider penetrance and variable expression in discussing prognosis
 - Make life decisions (marriage, reproduction, education/career)
- Negative results (e.g. no mutation identified)
 - True negative if mutation identified in family
 - Family members' risks can be adjusted
 - If the person has an unclear phenotype, a negative result remains uninformative
 - They could still carry a mutation in a different gene, or in a part of the gene that was not assessed by the specific genetic test
 - Family members' risks cannot be adjusted
- Uncertain results (dreaded Variant of Uncertain Sig.)
 - Uninformative – you don't know if it is a mutation or a benign polymorphism
 - Family members' risks cannot be adjusted

Clinical example: Clear-cut mutation

- You have a 26 yo patient of Jewish background who comes to you because her 32 year old sister has a diagnosis of *breast cancer*. She does not have breast cancer, and she wants to have a genetic test. Wisely, you suggest her sister be tested first, since she has the clinical diagnosis. She is found to carry a mutation in *BRCA2* (*one of the 3 founder mutations*).
 - **This provides diagnostic confirmation, and an explanation for the condition in the family**
 - **The mutation is highly penetrant – 60-80% lifetime risk of breast cancer**
 - **There may or may not be genotype/phenotype correlations**
 - **Can offer targeted surveillance for recurrence, change surgical management for patient's affected sister and offer testing to unaffected relatives**

Predictive Testing: To know or not?

- Family members can now undergo accurate genetic testing
 - Do people WANT to know genetic information if it's uncertain whether and when it will happen?
 - Presymptomatic detection leads to medical recommendations
 - Will you alter your healthcare? Will you alter your life planning?
 - Will you see yourself differently? Will people (including family) treat you differently? In a positive or negative manner?

- You have a 26 yo patient who comes to you because her 32 year old sister has a diagnosis of *breast cancer*. She does not have breast cancer, and she wants to have a genetic test. Wisely, you suggest her sister be tested first, since she has the clinical diagnosis.
- *No mutations are found. You send the sample for full sequencing. The lab finds a novel change, which is called a “Variant of Uncertain Significance.” (VUS)*
 - **In contrast to the last case, we don’t know if this variant is causally related to the breast cancer in the family.**
 - **Testing family members may not be clinically useful unless you can establish the VUS tracks with the condition**
- *What if we’d only tested the unaffected patient and found a VUS – how do we interpret it?*

Clinical example: VUS (Variant of Uncertain Significance)

Most of the data about how patients think about “variants of uncertain significance” comes from BRCA1/2 testing

- Patients tend to think in a binary fashion and aren’t that good at making meaning out of unclear results
- Patients may also be more frustrated and anxious with a variant than with a clearcut mutation

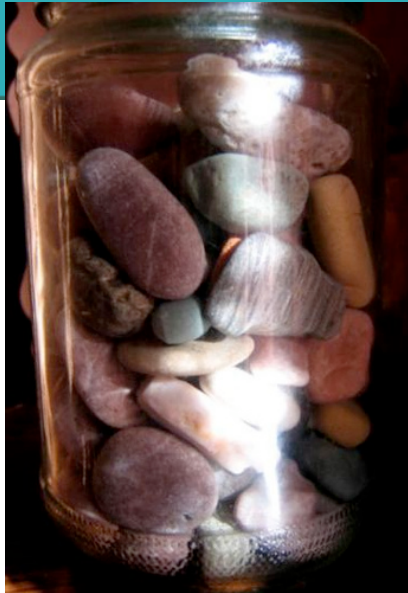
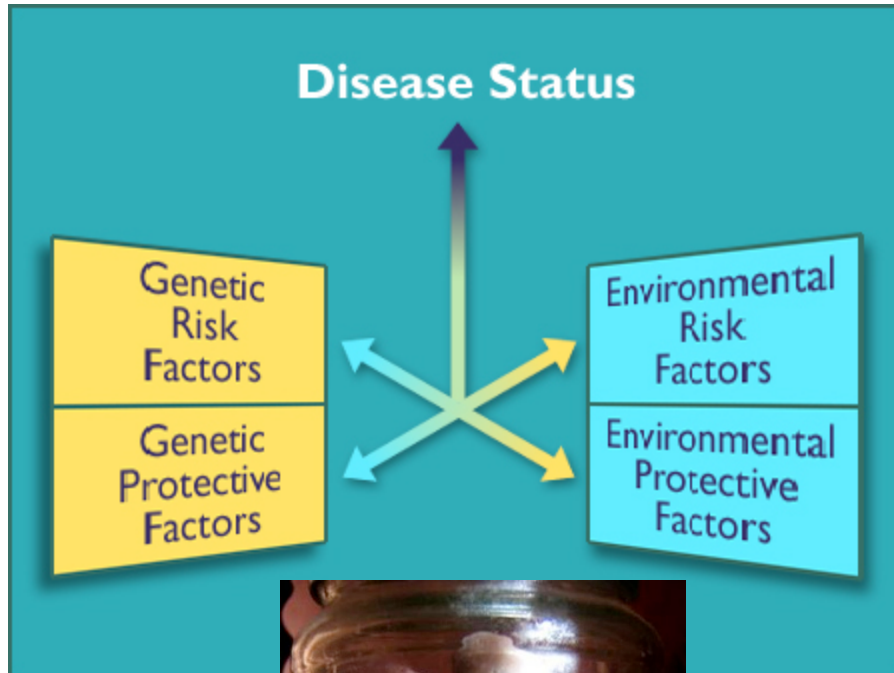
- As the physician, how (if at all) do you alter medical management on the basis of a variant?
- Presymptomatic detection may lead to changed management, but should it? It may inappropriately increase risks to patient

The “new” genetics of today and tomorrow

- Complex genetics 101
 - All the genetic rules are less clear
 - Addressing common conditions of adulthood
 - Involves both genetic and lifestyle components
 - Genome wide testing via SNPs and exome/genome sequencing
- Testing available for more and more conditions, but good prediction still a long way off for most common complex disease



“Multifactorial” Inheritance



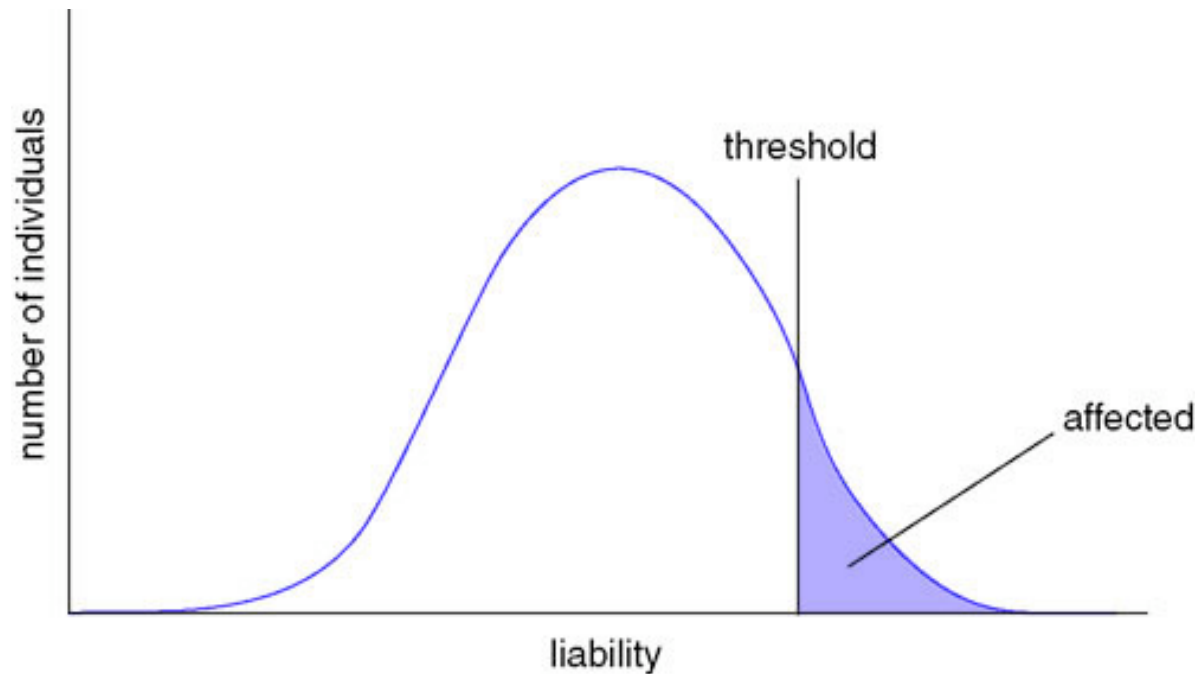
- **Polygenic** – Multiple genes act in concert, with each contributing a small amount to the overall genetic risk

- Often these conditions follow a normal, Gaussian, distribution

- “heritability” (h^2) is the term that addresses the genetic variance

- **Multifactorial** – both genetic and environmental factors contribute to the phenotype

The Threshold/Liability Model

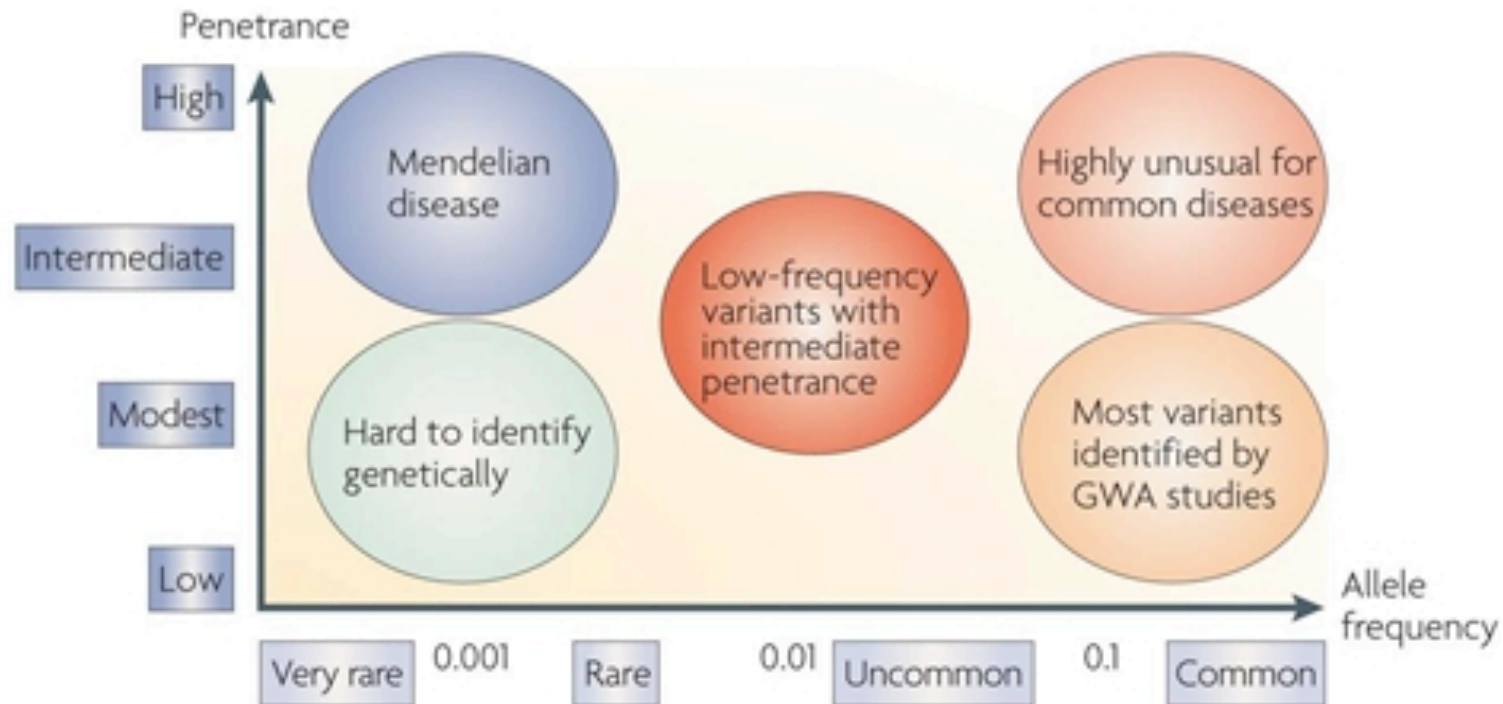


Important Factors

- Severity of disorder in proband
- Gender of proband
 - Less common gender inc. risk
- Number of affecteds in family
- Distance of relationship to proband
- Consanguinity
- Assumes that liability is normally distributed within the population
- Takes into account genetics and environmental liabilities

Single genes and beyond...

Box 7 | Low-frequency variants and disease susceptibility



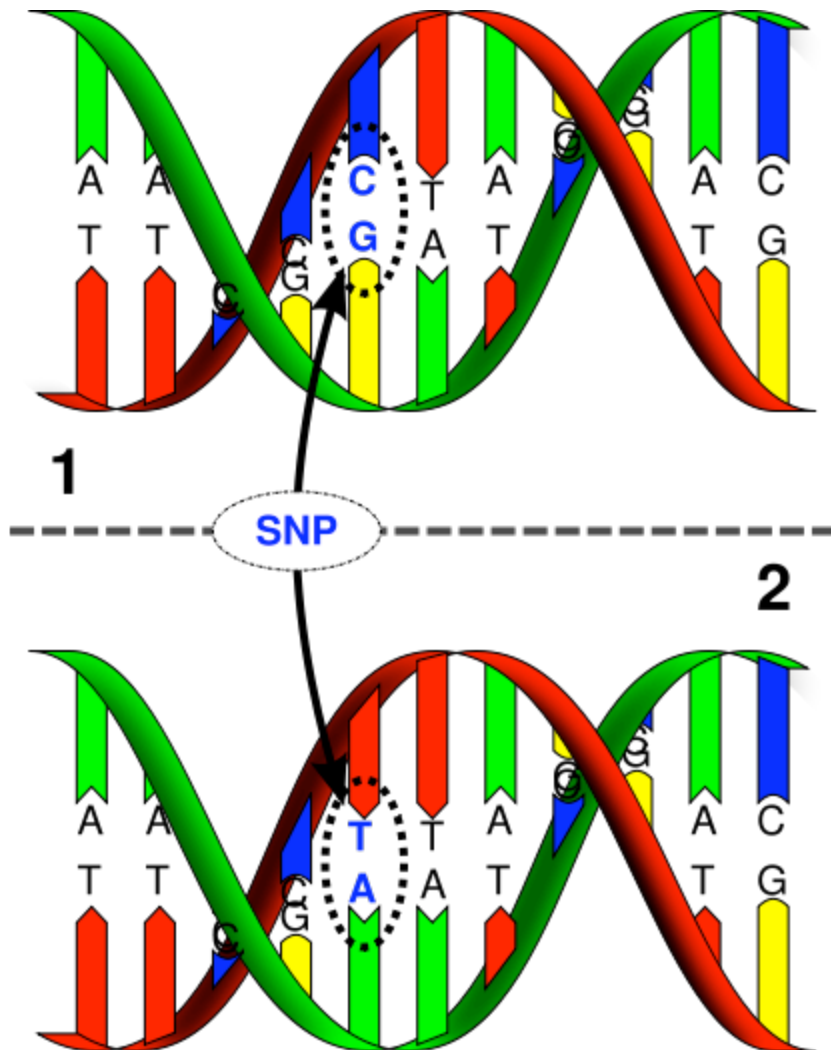
McCarthy
et al., 2009

What is a GWA Study anyway?

- Genome wide association study
- Allows you to “probe” the entire genome
- Find previously unsuspected associations between SNPs and phenotype
- Find lots of associations at the same time



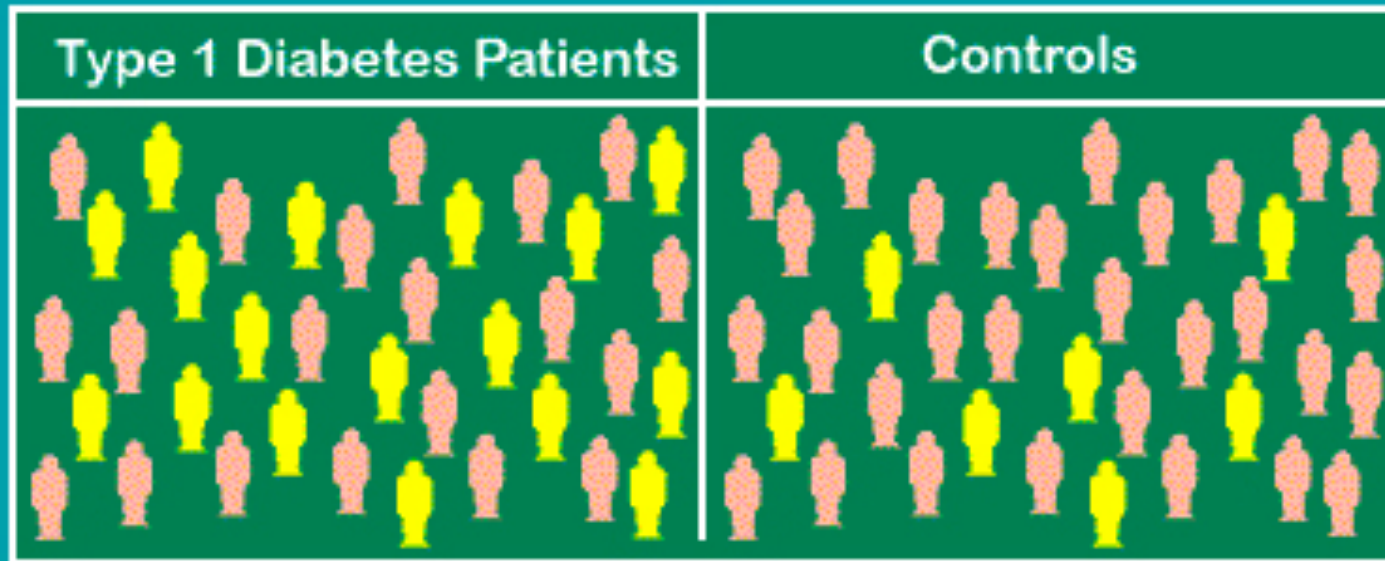
What is a SNP



- Single nucleotide polymorphism
- Estimated $\sim 1/1000$ base pairs
- If $\sim 3,300,000,000$ bp, that is several million SNPs in the genome!
- ~ 10 Million validated SNPs in dbSNP already
- dbSNP assigned reference SNP
 - (eg. rs709932)

<http://www.ncbi.nlm.nih.gov/About/primer/snps.html> for more basic info

Association Studies



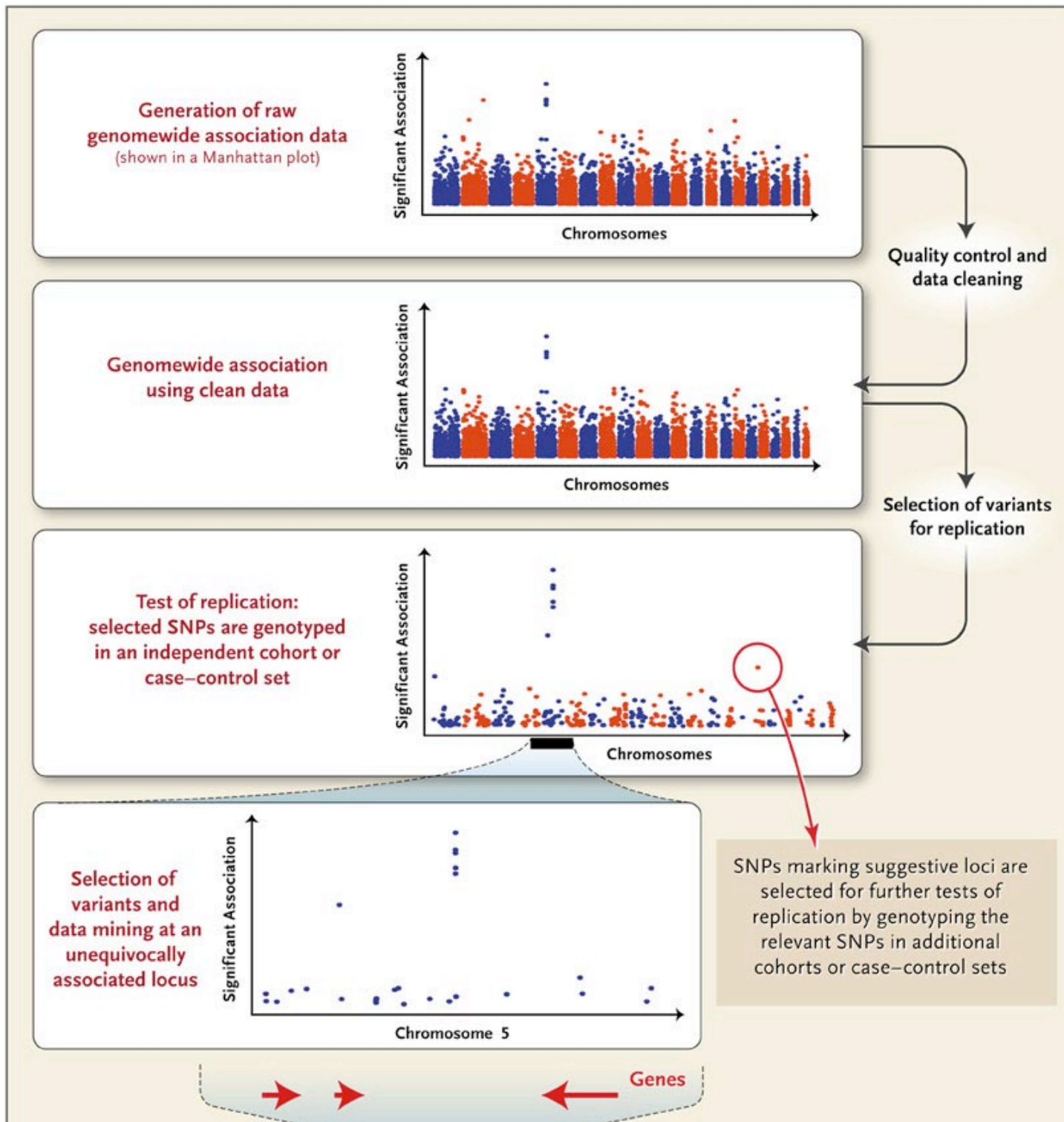
Genotype	Type 1	Controls	Total
HLA DR4	17	7	24
NON-HLA DR4	20	30	50
	37	37	

$$\chi^2_{.05} = 5.377$$

$$p < 0.025$$

 = HLA DR4

 = non-HLA DR4



Hardy,
2009

Interpreting the data

- If you look at 500,000-1M SNPs, odds are that many of them are going to appear positive just by chance alone...
- How do you know if it's real?
 - Bonferoni corrections - lead to much smaller p values
 - Use 5×10^{-7} (conservative)
 - Replication in similar populations...
 - Hirschorn et al. 2002 – of 166 early GWA studies, only 6 replicated in multiple studies
 - Currently ~ 450 **published GWA at $p \leq 5 \times 10^{-8}$**

Challenges interpreting GWA Studies

- Vast majority of data remains based on European Caucasian populations
- Population stratification issues
 - Populations may have different MAFs, which could lead to spurious associations
- Defining the phenotype (and controls) accurately
 - Ascertainment biases
- Study size
- Different platforms assess different things, but generally only pick up SNPs with a relatively 'common' minor allele frequency

“Missing heritability”

- Where’s all that “missing heritability”?
 - Age related Macular Degeneration – 5 loci, 50% of heritability
 - Crohn’s disease – 35 loci, 20% heritability
 - T2Diabetes – 18 loci, 6% heritability
 - Height – 40 loci, 5% heritability
 - Fasting glucose – 4 loci, 1.5% heritability
- ORs may underestimate actual risks b/c SNPs more distant from causal variant
- Low MAF alleles not currently being assessed
- (Manolio et al, 2009 – 2009 Oct 8;461(7265):747-53)

A primary reason doctors slow to adopt

ARTICLE

Evaluation of risk prediction updates from commercial genome-wide scans

*Raluca Mihaescu, MD¹, Mandy van Hoek, MD^{1,2}, Eric J. G. Sijbrands, MD, PhD²,
André G. Uitterlinden, PhD², Jacqueline C. M. Witteman, PhD¹, Albert Hofman, MD, PhD¹,
Cornelia M. van Duijn, PhD¹, and A. Cecile J. W. Janssens, PhD¹*

When considering the 5% of the population at highest risk for diabetes (N=5297 total population):

- *TCF7L2* only = 28.0% risk (AUC 0.55)
- All 18 polymorphisms = 29.7% risk (AUC 0.60)
- Clinical factors only (AUC =0.63)
- Clinical + *TCF7L2* (AUC =0.64)
- All 18 + clinical factors = 36.8% risk (AUC 0.66)

Table 1 Measures of model performance for dichotomizing predicted risk at average risk

	Model based on <i>TCF7L2</i> (%)	Model based on 18 polymorphisms (%)	Model based on 18 polymorphisms, age, sex, and body mass index (%)
Sensitivity	55.7	50.8	57.2
Specificity	51.8	62.7	64.5
PPV	21.8	24.7	28.0
NPV	82.9	84.1	86.2

Measurements are based on individuals with complete genotype and clinical information.
PPV, positive predictive value; NPV, negative predictive value.

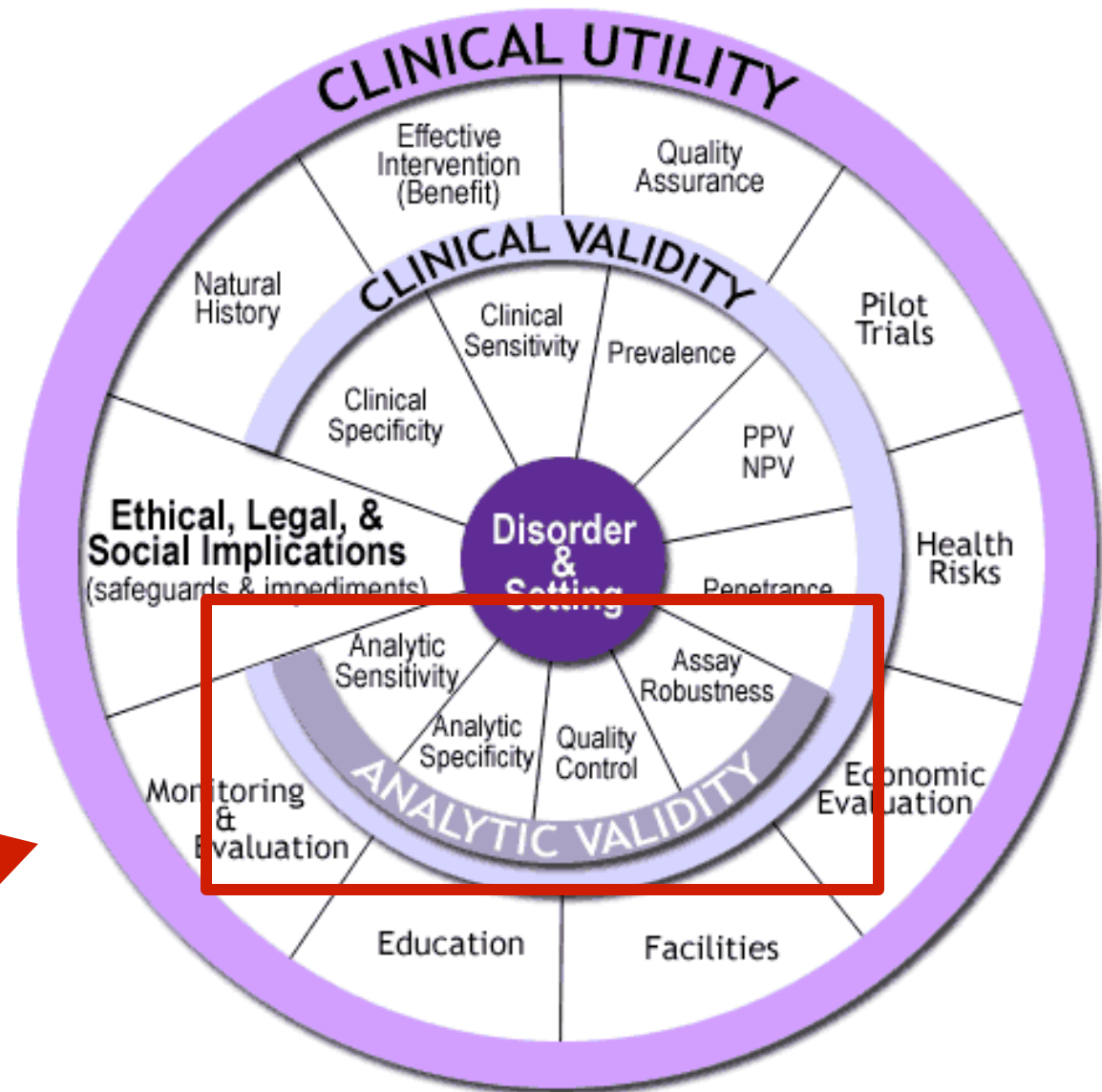
Comparison of individual risk factors for MI

Risk Assessment	Risk Factor	Effect (odds-ratio)
Positive Family History	parent with MI <50 yrs	1.52
Genetic Risk Factors	9p21	1.72
	MTHFD1L	1.53
Environmental Risk Factors	Stage 2-4 hypertension	1.92
	LDL>160	1.74
	HDL<35	1.46
	smoker 12 mos	1.71
	diabetes, type 2	1.47
	no exercise	1.39

- | Most individual genotypes will have a relatively low OR, but there is the possibility that in combination the impact will be larger
- | Range of effect sizes for genetic risk markers is similar to established environmental and family history risk factors

Modified from a slide by Elissa Levin, MS, CGC

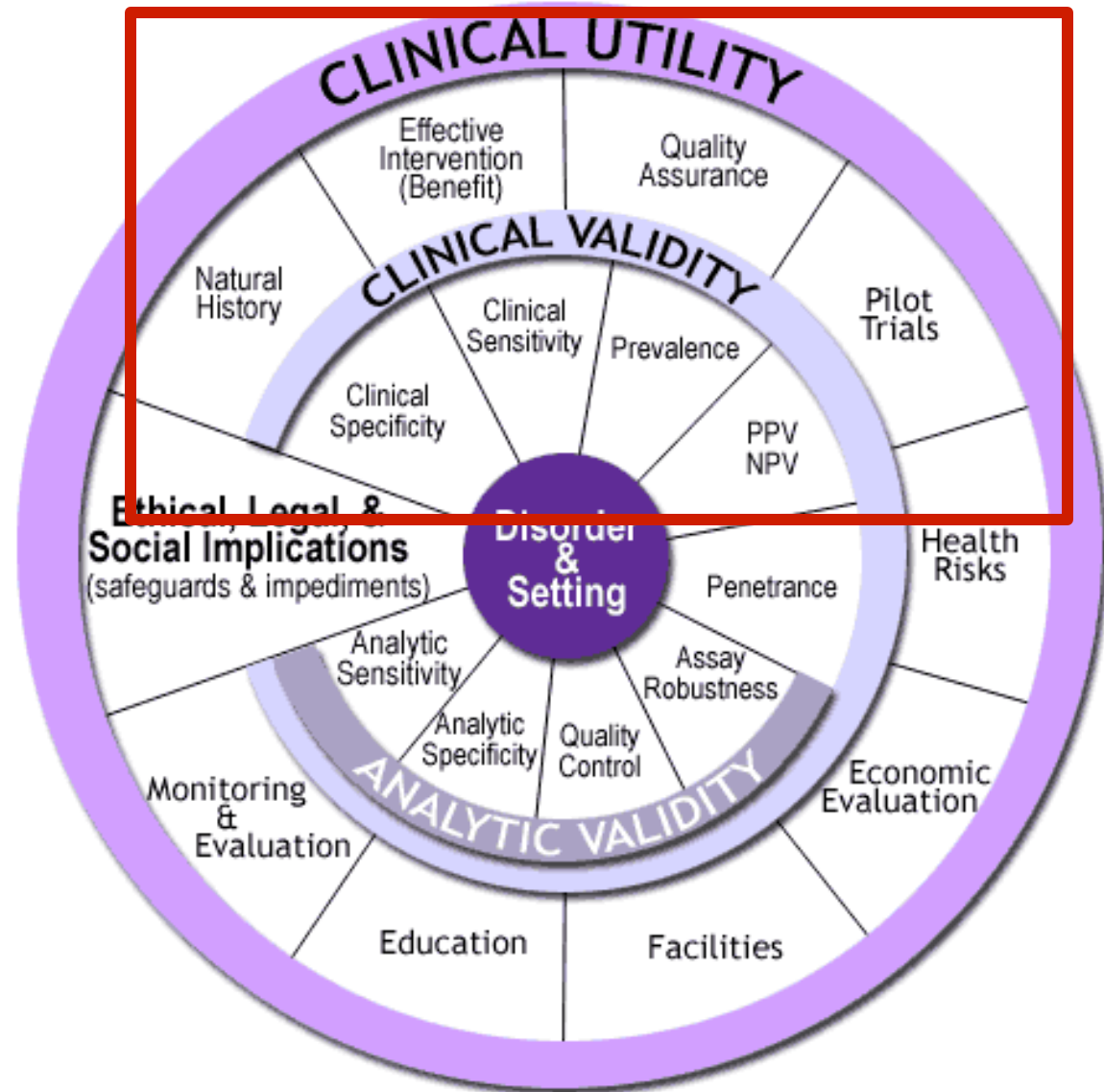
Evaluating the tests...



Laboratory focus

Evaluating the tests...

- Sensitivity and Specificity
 - Ability to correctly identify clinically affected persons with positive results and clinically unaffected persons with negative results
- PPV/NPV
 - considers prevalence
- Validation across all relevant populations
- Methods to resolve initial positive results diagnostically
- Knowledge of natural history
- Changes in medical management
- Psychological benefit?
- **The medical “so what”?**



Do SNPs meet the Clinical Validity “Test”?

(adapted from cdc.gov)

- How often is the test positive when the disorder is present?
- How often is the test negative when the disorder is not present?
- Are there methods to resolve clinical false positive results in a timely manner?

- What is the prevalence of the disorder in this setting?
- Has the test been adequately validated on all populations to which it may be offered?
- What are the positive and negative predictive values?

- What are the genotype/phenotype relationships?
- What are the genetic, environmental or other modifiers?

Ten Basic Questions to Ask About a Genome-wide Association Study Report

- 1. Are the cases defined clearly and reliably so that they can be compared with patients typically seen in clinical practice?
- 2. Are case and control participants demonstrated to be comparable to each other on important characteristics that might also be related to genetic variation and to the disease?
- 3. Was the study of sufficient size to detect modest odds ratios or relative risks (1.3-1.5)?
- 4. Was the genotyping platform of sufficient density to capture a large proportion of the variation in the population studied?
- 5. Were appropriate quality control measures applied to genotyping assays, including visual inspection of cluster plots and replication on an independent genotyping platform?

Top 10 questions (con't)

- 6. Did the study reliably detect associations with previously reported and replicated variants (known positives)?
- 7. Were stringent corrections applied for the many thousands of statistical tests performed in defining the P value for significant associations?
- 8. Were the results replicated in independent population samples?
- 9. Were the replication samples comparable in geographic origin and phenotype definition, and if not, did the differences extend the applicability of the findings?
- 10. Was evidence provided for a functional role for the gene polymorphism identified?
 - For a more detailed description of interpretation of genome-wide association studies, see NCI/NHGRI Working Group on Replication in Association Studies. (taken from *Pearson and Manolio 2008*)

- **What SNPs are included to develop the OR?**
 - Where does that data come from (size, population variances, etc.)
 - How good a job is done “cleaning” the data for spurious associations
 - Who/how to decide what is “legit” for inclusion?
 - Models for interactions and additive nature of the risk factors are becoming available (Drenos et al. 2007)
 - Data changing rapidly at this point – reanalysis? Recontact?
 - Do SNPs meet the clinical validity test?
 - Just because we can “know it”, does that make it useful?

So what will I learn if I undergo personal genotyping?

- Depends on the company!
 - (Louanne will discuss further)
- Medical conditions
 - Estimate risk for common complex diseases (may or may not be “actionable”)
 - Pharmacogenomic information
 - Some examine carrier status for various conditions
- Traits?
- Ancestry?
- Family relationships?

What sort of data will I get?

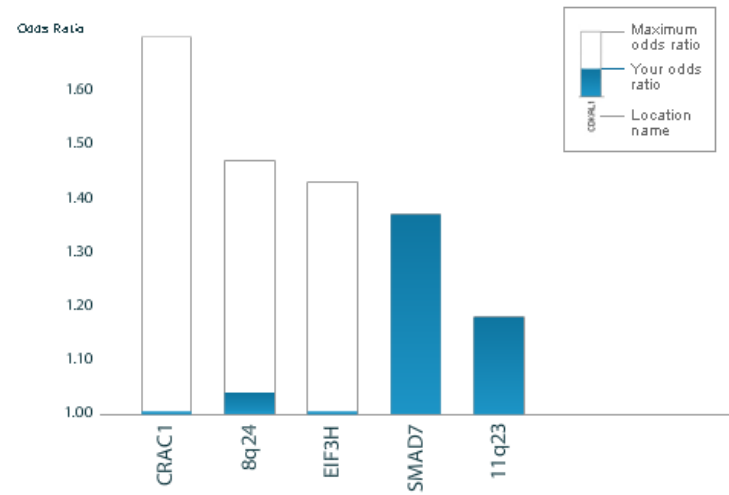
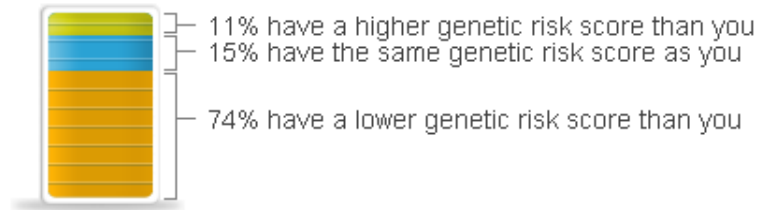
Heart attack

You: 28%

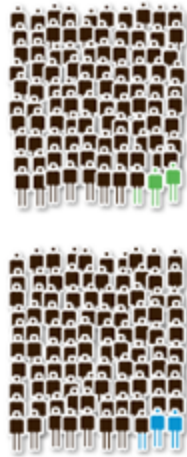
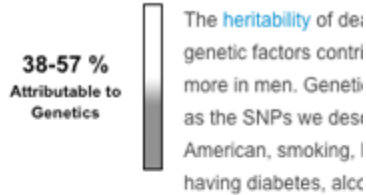
Avg: 25%

[more](#)

Here's another way to look at your risk. In a sample population:



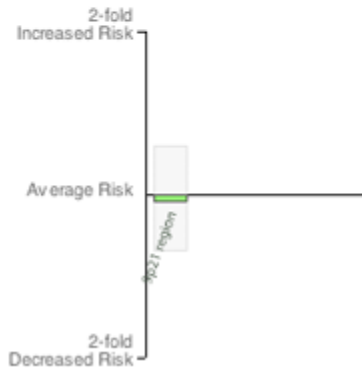
Genes vs. Environment



Robert Gramble
2.4 out of 100
people of European ethnicity who share Robert Gramble's genotype will get Heart Attack between the ages of 45 and 54.

Average
2.5 out of 100
people of European ethnicity will get Heart Attack between the ages of 45 and 54.

Marker Effects



Gene or location	Risk marker	Your markers	Odds ratio	Source
9p21	C	GG	1.0	Science, 2007
MTHFD1L	A	GG	1.0	New England Journal of Medicine, 2007

Navigenics.org; 23andme.com

What are the potential benefits of personal genotyping

- You may have some validation that you are at increased risk for specific common disorders present in your family
- If you are found to be at elevated risk, this may help you decide to make some lifestyle or behavioral changes to decrease your risks, or to get screening at an earlier or more frequent age than otherwise
- If you are adopted and don't know your family medical history, this may provide you with some information



What are the potential “risks” to personal genotyping

- There are minimal physical risks (spit in tube)
- There are minimal financial risks
 - Personal cost of test \$99
 - Insurance risks? GINA +/-



What are the potential “risks” to personal genotyping

- The emotional risks include:
 - You might learn that you have a high risk for something you were not previously aware of
 - Most risks from GWAS data are small odds ratios – this is not like testing for Huntington disease
 - 23andme does include BRCA1/2 Jewish founder mutations, which ARE highly penetrant
 - Depending on the test, you might learn about your risks for a condition like Alzheimer disease (Navigenics) or psychiatric illness risks for Bipolar or Schizophrenia (23andme)
 - In some cases you can opt out of learning this information if you don't want to learn it
 - You might learn something about your ancestry that makes you uncomfortable
 - If more than one person in your family gets tested, you might learn that family relationships are not what you expected

What about GINA?

- Genetic information nondiscrimination act (signed 5/2008)
- Federal provisions to protect against genetic discrimination in the realms of health insurance (5/09) and employment (11/09)
- No protections for life, disability and long-term care insurance
- Few actual reports of discrimination on the basis of presymptomatic mutation status, but this federal bill will provide additional protections and, hopefully, help patients and families feel more confident undergoing testing
- <http://www.genome.gov/10002328>

Are there any potential health risks?

- You might find out about an elevated health risk and decide to undergo an invasive screening test that wasn't really necessary, putting yourself at an increased risk for complications.
- You might find out about a decreased health risk and decide you no longer needed to undergo routine screening tests that are recommended to the general population, and there is always a chance you could still develop that condition (and have it detected at a later point, impacting prognosis).

What other factors should be considered

- The companies do both use CLIA approved laboratories, but are not regulated
- Each company uses a different algorithm to calculate your lifetime risks
- Your “risks” will change over time as the companies modify their algorithms and add additional SNPs
- What happens to your data?
 - Is the company going to use your DNA for future study? Do you opt in or out?
 - What if you decide you want your data removed from their databases?
 - What if the company goes bankrupt? Who gets the data?
 - How secure are the confidentiality protections via the websites?

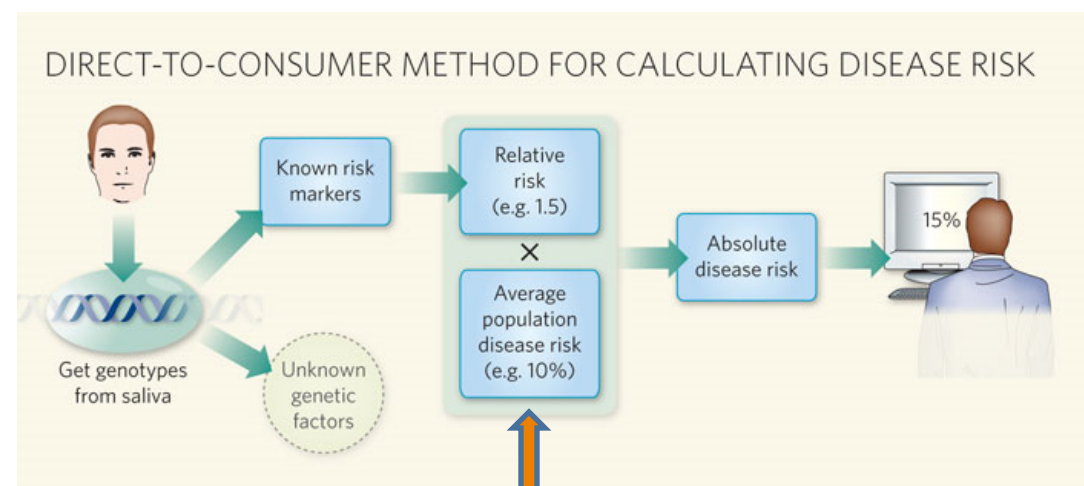
OPINION

An agenda for personalized medicine

Pauline C. Ng, Sarah S. Murray, Samuel Levy and J. Craig Venter find differences in results from two direct-to-consumer genetics-testing companies. They therefore give nine recommendations to improve predictions.

- Most (all?) of the current GWAS predications are currently being offered by direct-to-consumer companies

- Companies use unique algorithms for calculating risks and selecting which SNPs and population risks to consider in their calculations



99.7%
match

Variation in how pop risk
calculated (age, gender)

Both companies provide
absolute risk

Ng, 2009

21 of 58 risk predictions differed between the two companies

Only 4 diseases provided consistent risk prediction:

- Breast cancer
- Celiac disease
- Multiple sclerosis
- Rheumatoid arthritis

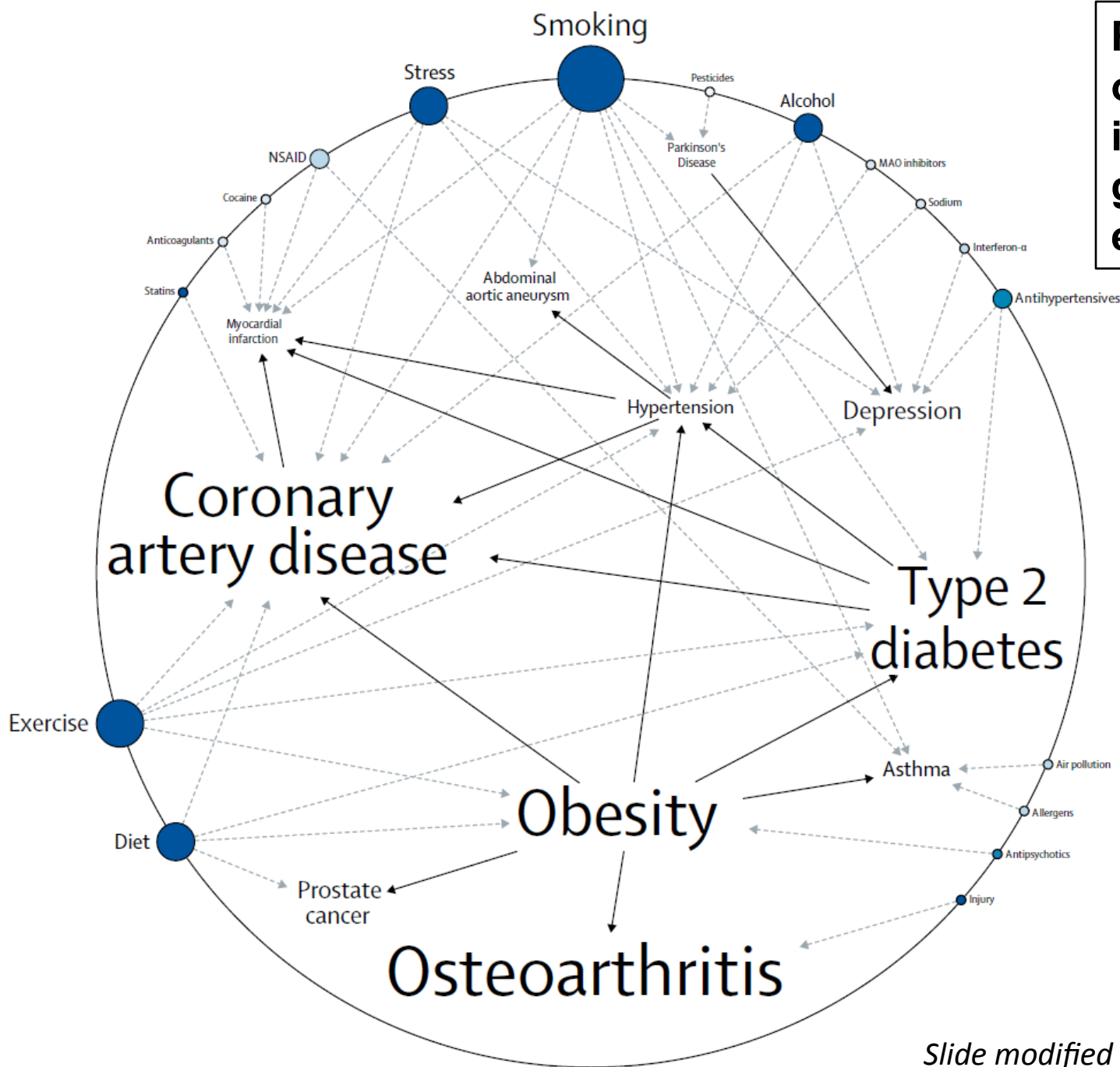
Mihaescu 2009 showed that if they adjusted the data every time a new marker was added, risks “yo-yo” back and forth, which could lead to patient confusion

TABLE 1: PREDICTIONS FOR DISEASE RELATIVE RISKS FOR FIVE INDIVIDUALS

Disease	Female A	Female B	Female C	Male D	Male E
Breast cancer	↑↑	↑↑	↓↓		
Coeliac disease	↓↓	↓↓	↓↓	↓↓	↓↓
Colon cancer	==	==	=↓	↑↑	=↓
Crohn's disease	↓↑	↓↑	↓↓	↓↓	↓=
Heart attack	↓↓	=↓	=↓	=↓	↑↑
Lupus	↑↓	↓↓	↓↓	↑=	↑=
Macular degeneration	↓↓	↓↓	↑=	↓↓	↓↓
Multiple sclerosis	↑↑		↓↓	↓↓	↓↓
Prostate cancer				↑↑	↓↑
Psoriasis	↓↑		↑↓	↑↑	↓↓
Restless legs syndrome	=↓	↑↑	↓=	↓↑	↑↑
Rheumatoid arthritis	↑↑	↑↑	↓↓	↓↓	↑↑
Type 2 diabetes	↓↓	=↓	↓↓	↑↓	=↓

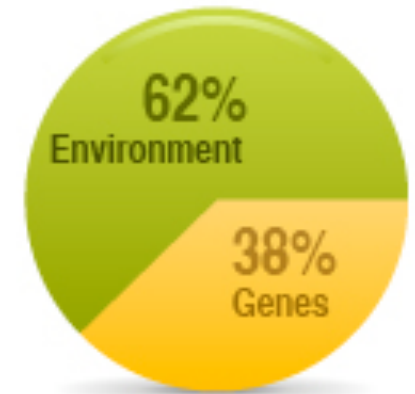
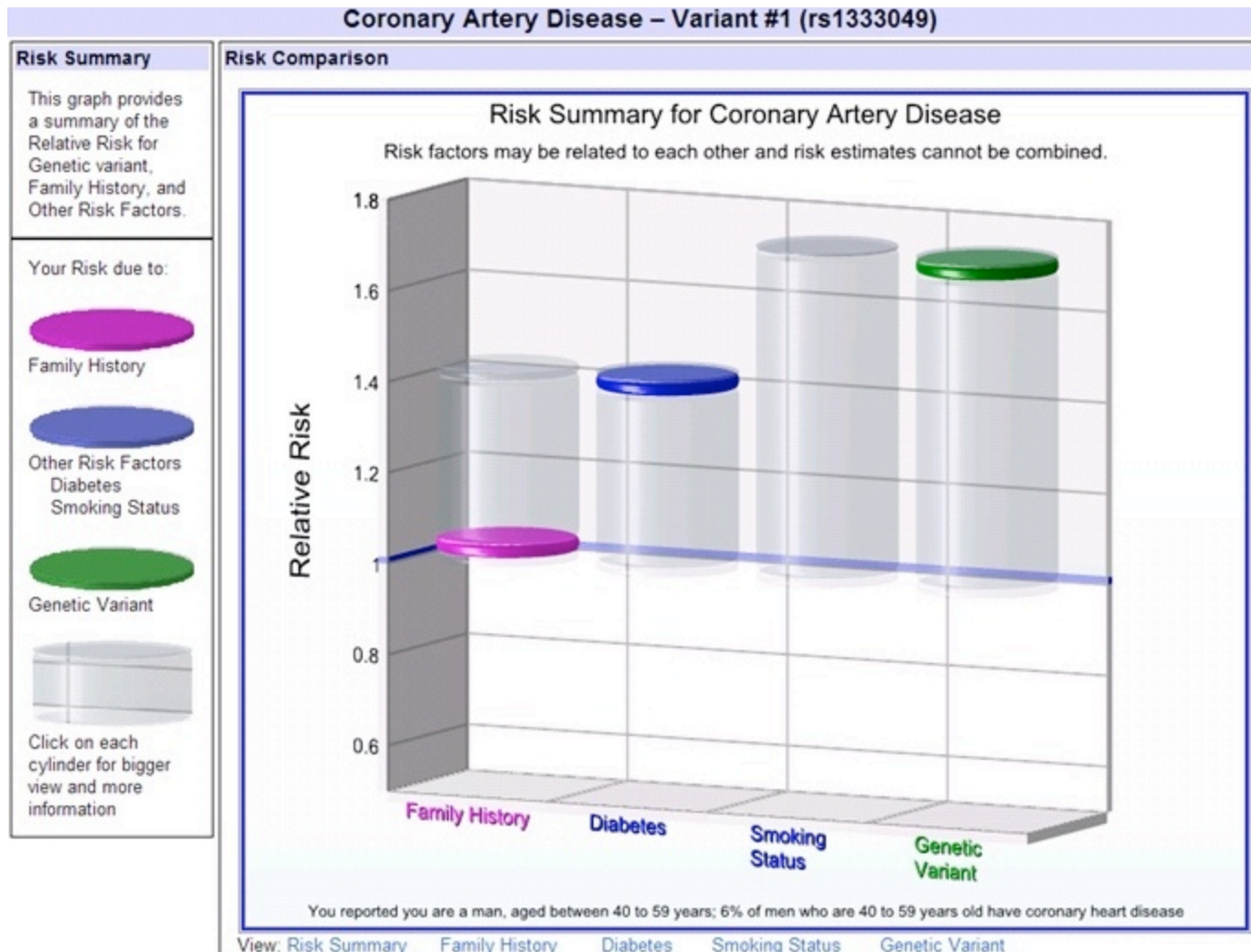
↑ increased risk (RR > 1.05), ↓ decreased risk (relative risk (RR) < 0.95), = average risk (0.95 ≤ RR ≤ 1.05). First prediction is from 23andMe; second prediction is from Navigenics. Different predictions are highlighted in beige.

Risks do not occur in isolation, either genetically or environmentally!



Slide modified from Atul Butte, 2010

Environmental risks may be as large, or larger, than genetic risks

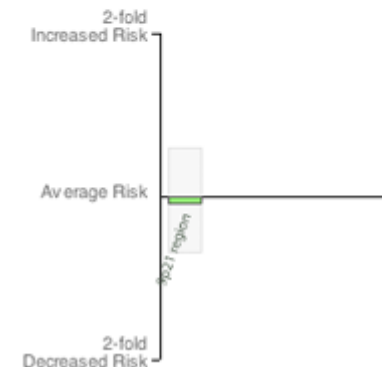


Genes vs. Environment

38-57 %
Attributable to
Genetics

The *heritability* of de:
genetic factors contri
more in men. Geneti
as the SNPs we des
American, smoking, l
having diabetes, alcc

Marker Effects



Do YOU want to know?

- Is there ANY sort of condition that you would NOT want to know about predictively?
- Fatal vs. Chronic Static vs. Progressive
- Is it treatable?
- Is screening available to promote early diagnosis?
- Is there anything you can do to reduce your risk?
- What is the typical age of onset
- Why might people NOT want to know

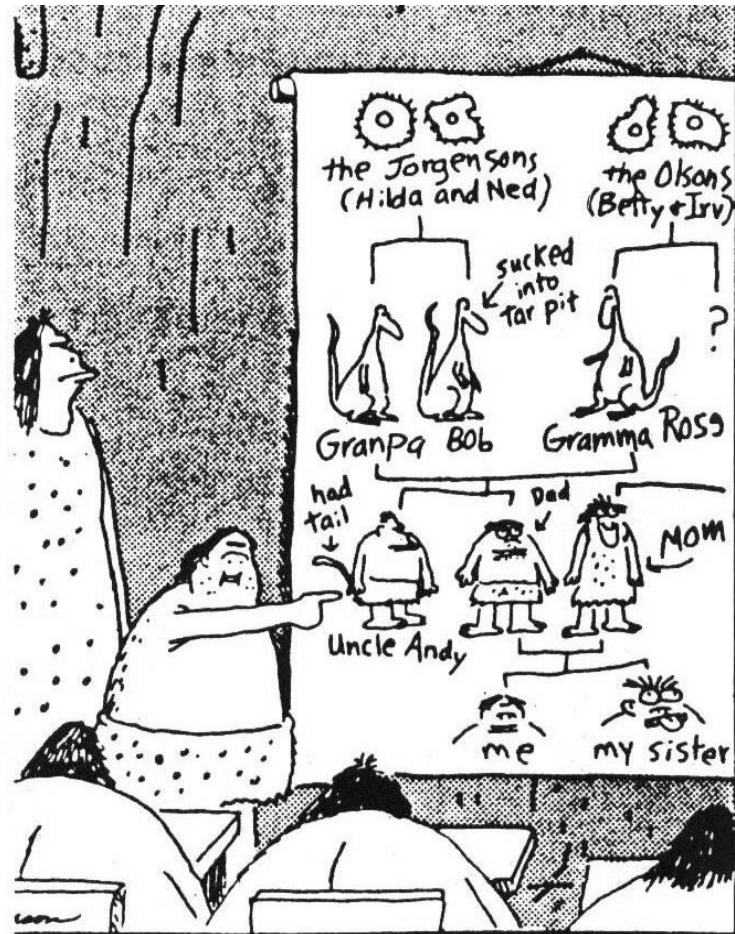


Questions you should think about...

- Why do you want to know?
- Why now versus at another time in your life?
 - As a medical student or graduate student, are knowing these risks going to make you more or less likely to worry about them?
 - How does your age, current health, relationship status and parenting status impact your decision?
- Have you told your family you are considering this?
What do they think?
 - Is there external pressure to get tested? Is this a good or bad thing?
- With whom will you share your results?
 - Family? Partner? Doctor? Friends? Classmates? Teachers?

- What result are you expecting? Why?
- How do they think you will respond if the result is not what you are expecting?
- What, if anything, do you think you will do about the conditions you learn you are at increased risk for?
- Are there behavioral or screening changes you can make without your genotyping results? What factors might be holding you back? How will genotype results *really* interact with the day-to-day barriers we all face for behavior change?

Before you test, assess your family history!



Dirk brings his family tree to class.

First degree relative means 2-5X risk for disease

Common diseases (age that defines early onset)

- coronary heart disease (60)
- sudden unexpected death (40)
- stroke/TIA (mini stroke) (60)
- hypertension (40)
- diabetes (20)
- blood clots in lungs or legs (40)
- emphysema/lung disease (50)
- kidney disease (50)
- breast, ovarian or endometrial cancer (50)
- prostate cancer (50)
- colon/colorectal cancer (50)
- thyroid cancer (50)
- kidney cancer (50)

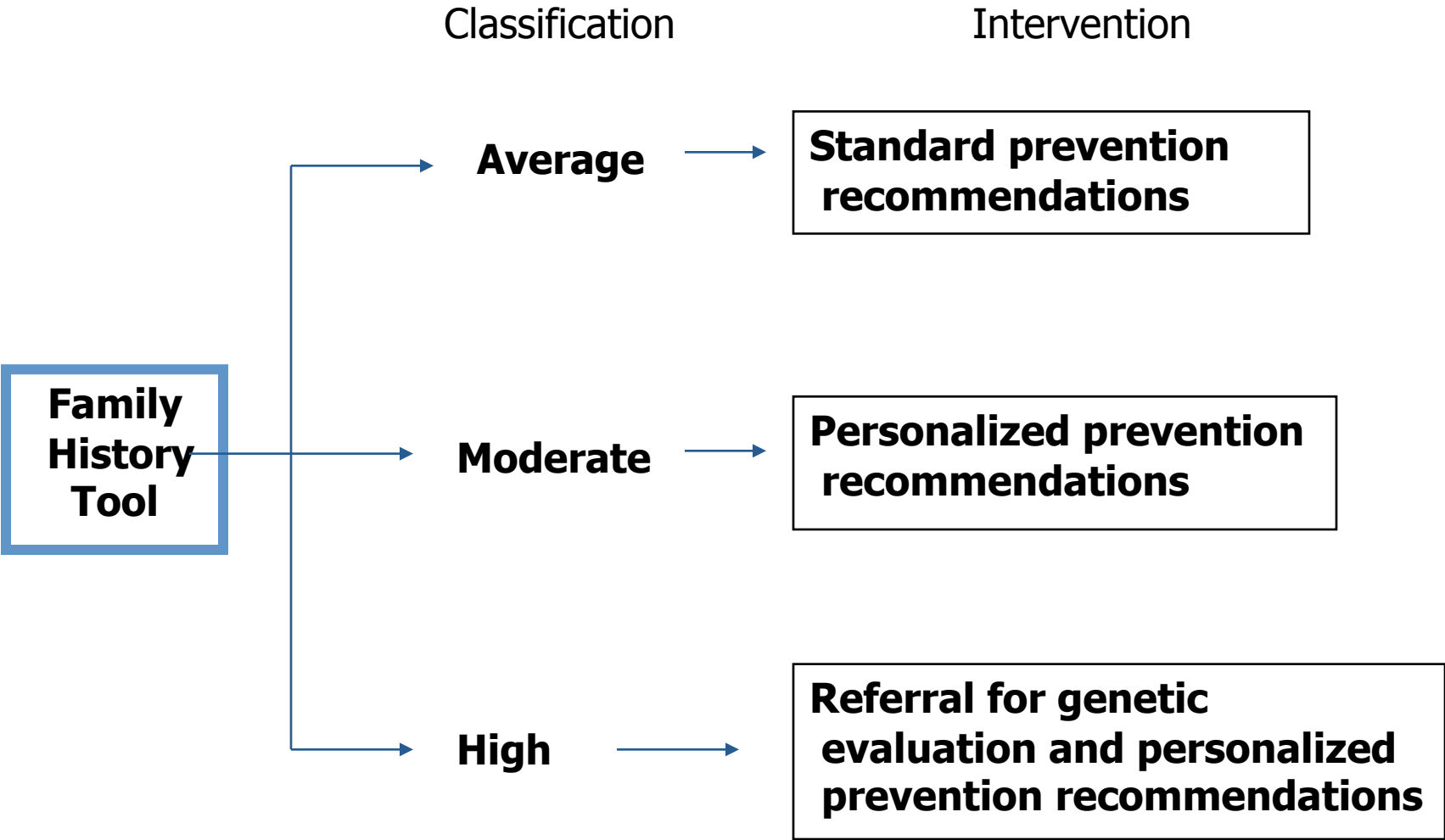
**Family
History
Tool**

1st draft

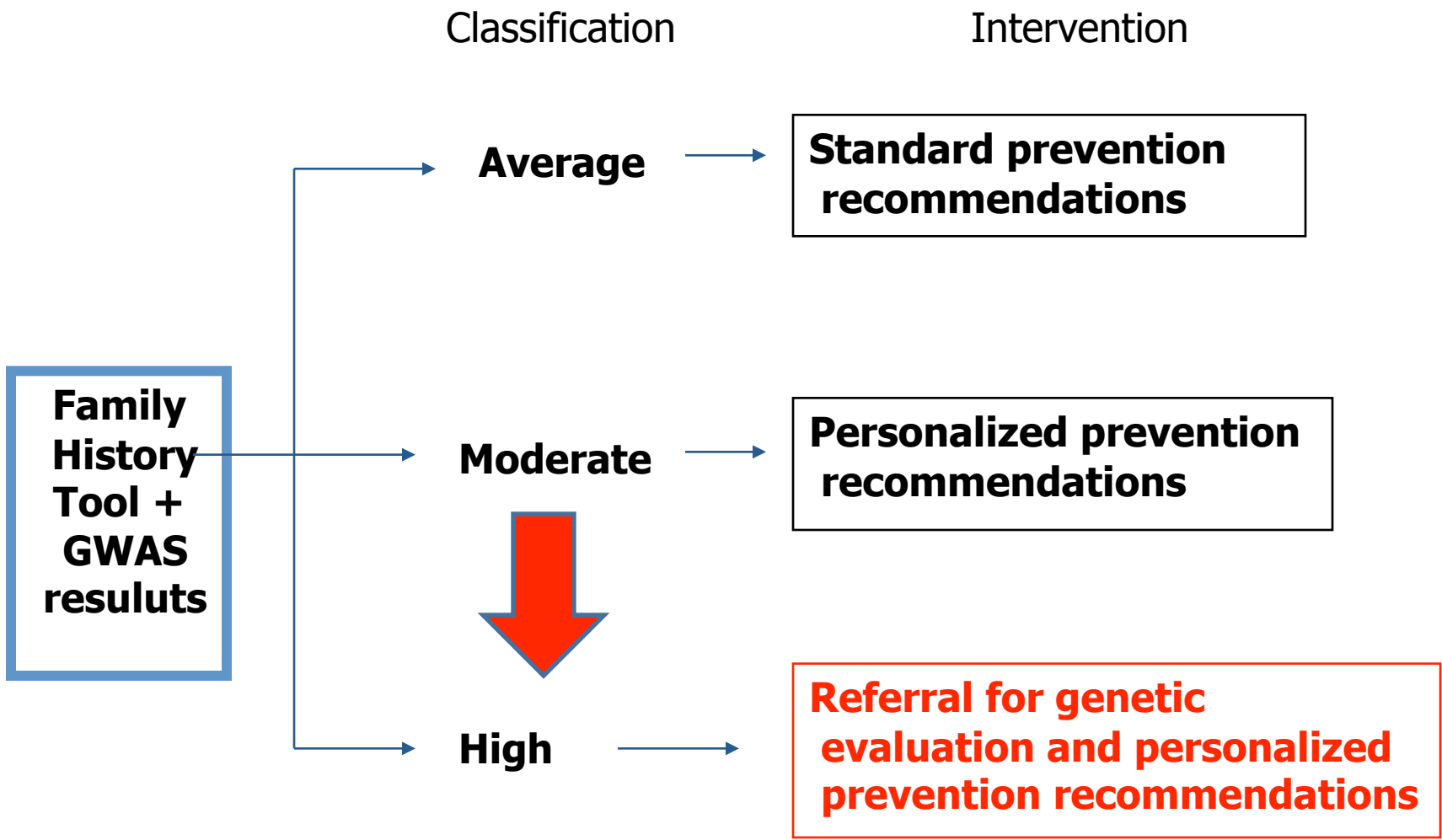
Bigger than
most
GWAS
odds
ratios!

**FHx will
predict
your GWAS
results**

Using family history for disease prevention



Using family history for disease prevention



Professional societies on DTC genetic testing

- <http://www.nsgc.org/about/position.cfm#DTC>
- http://www.acmg.net/StaticContent/StaticPages/DTC_Statement.pdf
- http://www.ashg.org/pdf/dtc_statement.pdf

How to choose a DTC genetic testing service

- What do you really want to know?
 - What are the conditions tested for?
 - How serious is each specific condition?
 - What is the age of onset for each specific condition?
 - What does this mean for my health and the health of my family members?
 - Will I change my behavior based on the results?
 - Will the results cause me and/or my family members undue anxiety?
 - Does the company provide someone to talk to if you have questions including a genetic counselor or geneticist?



- Overview
- How it works
- Our genetic testing
- Why Navigenics
- Genetic counseling
- Conditions we cover**
- Our policies
- FAQs
- Success stories
- Request information
- Tell a friend

Try Demo

Receive our newsletter

email address Sign Up

Conditions we cover

Navigenics analyzes your DNA for genetic risk markers associated with a wide variety of important health conditions

Abdominal aneurysm	Glaucoma	Obesity
Alzheimer's disease	Graves' disease	Osteoarthritis
Atrial fibrillation	Heart attack	Prostate cancer
Brain aneurysm	Hemochromatosis	Psoriasis
Breast cancer	Lactose intolerance	Restless legs syndrome
Celiac disease	Lung cancer	Rheumatoid arthritis
Colon cancer	Lupus	Sarcoidosis
Crohn's disease	Macular degeneration	Stomach cancer, diffuse
Deep vein thrombosis	Melanoma	
Diabetes, type 2	Multiple sclerosis	

A health investment that continues to grow

Navigenics Health Compass is an extensive, health-focused set of genetic testing services, offering genetic insights now and in the future. Our testing platform includes all of the conditions listed above, and then enables ongoing updates to bring you new genetic results for as long as you subscribe. At any step in the process, you'll be able to consult with our board-certified Genetic Counselors, health professionals who can help you understand your results and decide on next steps.

what is 23andMe?

- ▶ Health and Traits
- Ancestry
- Sharing and Community
- 23andMe Research

learn more

- How It Works
- Frequently Asked Questions
- Scientific Standards
- Considerations

23andMe for...

- Health Conscious
- Genealogists
- Mixed Ethnicities
- Physicians
- Scientists
- Students

health and traits: complete list

Your 23andMe scan includes genetic analysis on all of the following diseases, traits, and conditions. This list grows every month as new research is published.

Clinical Reports (30)

Clinical Reports give you information about conditions and traits for which there are genetic associations supported by multiple, large, peer-reviewed studies. Those associations must also have a substantial influence on a person's chances of developing the disease or having the trait. Because these associations are widely regarded as reliable, we use them to develop quantitative estimates and definitive explanations of what they mean for you.

- | | |
|---|---|
| Age-related Macular Degeneration | Lactose Intolerance |
| Alcohol Flush Reaction | Malaria Resistance (Duffy Antigen) |
| Alpha-1 Antitrypsin Deficiency | Muscle Performance |
| BRCA Cancer Mutations (Selected) | Non-ABO Blood Groups |
| Bitter Taste Perception | Norovirus Resistance |
| Bloom's Syndrome | Parkinson's Disease |
| Celiac Disease | Prostate Cancer |
| Clopidogrel (Plavix®) Efficacy | Psoriasis |
| Crohn's Disease | Resistance to HIV/AIDS |
| Cystic Fibrosis (Delta F508 mutation) | Rheumatoid Arthritis |
| Earwax Type | Sickle Cell Anemia & Malaria Resistance |
| Eye Color | Type 1 Diabetes |
| G6PD Deficiency | Type 2 Diabetes |
| Glycogen Storage Disease Type 1a | Venous Thromboembolism |
| Hemochromatosis | Warfarin (Coumadin®) Sensitivity |

Research Reports (86)

<http://virtualmentor.ama-assn.org/2009/09/pdf/pfor1-0909.pdf>



[buy \\$399 USD](#)

[try a demo](#)



- Overview
- How it works
- Our genetic testing
- Why Navigenics
- Genetic counseling
- Conditions we cover**
- Our policies
- FAQs
- Success stories
- Request information
- Tell a friend

Conditions we cover

Navigenics analyzes your DNA for genetic risk markers associated with a wide variety of important health conditions

Abdominal aneurysm

Alzheimer's disease

Atrial fibrillation

Brain aneurysm

Breast cancer

Celiac disease

Colon cancer

Crohn's disease

Deep vein thrombosis

Diabetes, type 2

Glaucoma

Graves' disease

Heart attack

Hemochromatosis

Lactose intolerance

Lung cancer

Lupus

Macular degeneration

Melanoma

Multiple sclerosis

Obesity

Osteoarthritis

Prostate cancer

Psoriasis

Restless legs syndrome

Rheumatoid arthritis

Sarcoidosis

Stomach cancer, diffuse

Try Demo

Receive our newsletter

email address

Sign Up

A health investment that continues to grow

Navigenics Health Compass is an extensive, health-focused set of genetic testing services, offering genetic insights now and in the future. Our testing platform includes all of the conditions listed above, and then enables ongoing updates to bring you new genetic results for as long as you subscribe. At any step in the process, you'll be able to consult with our board-certified Genetic Counselors, health professionals who can help you understand your results and decide on next steps.

what is 23andMe?

- ▶ Health and Traits
- Ancestry
- Sharing and Community
- 23andMe Research

learn more

- How It Works
- Frequently Asked Questions
- Scientific Standards
- Considerations

23andMe for...

- Health Conscious
- Genealogists
- Mixed Ethnicities
- Physicians
- Scientists
- Students

health and traits: complete list

Your 23andMe scan includes genetic analysis on all of the following diseases, traits, and conditions. This list grows every month as new research is published.

Clinical Reports (30)

Clinical Reports give you information about conditions and traits for which there are genetic associations supported by multiple, large, peer-reviewed studies. Those associations must also have a substantial influence on a person's chances of developing the disease or having the trait. Because these associations are widely regarded as reliable, we use them to develop quantitative estimates and definitive explanations of what they mean for you.

Age-related Macular Degeneration

- Alcohol Flush Reaction
- Alpha-1 Antitrypsin Deficiency
- BRCA Cancer Mutations (Selected)
- Bitter Taste Perception
- Bloom's Syndrome

Celiac Disease

- Clopidogrel (Plavix®) Efficacy

Crohn's Disease

- Cystic Fibrosis (Delta F508 mutation)
- Earwax Type
- Eye Color
- G6PD Deficiency
- Glycogen Storage Disease Type 1a

Hemochromatosis

Lactose Intolerance

- Malaria Resistance (Duffy Antigen)
- Muscle Performance
- Non-ABO Blood Groups
- Norovirus Resistance
- Parkinson's Disease

Prostate Cancer

Psoriasis

- Resistance to HIV/AIDS

Rheumatoid Arthritis

- Sickle Cell Anemia & Malaria Resistance

Type 1 Diabetes

Type 2 Diabetes

Venous Thromboembolism

- Warfarin (Coumadin®) Sensitivity

Research Reports (86)



buy \$399 USD

try a demo

http://virtualmentor.ama-assn.org/2009/09/pdf/pfor1-0909.pdf

Resources

- Company's website
- Gene Tests/Gene Reviews: genetests.org
- <http://www.accessdna.com/blog/2010/02/personal-genomic-company-test-comparisons/>
- OMIM: <http://www.ncbi.nlm.nih.gov/omim/>



- Overview
- How it works
- Our genetic analysis
- Why Navigenics
- Genetic counseling
- Conditions & medications**
- Our policies
- FAQs
- Success stories
- Request information

Breast cancer

[View all](#)

- > **Fact:** Breast cancer strikes one in eight women during their lives. It kills more American women than any other cancer except lung cancer.
- > **Proportion of risk that's in your genes:** 27 percent.
- > **What you can do:** Our gene test gauges the extent of your genetic risk. Exercising more, smoking less, maintaining a healthy weight and avoiding long-term hormone replacement therapy can help prevent breast cancer. Early detection of the disease through regular mammograms and breast self-examinations can detect the cancer when it is small and has not spread, significantly increasing the chances of survival.
- > **Did you know?** Drinking two alcoholic drinks a day increases your risk of developing breast cancer.

Breast cancer is a disease in which cells in the breast grow out of control. These extra cells can form a mass of tissue called a tumor, and sometimes break away and invade and damage nearby tissues and organs.

Women in North America have the highest rate of breast cancer in the world, with more than 180,000 new cases diagnosed every year.

For most women, genes play only a minor role in their breast cancer risk, with lifestyle, environment and behavior playing a much more important part. You've probably heard about the BRCA genes, the first genes linked to familial breast and ovarian cancer that are most commonly found in women of Ashkenazi (Eastern European) Jewish descent. Navigenics does not currently test for the BRCA variants, because the bulk of a woman's inherited risk appears to result from combinations of more common genetic variants. The Navigenics DNA tests currently look for these more common genetic variants.

Being at high risk of breast cancer is not a death sentence. If caught early enough, the health condition is highly treatable, and today more than 2.5 million American women can call themselves breast cancer survivors.

Genetic testing can help you understand whether you have an above-average genetic risk of breast cancer. Those at extremely high risk for the disease can talk to their doctor about early detection strategies and aggressive preventive measures, including surgery to remove the breasts or preventive medication. The average woman, however, can be well served by maintaining a healthy weight, exercising, limiting alcohol, eating nutritious meals that are low in animal fat, and following recommended breast cancer screening guidelines. Breast cancer tests include ultrasounds, mammograms and MRIs.

Explore other conditions and medications

Health Conditions

- | | | |
|---------------------|---------------------|------------------------|
| Abdominal aneurysm | Glaucoma | Obesity |
| Alzheimer's disease | Graves' disease | Osteoarthritis |
| Atrial fibrillation | Heart attack | Prostate cancer |
| Brain aneurysm | Hemochromatosis | Psoriasis |
| Breast cancer | Lactose intolerance | Restless legs syndrome |
| Celiac disease | Lung cancer | Rheumatoid arthritis |

Receive our newsletter

email address

Success story:

I think it's important to know as much as you can, so you can make decisions that will enable you to control your life, how long you're going to live, and especially what the quality of your life is going to be.

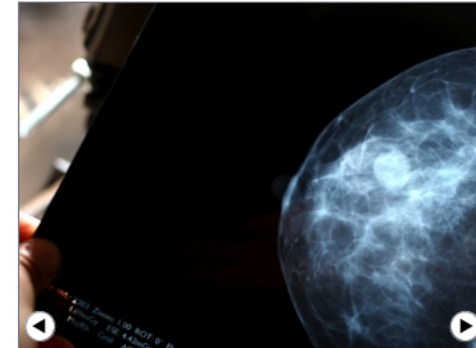
-Tony,
retired attorney

try a demo

About Breast Cancer

Breast cancer can affect both sexes, but it is mainly a concern for women— one in eight will face the disease at some point in their lifetimes. Next to lung cancer, it is the second leading cause of cancer-related deaths in women. The good news is that the number of these deaths is steadily decreasing. Medicine is making great strides against the disease thanks to early detection and better treatments.

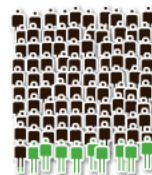
[Learn more about the biology of Breast Cancer...](#)
[Major discoveries in Breast Cancer...](#)



1 of 4. Having a regular mammogram can help detect breast cancer early, allowing more treatment options.

Example Genetic Data

Information for Lilly Mendel (Mom) assuming European ethnicity and an age range of 30-79



Lilly Mendel (Mom)
9.1 out of 100

women of European ethnicity who share Lilly Mendel (Mom)'s genotype will get Breast Cancer between the ages of 30 and 79.



Average
12.5 out of 100

women of European ethnicity will get Breast Cancer between the ages of 30 and 79.

What does the Odds Calculator show me?

Use the ethnicity and age range selectors above to see the estimated incidence of Breast Cancer due to genetics for women with **Lilly Mendel (Mom)**'s genotype. The 23andMe Odds Calculator assumes that a person is free of the condition at the lower age in the range. You can use the name selector above to see the estimated incidence of Breast Cancer for the genotypes of other people in your account.

The 23andMe Odds Calculator only takes into account effects of markers with known associations that are also on our genotyping chip. Keep in mind that aside from genetics, environment and lifestyle may also contribute to one's chances of developing breast cancer (if you are a woman).

Genes vs. Environment

27-40%
Attributable to
Genetics

The **heritability** of breast cancer is estimated to be 27-40%. This means that **environmental factors** contribute more to differences in risk for this condition than do genetic factors. Genetic factors that play a role in breast cancer include both unknown and known factors. Known factors include the rare but high-risk mutations in the **BRCA1** and **BRCA2** genes as well as the SNPs described here. Other factors that can increase your risk include being female, being older, a family history of breast or ovarian cancer, an abnormal breast biopsy, previous chest radiation, early menarche or late menopause, exposure to diethylstilbestrol (DES) in utero, not having children or having children after the age of 30, recent oral contraceptive use, long term post-menopausal **hormone** therapy

Summary

Disease characteristics. [Mutations](#) in *BRCA1* or *BRCA2* predispose to breast cancer and ovarian cancer as well as prostate cancer (*BRCA1*) and other cancers (*BRCA2*). The risk of developing cancer that is associated with a *BRCA1* or *BRCA2* [predisposing mutation](#) is not known and appears to be variable even within families of similar ethnic background with the same [mutation](#). Estimates of breast cancer and ovarian cancer risks have been derived from families with multiple individuals as well as from families with few [affected](#) individuals and from population-based studies. Prognosis for breast cancer survival depends upon the stage at which breast cancer is diagnosed. Prognosis for individuals with *BRCA1* cancer-[predisposing mutations](#) may not be different from that for controls.

Diagnosis/testing. [Molecular genetic testing](#) for *BRCA1* and *BRCA2* cancer-[predisposing mutations](#) is available on a clinical basis for [probands](#) who are identified to be at high risk for a *BRCA1* or *BRCA2* cancer-[predisposing mutation](#) and for relatives of an individual with an identified *BRCA1* or *BRCA2* cancer-[predisposing mutation](#). No currently available technique can guarantee the identification of all cancer-[predisposing mutations](#) in the *BRCA1* [gene](#) or in the *BRCA2* [gene](#). For [mutations](#) of uncertain clinical significance may be identified.

Management. *Treatment of manifestations:* Treatment of breast and ovarian cancer in individuals with *BRCA1*- or *BRCA2*-related tumors is similar to that for [sporadic](#) forms of these cancers. *Prevention of primary manifestations:* Prophylactic mastectomy and/or oophorectomy and chemoprevention using tamoxifen (a partial estrogen antagonist) have been used, but have not been assessed by randomized trials or case-control studies in high-risk women. *Surveillance:* Recommended cancer surveillance strategies, which need to be modified based on the earliest age of onset in family, have not been assessed by randomized trials or case-control studies. Breast cancer [screening](#) in women and men relies on a combination of monthly breast self-examination, annual or semiannual clinical breast examination, annual mammography, and breast MRI. Ovarian cancer [screening](#) relies on a combination of annual or semiannual pelvic examination, annual or semiannual transvaginal ultrasound examination with color Doppler, and annual serum CA-125 concentration. Prostate cancer [screening](#) relies on annual digital rectal examination and prostate-specific antigen (PSA) testing. *Testing of relatives at risk:* Once a *BRCA1* or *BRCA2* cancer-[predisposing mutation](#) has been identified in an individual, testing at-risk relatives can identify those family members with the [family-specific mutation](#) who will benefit from surveillance and early intervention when a cancer is identified.

Genetic counseling. Cancer-[predisposing mutations](#) in the *BRCA1* and *BRCA2* [genes](#) are inherited in an [autosomal dominant](#) manner. Each offspring of an individual with a *BRCA1* or *BRCA2* cancer-[predisposing mutation](#) has a 50% chance of inheriting the [mutation](#). [Molecular genetic testing](#) of asymptomatic family members at risk of inheriting either a *BRCA1* or *BRCA2* cancer-[predisposing mutation](#) is possible once the [family-specific mutation](#) has been identified. Prenatal testing is possible for pregnancies at increased risk; however, requests for [prenatal diagnosis](#) of adult-onset diseases are uncommon and require careful [genetic counseling](#).

Diagnosis

Clinical Diagnosis

BRCA1 or *BRCA2* hereditary breast/ovarian cancer is suspected in an individual who has one or more of the following:

- A personal history of early-onset (before age 50 years) breast cancer or early-onset breast and ovarian cancer at any age and/or bilateral (or multifocal) disease
- A [family history](#) of breast cancer or breast and ovarian cancer consistent with [autosomal dominant](#) inheritance
- A personal or [family history](#) of male breast cancer

Probability models have been developed to estimate the likelihood that an individual or family has a [mutation](#) in *BRCA1* or *BRCA2*.

- Four older prior probability models [[Couch et al 1997](#), [Shattuck-Eidens et al 1997](#), [Frank et al 1998](#)] and BRCAPRO [[Parmigiani et al 1998](#)] are available. Each has unique attributes determined by the methods, sample size, and population used to create the model.

Note: The BRCAPRO model is frequently updated; this is not reflected in the date of the citation.

AccessDNA[®] beta
know your genetics

GeneTrends[™]
By Jordanna Joaquina, MS, CGC



ShareThis | Subscribe to Feed

« MD calls for widespread recognition of genetic counselors | Media Returns Focus to Classic Genetic Diseases »

Personal Genomic Company Test Comparisons

February 10th, 2010 | Author: jordannajoaquina
SNPs are small variations in a single "letter" of DNA that can be found throughout our entire genetic make-up. Personal genomic companies, such as 23andMe, Navigenics, Pathway Genomics, Gene Essence, and deCODEme, analyze thousands of SNPs at once related to various diseases and traits.

Because a number of individuals have shared their personal risk analyses and genotypes, we know that there are differences between personal genomic companies' disease risk predictions. These discrepancies are largely due to the absence of accepted standards for selecting disease risk markers.

To easily compare testing options presently available directly to consumers, the following charts highlight the wide variation between SNPs analyzed by these companies. To be complete, Coriell Personalized Medicine Institute, who in contrast tests for very few SNPs, is included in the review comparison.

Reported risk markers change frequently. Consequently, these charts will be updated periodically. Comments and suggestions are appreciated.

Lung Cancer Overview:

- Whole genome scan home DNA tests for SNPs associated with lung cancer.

Alzheimer's Disease Overview:

- Whole genome scan home DNA tests for SNPs associated with Alzheimer's disease.

Breast Cancer Overview:

- Whole genome scan home DNA tests for SNPs associated with breast cancer.

About AccessDNA

AccessDNA is the leading online consumer resource for genetics. The company combines high-quality content about genetics with access to, and evaluation of, relevant testing, counseling and support services.

By providing insight into the genetics of disease, AccessDNA helps people better understand their treatment, management and prevention options.

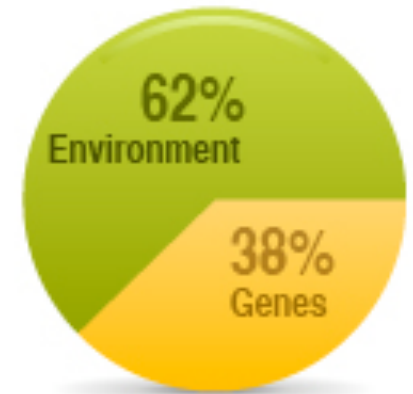
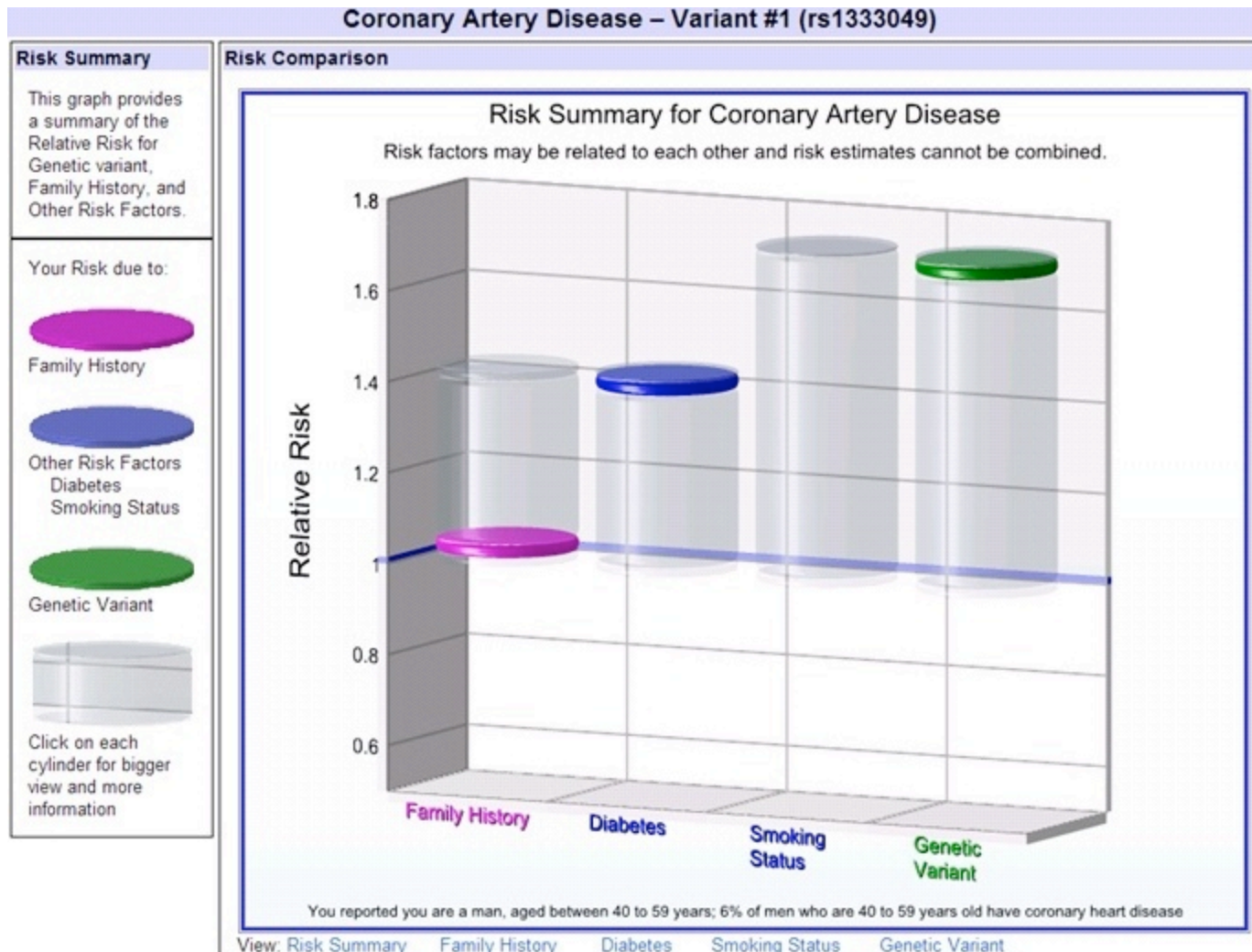
About Jordanna Joaquina

Jordanna Joaquina, MS, CGC is Director of Genetics and a Co-Founder of AccessDNA. She has a clinical background in multiple disciplines of genetics, including prenatal, adult onset and pediatric.

Recent Posts

- » Weekly Twitter Digest for June 11, 2010
- » Pathway Genomics Makes Personal Genetic Testing

Conveying genetics v. environment



Genes vs. Environment

38-57 %
Attributable to
Genetics

The *heritability* of de: genetic factors contri more in men. Geneti as the SNPs we des: American, smoking, l having diabetes, alcc

Marker Effects

