Genetic Testing: What it is and the Actuarial Impact

Dr. Wayne Heidenreich, MD
Medical Director
Northwestern Mutual

Alexandre Lemieux, FSA, MAAA
Director of Actuarial Services
PwC

John Hebig, FSA, MAAA
Actuary
Milliman, Inc.

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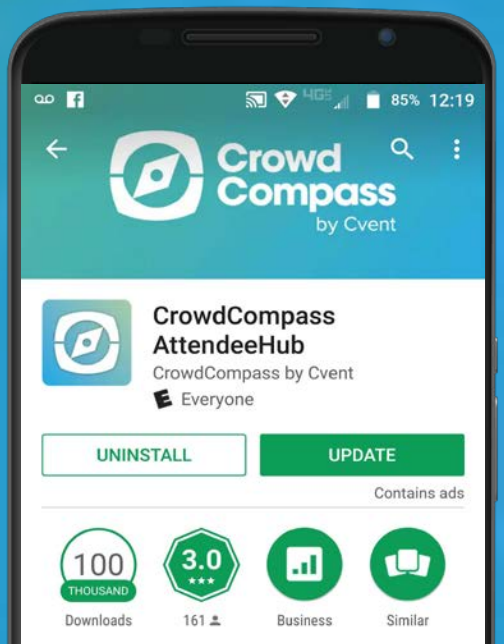

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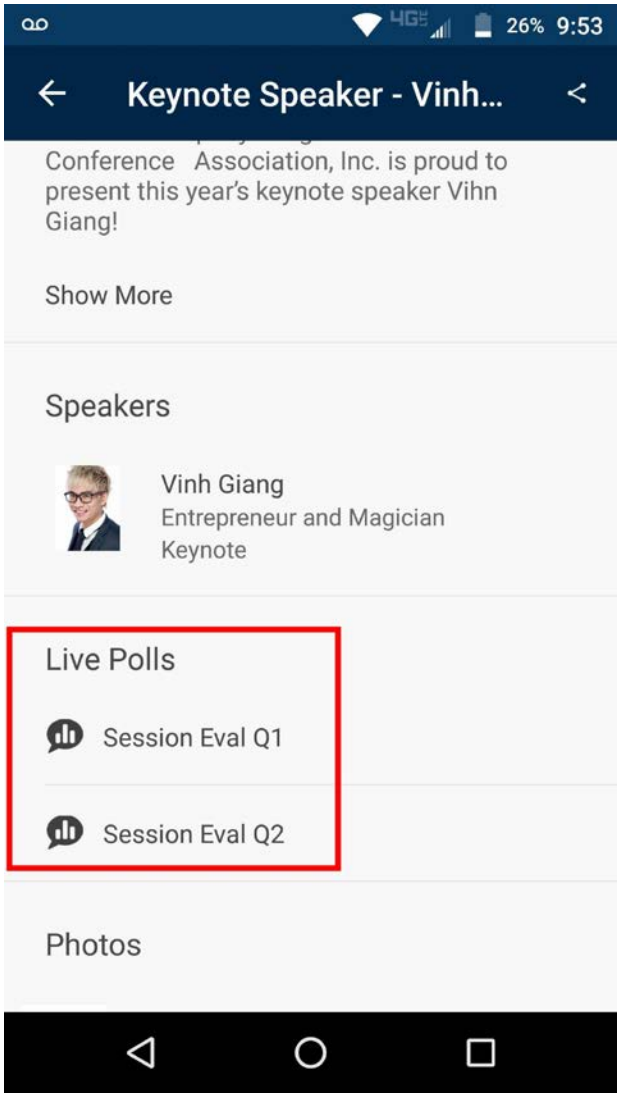

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Agenda

- The science of genetics
- Direct to Consumer testing
- Genetic Disease Identification

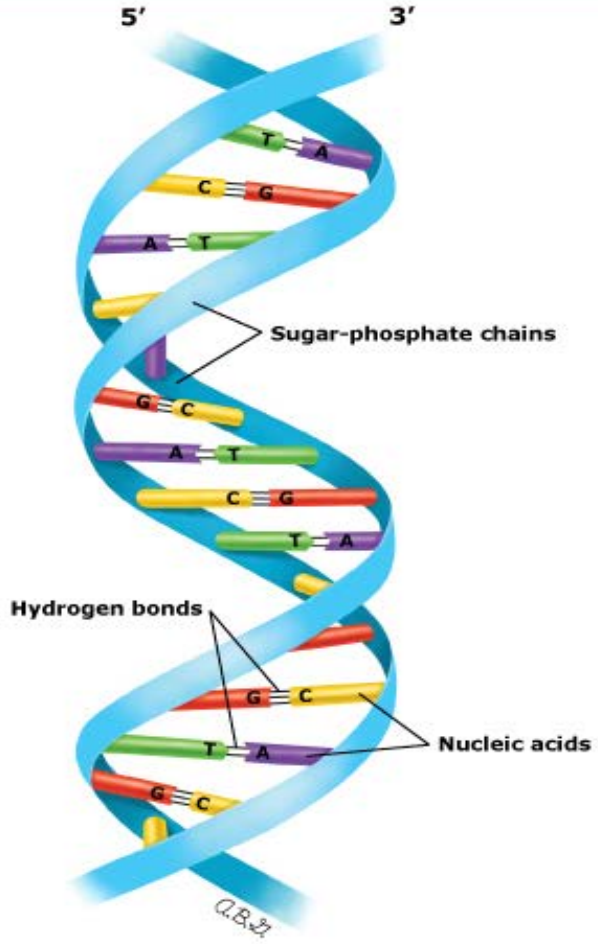
Genetic Testing: The Substrate

- Explosion of genetic science knowledge and technology
  - Human Genome Project began in 1990
  - 3.3 billion base pairs
  - 30,000 genes identified
  - 99% identical across different people
  - The remaining 1% leaves 12 million potential variations between two peoples genomes
    - A variation seen less than 1% of the time, is known as a “mutation”
    - A variation that occurs greater than or equal to 1% of the time is called a “polymorphism”

What is “Genetic Testing” Today?

- Definition from the Genetic Information Non-discrimination Act (GINA)?
  - *the analysis of human DNA, RNA, chromosomes, proteins, or metabolites that detects genotypes, mutations, or chromosomal changes*.
- Identify the sequence of DNA nucleosides that pair with a complement chain to form a chromosome.
  - adenosine ⇔ thymidine
  - cytosine ⇔ guanosine

Structure of DNA



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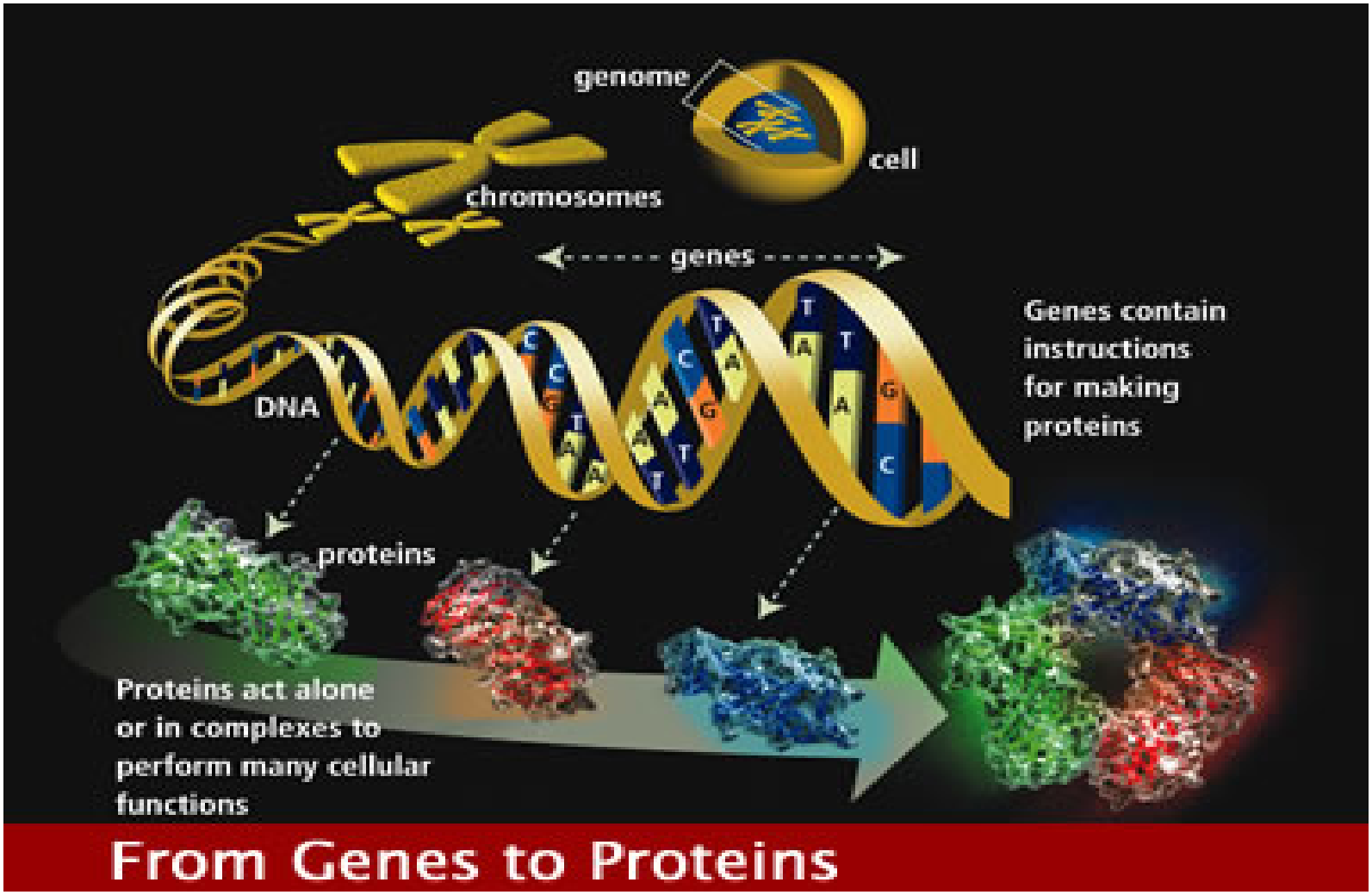
Basic Concepts

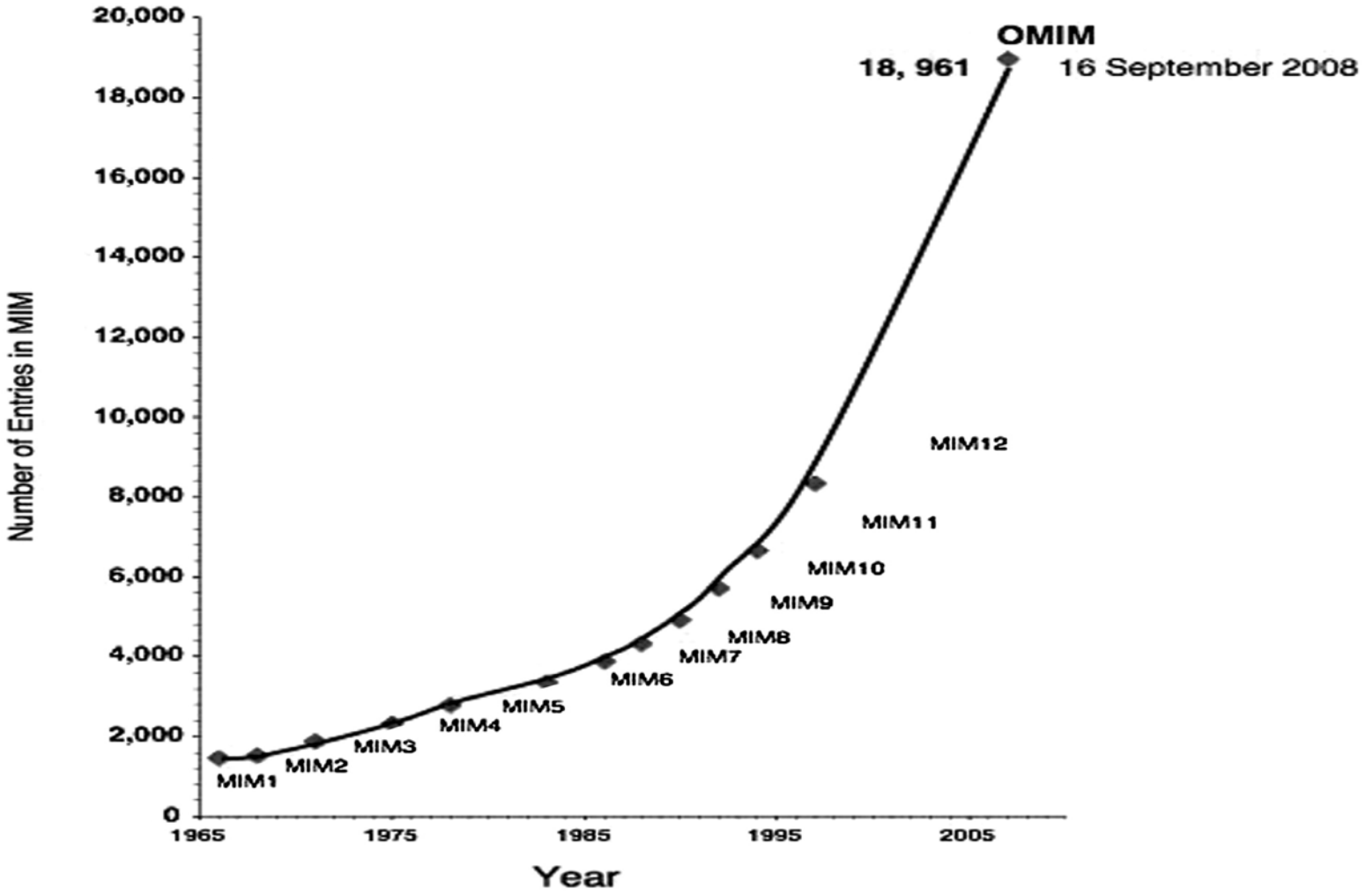
- “Gene” refers to location on the DNA chromosome that codes for one protein
- “Alleles” are the different code sequences that can be found in the gene.
  - Might be referred to as different “variants” or “mutations” of the gene
  - Different proportions of people share the same alleles.

Cell => Chromosome => DNA => RNA=> Protein



http://www.ornl.gov/sci/techresources/Human_Genome/project/info.shtml

Number of Entries in Mendelian Inheritance in Man



Mendelian Inheritance

- Simple model of genetic disorder
  - Mutation of one gene => disease
  - Example: one specific base nucleoside pair variation causes sickle cell anemia
- “Mendelian” inheritance
  - Dominant: inheritance from one parent
  - Recessive: both parents must contribute mutation

Mendelian Disorders Usually Manifest by Age 30

- One gene causes disorder
  - Can manifest in Family History pedigree (the family tree)
- Most disorders manifest by age 30
  - There are exceptions:
    - Huntington's Disease
    - Familial Polycystic Kidney Disease
    - Others include
      - Rare mutations for Familial Early Onset Alzheimer's Disease: dementia onset in 40's and 50's
      - Other rare disorders like Spinocerebellar ataxia, etc.

High risk genetic diseases that require monitoring and modeling

Table 1-3 Frequency of Some Common Monogenic

Disorder	Estimated Frequency*
Autosomal dominant	
Familial hypercholesterolemia	1 in 500 heterozygote
Hereditary nonpolyposis colon cancer	1 in 200–1000
Polyposis of the colon	1 in 15,000
BRCA1 and BRCA2 breast cancer	1 in 1000; 1 in 100 in Ashkenazim
Marfan syndrome	1 in 20,000
Hereditary spherocytosis	1 in 5000
Adult polycystic kidney disease	1 in 1250
Huntington chorea	1 in 25000
Acute intermittent prophyria	1 in 15,000
Osteogenesis imperfecta	1 in 20,000
Von Willebrand disease	1 in 8000
Myotonic dystropy	1 in 10,000
Familial hypertrophic cardiomyopathy	1 in 5000
Neurofibromatosis I	1 in 3000
Tuberous sclerosis	1 in 15,000
Achondroplasia	1 in 50,000

Can we Quantitate Impact?

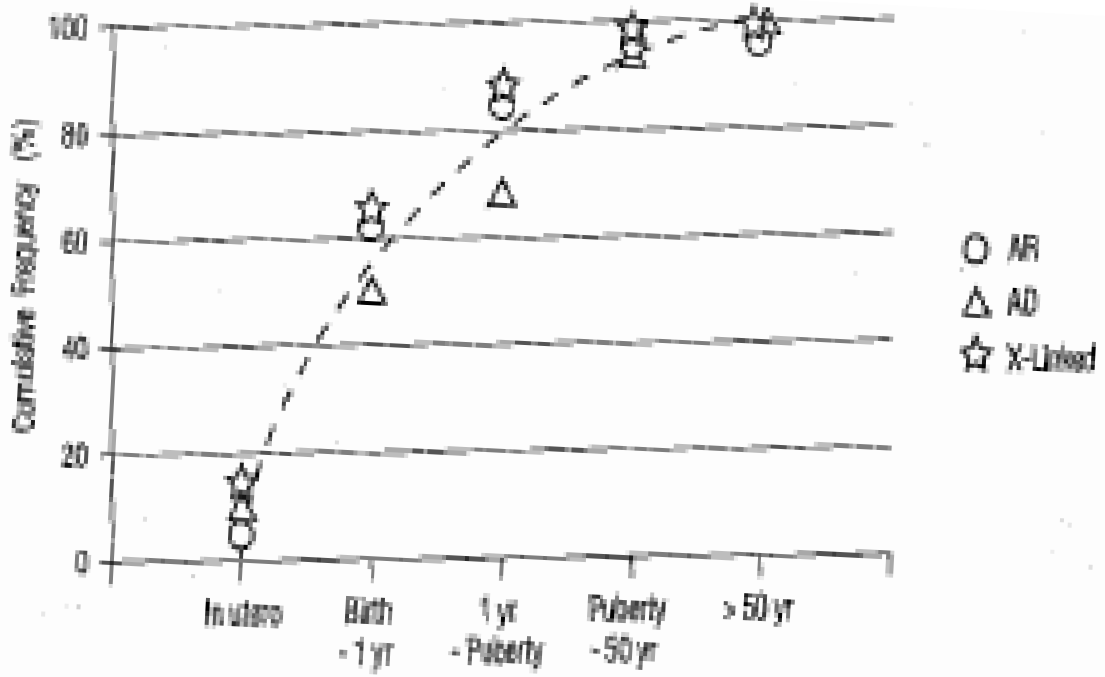


Fig. 4-2 The relationship between age at onset of clinical symptoms and cumulative frequency of the disorder grouped by mode of inheritance.

Polygenic Inheritance

- Inheritance of variations in multiple genes combine to produce disorder.

JANUARY 12, 2018

Top News in Internal Medicine #1 of 9

Polygenic risk score predicts early-onset coronary artery disease

Reuters Health News

A risk score based on 182 independent genetic variants might be useful for identifying individuals likely to develop early-onset coronary artery disease (CAD), researchers from Canada report.

Genome Wide Sequencing (GWS)

- Sequencing *entire genome*
  - Single Nucleotide Polymorphism or SNP's within gene sequences
- Association studies or Genome Wide Association Study
  - Identifying variances sometimes before knowing *how* they interact with one another
- "Direct-to-Consumer" labs can do parts of a GWS

Genome wide association studies use: “SNP’s” or Single Nucleotide Polymorphisms

- Your speaker:

ATCGTATCGATTAGTCTAGTATCGTAGCT
AGTATAAATGATCGTAGTATCGTAGATC
GATATGCTGATATGCTCTGATATAGCTCA
ATCGATTGATGATCTAGATCGCTGATAG
CTGATTAGCATCGTATCGATTAGTCTAG
TATCGTAGCTAGTATAAATGATCGTAGTA
TCGTAGATCGATATGCTGATATGCTCTG
ATATAGCTGATATCGATTGATGATCTAGA
TCGCTGATAGCTGATTAGCATCGTATCG
ATTAGTCTAGTATCGTAGCTAGTATAAAT
GATCGTAGTATCGTAGATCGATATGCTG
ATATGCTCTGATATAGCTGATATCGATTG
ATGATCTAGATCGCTGATAGCTGATTAG
CATCGTATCGATTAGTCTAGTATCGTAG
CTAGTATAAATGATCGTAGTATCGTAGAT
CGATATGCTGATATGCTCTGATATAGCT
GATATCGATTGATGATCTAGATCGCTGA
TAGCTGATTAGC

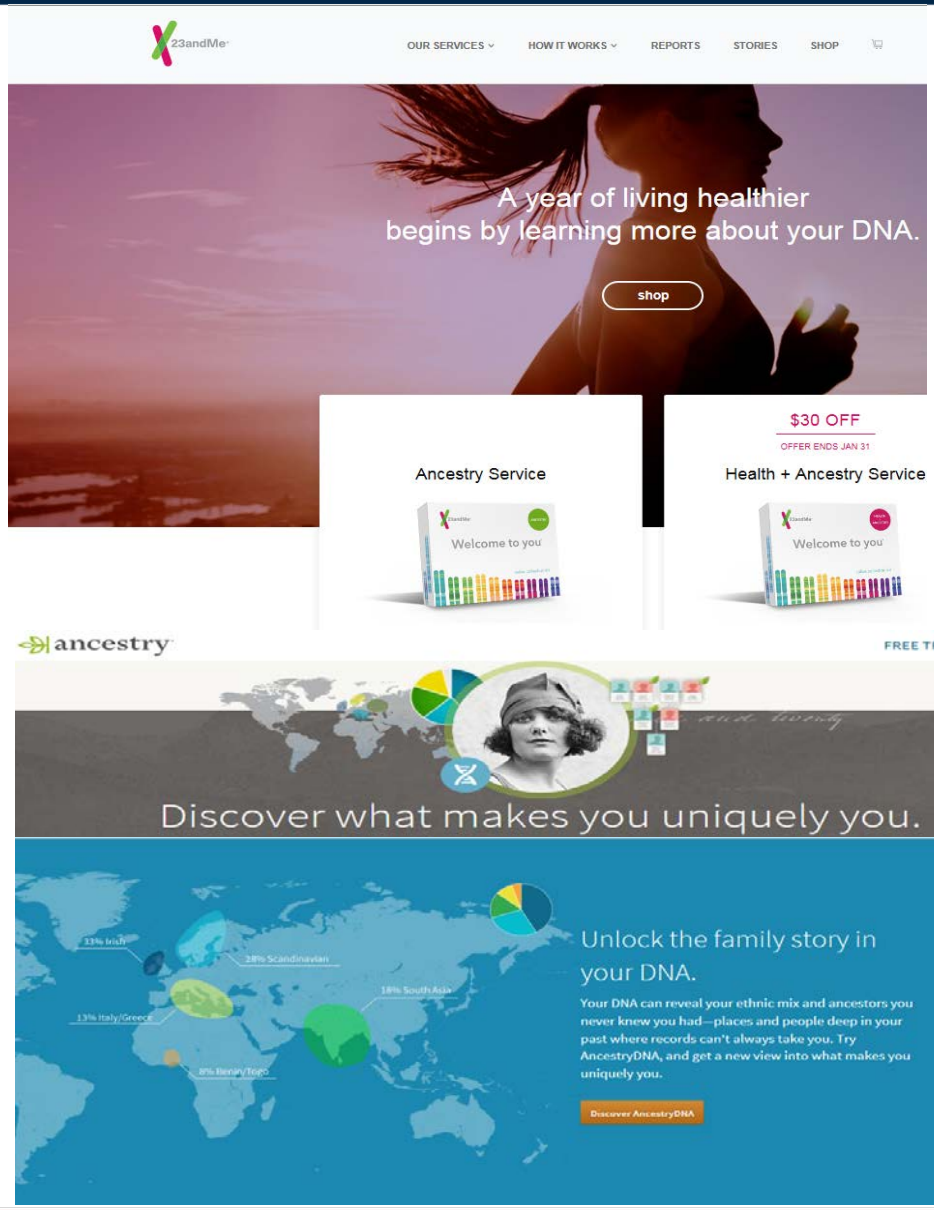
- Selected from the audience:

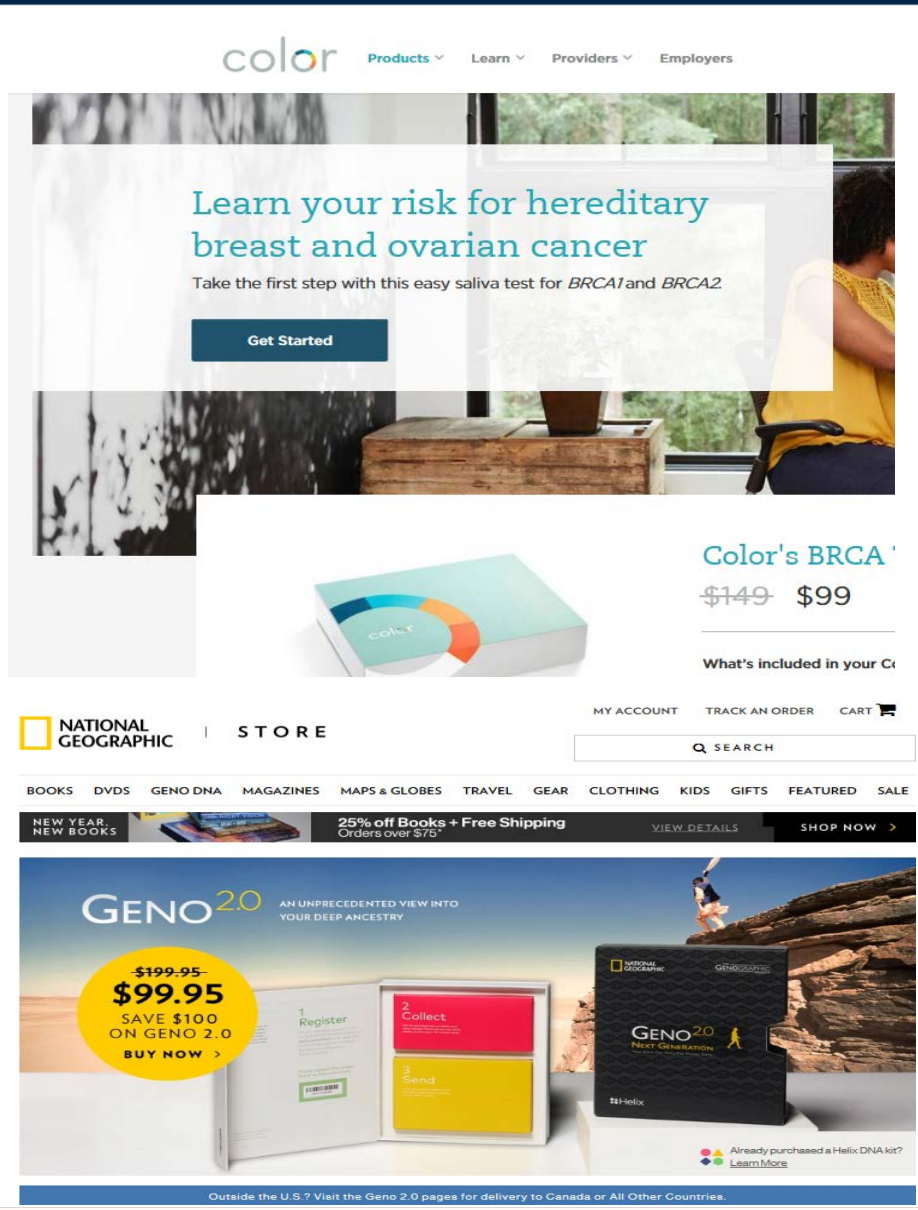
ATCGTATCGATTAGTCTAGTATCGTAGCT
AGTATAAATGATCGTAGTATCGTAGATC
GATATGCTGATATGCTCTGATATAGCTAA
ATCGATTGATGATCTAGATCGCTGATAG
CTGATTAGCATCGTATCGATTAGTCTAG
TATCGTAGCTAGTATAAATGATCGTAGTA
TCGTAGATCGATATGCTGATATGCTTTG
ATATAGCTGATATCGATTGATGATCTAGA
TCGCTGATAGCTGATTAGCATCGTATCG
ATTAGTCTAGTATCGTAGCTAGTATAAAT
GATCGTAGTATCGTAGATCGATATGCTG
ATATGCTCTGATATAGCTGATATCGATTG
ATGATCTAGATCGCTGATAGCTGATTAG
CATCGTCTCGATTAGTCTAGTATCGTAG
CTAGTATAAATGATCGTAGTATCGTAGAT
CGATATGCTGATATGCTCTGATATAGCT
GATATCGATTGATGATCTAGATCGCTGA
TAGCTGATTAGC

What is “Direct to Consumer” Testing

- “Self-directed” by consumer ordering it
- Physician ordered via online services
- Technology
  - Costs of sequencing have come way down
  - Complete genome for less than $1000
- Companies
  - Self-directed
    - 23andMe
  - Physician ordered
    - Color
    - others

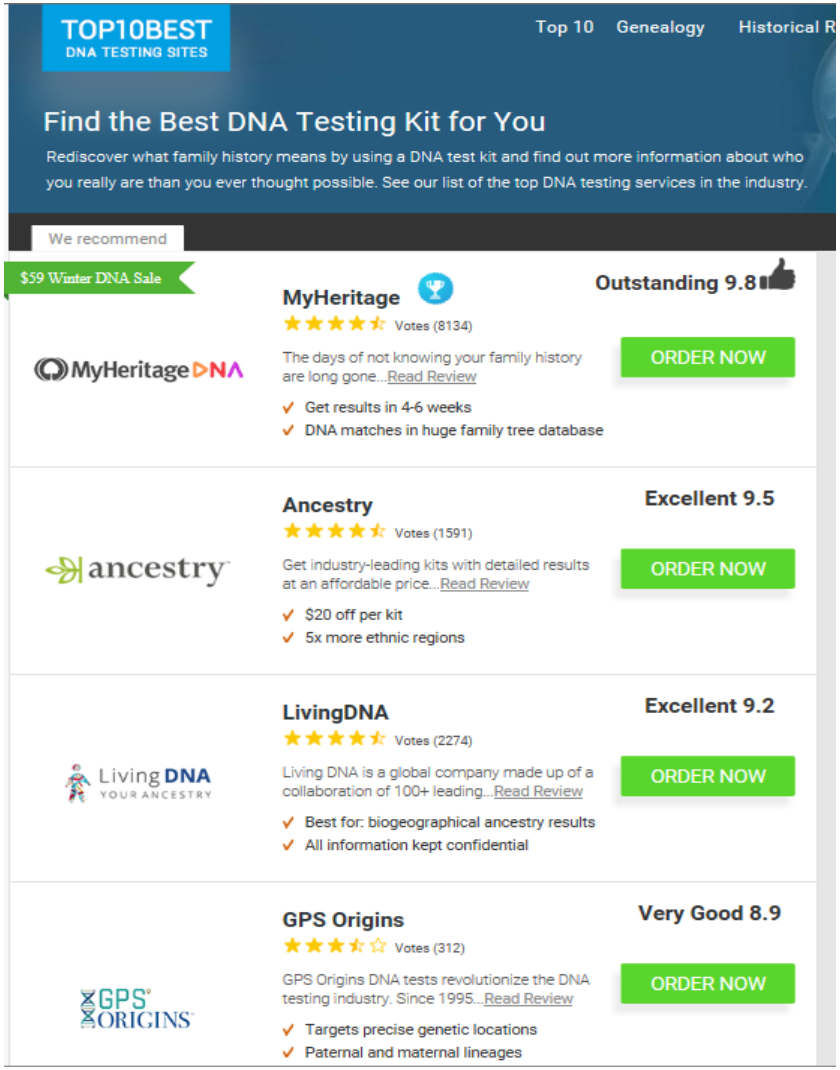
Who is doing this testing?





Direct to consumer companies sales increasing

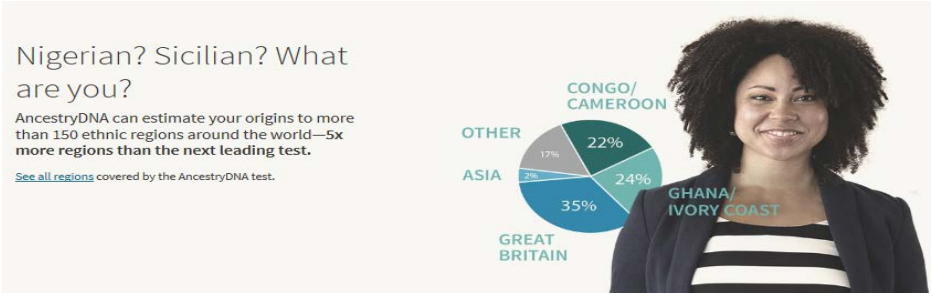
- One top 20 list of DTC labs
  - 23andMe
  - Any Lab Test Now
  - Color Genomics
  - Counsyl
  - Direct Laboratory Services
  - Gene by Gene
  - HealthCheck USA
  - Home Access Health
  - Laboratory Corp.
  - MyMedLab
  - Mapmygenome
  - Pathway Genomics
  - Positive Bioscience
  - Quest Diagnositics
  - Request A Test
  - Sonora Quest Labs
  - Theranos
  - Walk-in Lab
  - WellnessFX
  - Xcode Life Sciences



https://medcitynews.com/2016/01/20-key-players-in-the-direct-to-consumer-lab-testing-ma...

Why get tested

- For interest in ancestry



- For entertainment
  - For traits 15 +

Traits reports

15+ traits

Asparagus Odor Detection
Back Hair (available for men only)
Bald Spot (available for men only)
Bitter Taste Perception
Cheek Dimples
Cleft Chin
Earlobe Type
Earwax Type
Eye Color

Historical genius matches

Learn which historical geniuses, like Benjamin Franklin or Nikola Tesla, you might be related to

- Paternity
- For carrier status 40 +

Congenital Disorder of Glycosylation Type 1a (PMM2-CDG)
2 variants in the PMM2 gene; relevant for Danish descent

Cystic Fibrosis
28 variants in the CFTR gene; relevant for European, Hispanic/Latino, Ashkenazi Jewish descent

- For diagnostic susceptibilities

Direct to Consumer Testing

2010	2013	2017
30 companies	FDA moratorium	23andme
100s of tests		10 tests
Questionable Validity		“Non-Diagnostic”
Unclear relevance to underwriting		Late Onset Alzheimer’s (ApoE) of concern mostly to LTC product

23andMe

- 23andme
  - April 6, 2017 FDA allowed marketing of 23andMe Personal Genome Service Genetic Health Risk tests
  - 1st tests that provide information on an individual's genetic predisposition for certain medical diseases
  - May help individual make decisions on lifestyle choices or inform discussions with health care providers
  - Predictive not determinative
    - Likelihood or probability
    - Not diagnostic

What diagnostic diseases are tested by 23andMe

- 7 Diseases with 11 gene variants
  - Late-onset Alzheimer's disease: ApoE gene
  - Parkinson's disease: 2 variants in LRRK2 and GBA
  - Celiac disease: One variant each in HLA-DQA1 & HLA-DQB1
  - Age-related macular degeneration: 1 variant each in ARMS2 and CFH genes
  - Alpha1 antitrypsin deficiency: 2 variants in the SERPINA1 gene
  - Hereditary hemochromatosis: 2 variants of HFE gene
  - Hereditary thrombophilia: 1 variant each in the F2 and F5 genes

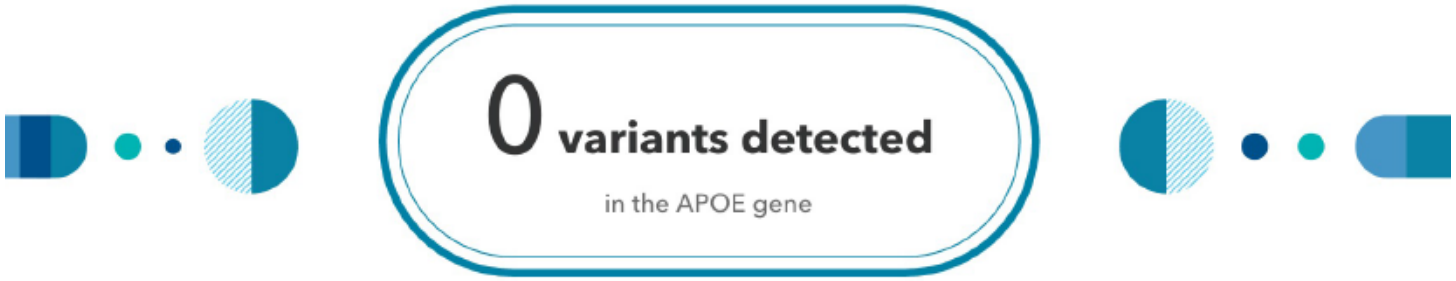
Sample report

Late-Onset Alzheimer's Disease

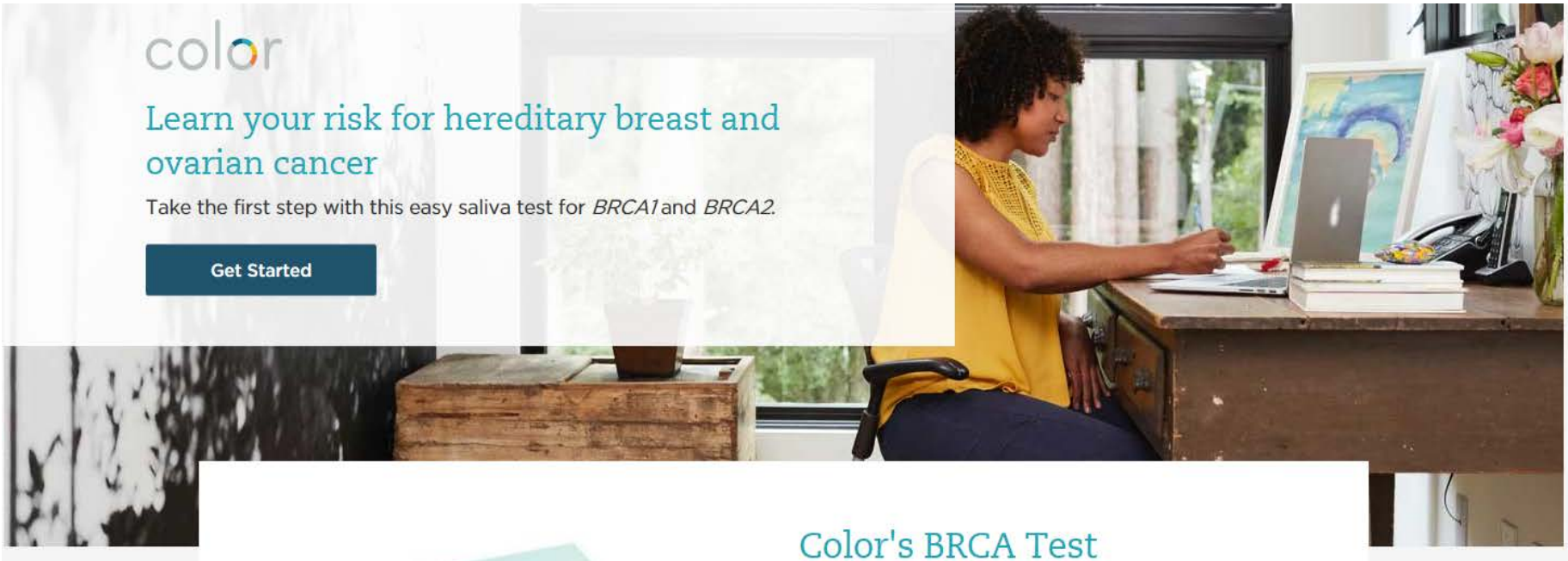
Alzheimer's disease is characterized by memory loss, cognitive decline, and personality changes. Late-onset Alzheimer's disease is the most common form of Alzheimer's disease, developing after age 65. Many factors, including genetics, can influence a person's chances of developing the condition. This test includes the most common genetic variant associated with late-onset Alzheimer's disease.

Jamie, you **do not have** the ε4 variant we tested.

Your risk for Alzheimer's disease also depends on other factors, including lifestyle, environment, and genetic variants not covered by this test.



Color



Color's BRCA Test

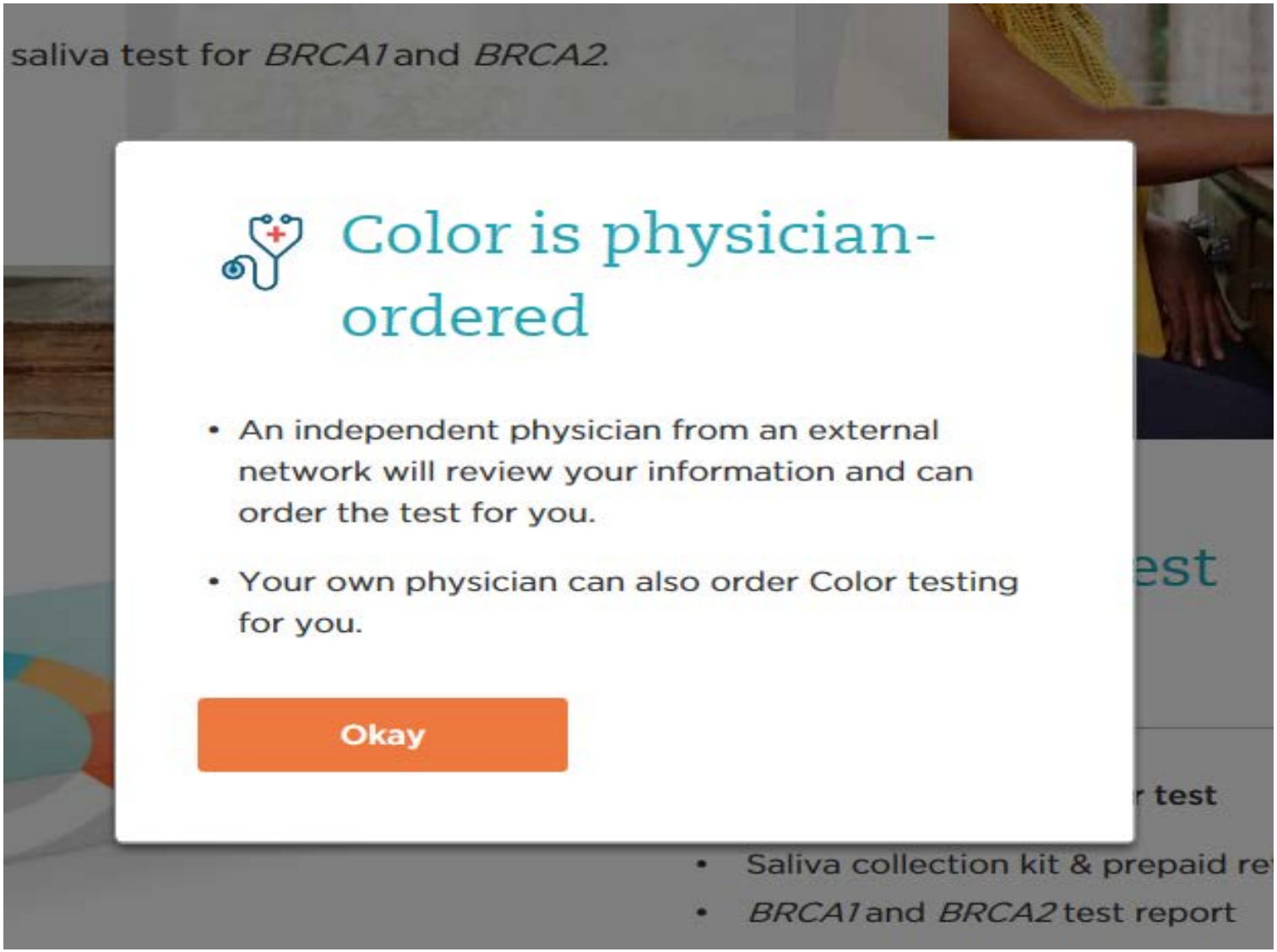
~~$149~~ $99

What's included in your Color test

- Saliva collection kit & prepaid return label
- *BRCA1* and *BRCA2* test report
- Expert genetic counseling
- Latest genetics news that matters to you
- All Color tests are physician-ordered Learn more ›

Buy Color

*You must be at least 18 to use Color.


saliva test for *BRCA1* and *BRCA2*.
Color is physician-ordered
• An independent physician from an external network will review your information and can order the test for you.
• Your own physician can also order Color testing for you.
Okay
• Saliva collection kit & prepaid re
• *BRCA1* and *BRCA2* test report

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Hereditary Cancer Test

Learn your risk for common hereditary cancers and how you can use that information.

Buy Color $249

Discounted pricing available for current clients Learn more

You must be at least 18 to use Color.

HOW COLOR WORKS WHAT'S INCLUDED CLIENT STORIES PRICING

Genetic counseling included

Every Color test includes access to a complimentary board-certified genetic counselor, who will help answer relevant questions such as:

- What do your results mean?
- What are your risk and personalized screening guidelines?
- How should you discuss your results with your healthcare provider and family?

Learn more about genetic counseling ›

You will be asked whether you want to receive certain Genetic Health Risk reports

Some of our reports are about serious diseases that may not have an effective treatment or cure. Some people may be upset by learning about personal risks, and risks for family members who share DNA. Knowing about genetic risks could affect your ability to get some kinds of insurance. 23andMe will not share your personal information with an insurance company without your explicit consent.

- 23andMe: opt in to receive ApoE and Parkinson's gene results

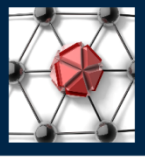
Apolipoprotein E: risk for late onset Alzheimer's

- **One of the 23andMe genes is "ApoE"**
  - Three forms of this gene: ApoE2, ApoE3, and ApoE4
  - An ApoE4 gene increases risk of "late onset Alzheimer's" after age 70
  - Two copies of ApoE4 gene has 10 x the risk for Alzheimer's Disease
- **Lifetime Risk of Alzheimer's: % who live to develop AD**

Risk Group	Male	Female
General Population	10	14
One ApoE4	23	30
Two ApoE4	51	60

- **Represents a source of potential adverse selection risk**

Three Genes of Note in 23andMe



Disease Gene	Prevalence per 100k General Population	% of Individuals that Manifest Disease	Age of Onset Significant Disease
Late Onset Alzheimer's Disease: ApoE4E4	**2000**	**35-50%**	**68**
Parkinson's: GBA mutation N370S	480	6%	80
Parkinson's: LRRK2 mutation G2019S	80	50%	69

10 Mutations of Concern for LTC

Disease Gene	Prevalence / 100k General Population	% of Individuals that Manifest Disease	Age of Onset	Likelihood for inclusion in DTC Test
Huntington's Disease	7	100%	40	Low
AD: ApoE4E4	1000	15%	75	Current
AD: Presenilin 1	3	100%	43	Low
AD: Presenilin 2	1	95%	54	Low
AD: Amyloid Precursor Protein (APP)	1	100%	49	Low
Parkinson's: N370S in GBA	480	6%	80	Current
Parkinson's: G2019S in LRKK2	80	50%	69	Current
Autosomal Dominant Polycystic Kidney Disease	100	100%	30	Low
Spinocerebellar Ataxia: 38 mutations	3	100%	30's	Low
Frontotemporal Dementia: C9ORF72, GRN, and MAPT	80	100%	58	Low

Do Results Cause People to Act on Insurance?

- Huntington's mutation: Oster E, et.al, *Nat Bureau Economic Research, 2009*
  - Individuals positive with Huntington's mutation up to 5 times as likely as general population to own LTCi

- ApoE genetic results: Zick C, et.al, *Health Affairs, 2005*
  - Study to determine impact of giving people genetic results
  - 148 cognitively normal people
  - Impact of positive ApoE on insurance
    - Those who tested positive were 5.76 times more likely to have altered their LTCi

- Huntington's: insurer reports increased rate of exposure that is 2.1 x population prevalence

Brave New World

- Genetic testing is here to stay
- Will bring many benefits to health care
- Some in society see need for “exceptionalism” of genetic information from underwriting
- Impact will need to be continuously considered

Actuarial Implications of Genetic Testing

Agenda

- Genetic Underwriting
- Anti-selection
- Regulations in other jurisdictions

November 2017

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The New York Times

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Sunday Review

What if You Knew Alzheimer's Was Coming for You?

Simple blood tests may soon be able to deliver alarming news about your cognitive health.

By PAGAN KENNEDY NOV. 17, 2017

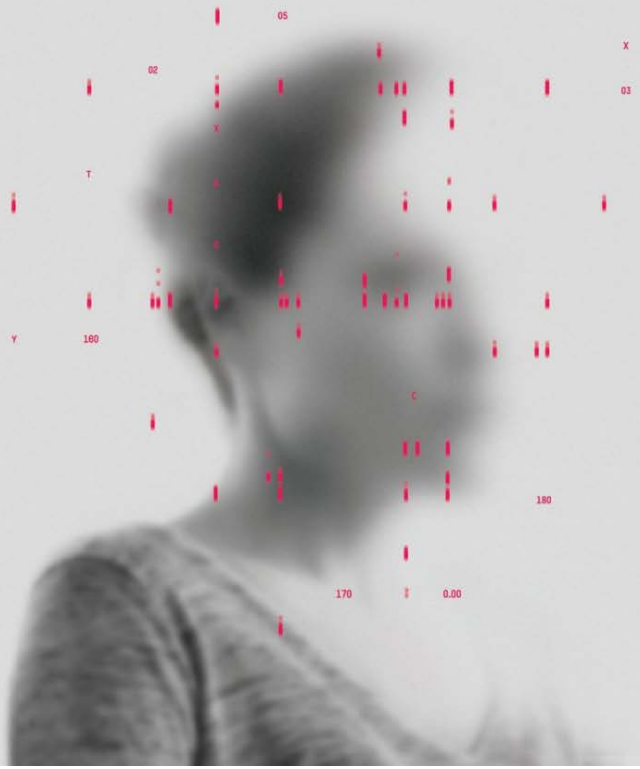


Illustration by Mike McQuade; Photograph

Thursday, January 18, 2018

What is genetic underwriting?

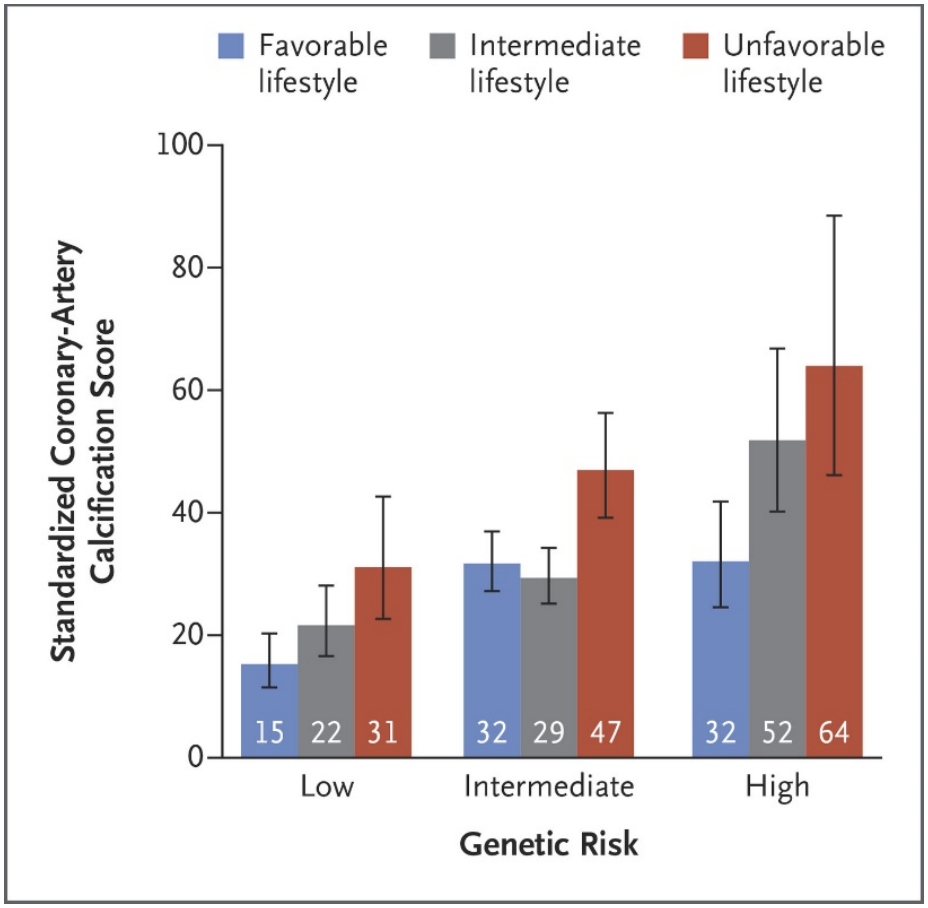
- As mentioned genetic testing can be:
  - Administered by a doctor for a specific medical condition – these results are often 100% predictive and shared with the insurance company (most common example is a test for Huntington's)
  - Retail testing direct to consumers who can use it for fun or for information – These tests are predictive and may offer tendencies but not 100% predictive
- The example from the NY Times article on the previous page was testing for ApoE4
- The increase in late-onset Alzheimer's disease is an increase in frequency of x10 to x30 (in certain populations)

Anti-selection

- Example: Buying house insurance when the house is on fire

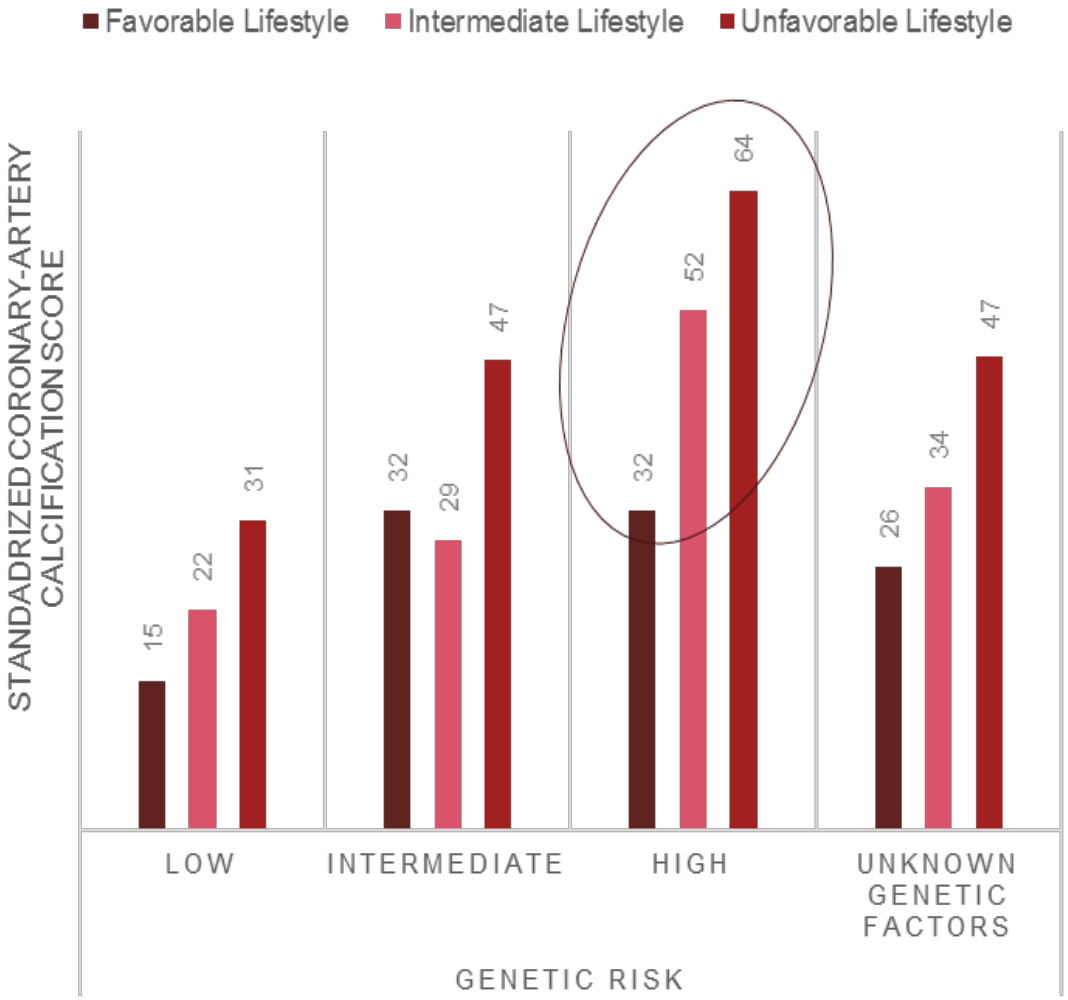
- **Adverse selection** refers to a situation where policyholders have information that insurance companies do not, or vice versa
- Can occur when policyholders know something about themselves that the insurer can't test or underwrite for
- Not all things result in anti-selective behavior– gender neutral pricing on annuities isn't anti-selective
- Policyholder ability to take advantage of non-differentiated pricing can result in loss cycle

Genetic Likelihood – Risk of Coronary-Artery Calcification



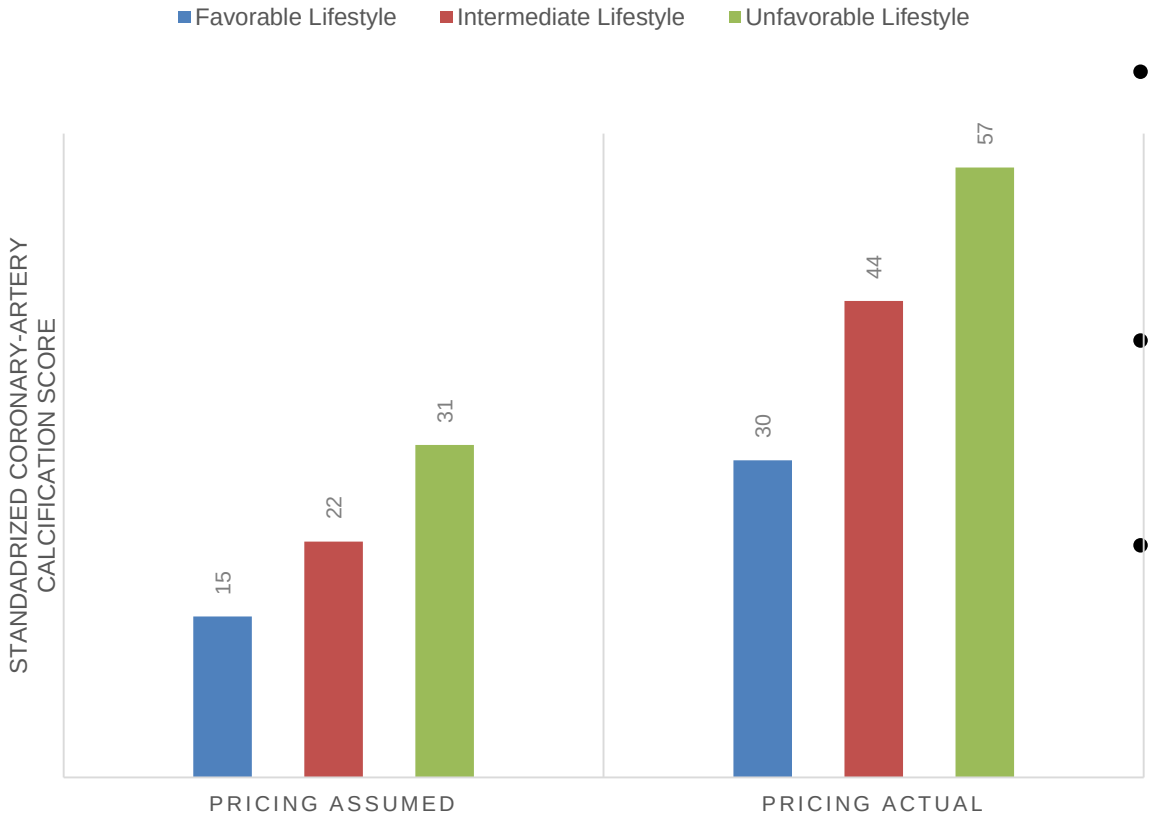
Relative Risk Data Source: Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. Khera et al, November 2016, DOI: 10.1056/NEJMoa1605086

Anti-Selection distribution assuming equal policy sizes



- Risk of anti-selection is if policyholders in the high risk pool buy more than expectation
- Pricing currently based on unknown genetic factors which on average is profitable
- Note lifestyle also has significant impact on risk

Anti-Selection distribution assuming high genetic risks buy 5x the insurance size



- Knowledge of underlying genetic risks could drive policyholders to select more coverage
- Without this knowledge loss ratios can quickly spiral out of control
- Note again that risk is increased, risk is not absolute

US Regulations for genetic testing

- Genetic Information Nondiscrimination Act (GINA) issued 2008 protects genetic and family history for underwriting of:
  - Health insurers may not use genetic information to make eligibility, coverage, underwriting, or premium-setting decisions.
  - Health insurers may not request or require individuals or their family members to undergo genetic testing or to provide genetic information.
  - Insurers cannot use genetic information obtained intentionally or unintentionally in decisions about enrollment or coverage.
  - The use of genetic information as a preexisting condition is prohibited in both the Medicare supplemental policy and individual health insurance markets.

No similar regulation exists for life, annuity, or long term care at the federal level though states may have variations

Foreign Jurisdictions

- Canadian Institute of Actuaries - Statement on Genetic Testing and Insurance:
  - Proposed not allowing the use of genetic underwriting in insurance company underwriting
  - Addition of question to policyholder about whether they have genetic testing results
  - Requirement to disclose results of genetic testing if policyholder has the information

Foreign Jurisdictions

- Association of British Insurers - Concordat and Moratorium on Genetics and Insurance:
  - Proposed moratorium on the use of genetic underwriting in insurance company underwriting
  - Costumers who have taken a predictive test will not be required to disclose this to insurers unless purchasing insurance above prescribed limits:
    - » $700,000 Face Amount on Life Insurance
    - » $415,000 Face Amount on Critical Illness
    - » $40,000 of Annual Income Protection

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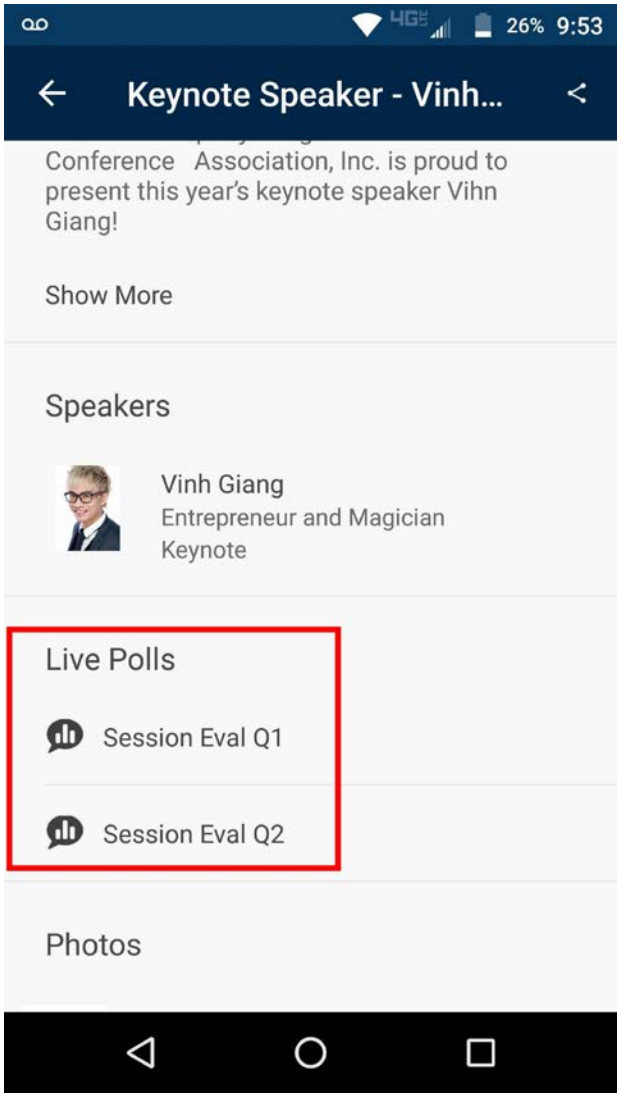

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Questions?

Thank you!