

# Direct-To-Consumer Genetic Testing

Cancer Risk and Prevention Conference  
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## Disclosures

I have no financial disclosures

I have not participated in Direct-to-consumer genetic testing



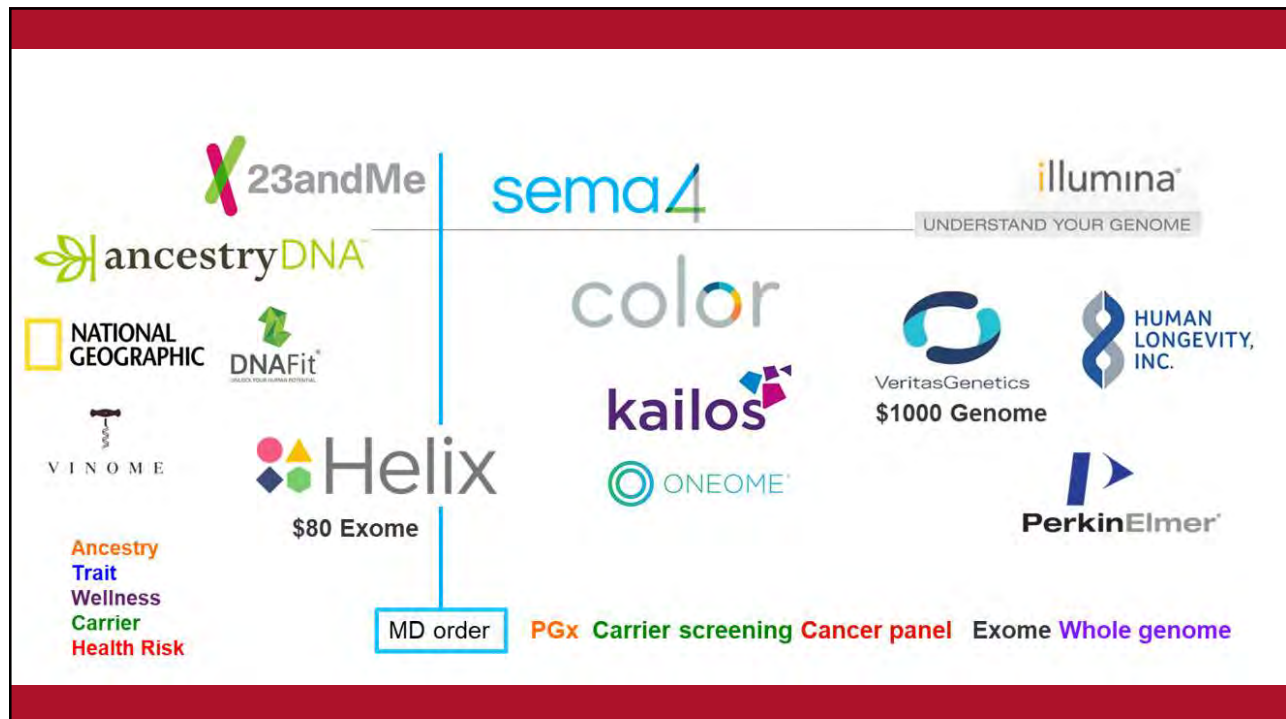
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## Objectives

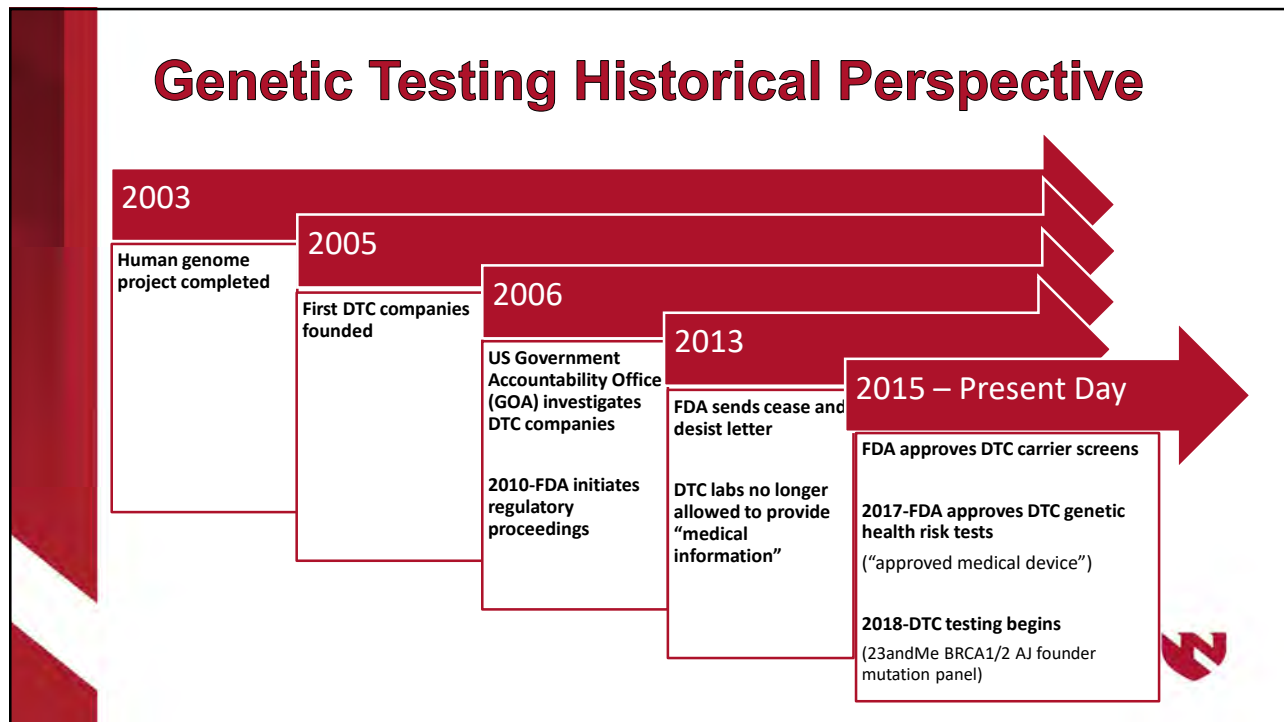
1. Define Direct-To-Consumer (DOT) genetic testing.
2. Compare and contrast the different types of DTC genetic testing options and potential uses.
3. Describe the potential limitations, benefits, and pitfalls of DTC for patients and their families.



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## What is Direct-To-Consumer Testing?

**DTC ≠ Diagnostic Clinical Genetic Testing**

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## What is Direct-to-Consumer Testing?

### Direct to Consumer (DTC) Testing

- Initiated by consumer
- No MD/clinician involved
- Often ordered online
- Genotyping for particular variants/SNPs
- Patient self-pay
- Examples: ancestry, genetic traits, and some disease risk

### Patient Initiated/Consumer Directed Testing

- Patient initiated, but...
- Doctor “approved”
- Typically full genetic analysis/sequencing
- May be covered by health insurance or self-pay options
- Examples: Cancer panels, carrier screening, pharmacogenomics

### Patient Initiated/Clinician Directed

- Patient initiated
- Lab provider/contractor orders test
- Typically full genetic analysis/sequencing
- May be covered by health insurance or self-pay options
- Examples: Cancer panels, carrier screening, pharmacogenomics

### Provider Initiated Testing

- Provider recommends test, chooses lab, and coordinates testing
- Diagnostic tests
- Often covered by health insurance when certain criteria are met
- Examples: Hereditary cancer risk panels, cardiogenetic panels

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## Appeal of DTC Genetic Testing

### Access to information

### Promotes awareness of genetic disease

### Personalized information about health, risks and traits

### May help to be proactive about health

### Can connect with ancestry or distant/lost relatives

### Protection of health information for families/concern for genetic discrimination

### Does not require approval from HCP or insurance company

### Convenience-can do testing from home

### Information seekers/early adopters

### Fun information to know

“I didn’t have much of a family history of breast cancer, but learned through DTC DNA testing that I carry a BRCA1 pathogenic variant. I am now more diligent about my screenings and get a mammogram and breast MRI every year.”

Horton, et al, Direct-to-consumer genetic testing, *BMJ*



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## Patient perceived Expectations/Benefits of DTC

Results are valid

Negative test results rule out risks

Results will be impactful for their healthcare

DNA data is “protected” from medical record systems and insurers

DTC cheaper than doctor visits and traditional lab tests

Marzulla et al. Genetic counseling following direct-to-consumer testing: Consumer perspectives. *J Genet Couns*



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## DTC Laboratory Methodologies

### SNP

“Single Nucleotide Polymorphism”

Single base pair change to the DNA

Used as “markers” for genetic disease or trait  
– May not be causative

COMMON!

Occurs in >1% of population

### MUTATION

DNA change that causes disease or increases risk.

– Includes single base pair change, large deletion/duplications, etc.

RARE!

Occurs in <1% of the population



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# DTC Laboratory Methodologies

## GENOTYPING

### Focuses on specific variants/SNPs

- Limited information
- May miss known genetic variant
  - deletions/duplications
  - rare variants
  - trinucleotide repeats

Looks for specific common disease-causing changes in your DNA



## DNA SEQUENCING

### Full gene analysis for different types of mutations

- More thorough
- Single gene
- Whole genome/exome

Looks throughout the gene for both common and rare disease-causing changes in your DNA



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# Types of Direct-To-Consumer Testing

Ancestry Testing

Entertainment vs Health

Traits

Wellness

Carrier Status

Genetic Health Risk

Hereditary Cancer Susceptibility

Circulating Tumor Cells



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# DTC: Ancestry Testing



Compares SNPs with database to estimate ethnic background

Report may include:

Ancient/Neanderthal DNA

mtDNA

Y chromosome DNA

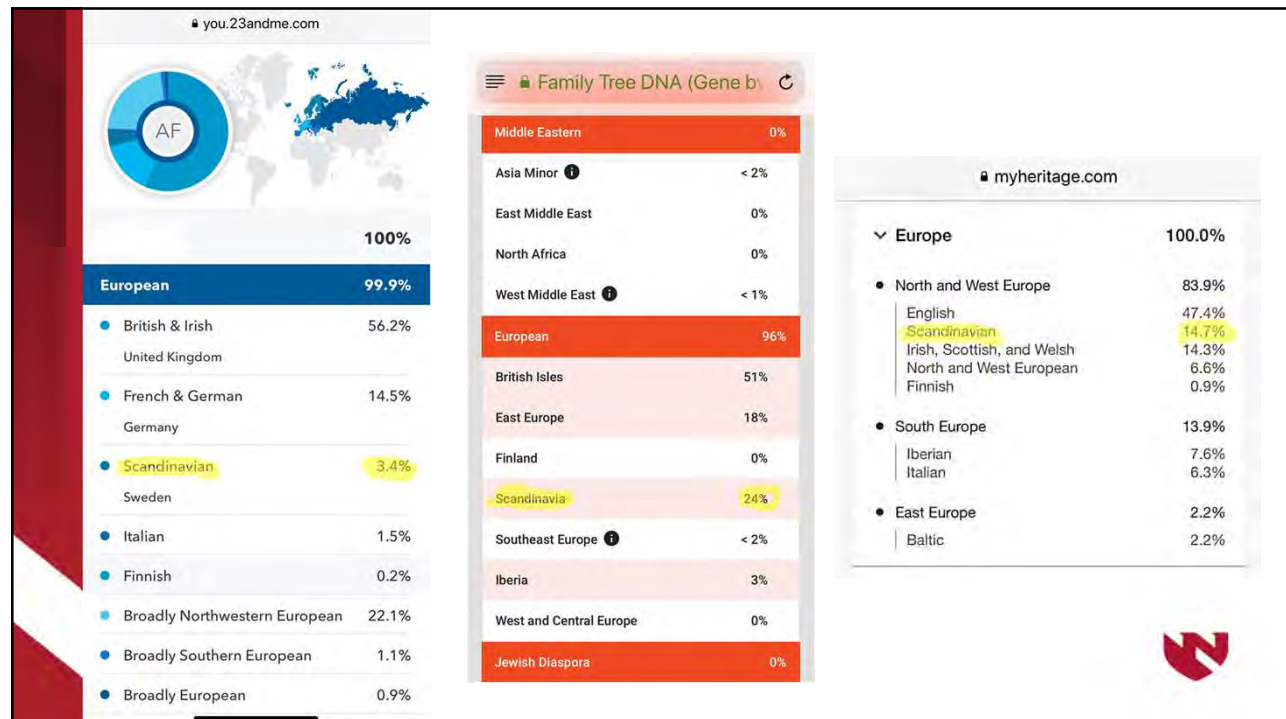
Human migration patterns can complicate assessment

Different companies use different databases

**Not always consistent!**



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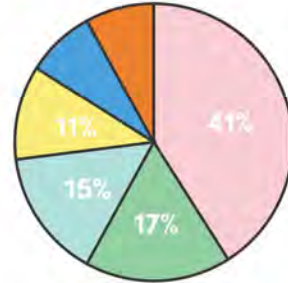
# {Gwen's DTC Testing: Ancestry}

DISCLAIMER: DNA Friend is not a real genetic testing company. This is a parody website. DNA Friend does not collect anyone's DNA, nor does it receive, view, or keep any photos captured by users onsite.

## Your Ancestry at a Glance

Your genes contain distinct markers that allow us to determine your ancestral origins. Please note that for accuracy, these figures take into account relatives who were either purposely forgotten or expunged from your official family history for having stained it irreparably.

- Guy Hanging Around Ellis Island Looking To Bed Anything Without Tuberculosis – 41%
- North African By Way Of Morocco; New York; Allentown, Pennsylvania; And Then Glendale, Arizona – 8%
- Extremely Unethical Sperm Bank Employee – 8%
- Highly Infectious Strain Of Super-Irish – 17%
- Italian – 15%
  - Proud Italian – 4%
  - Really Proud Italian – 11%
- Billionaire's Private Tahitian Island – 11%
  - Orgy Cove – 5%
  - Mysterious Jungle Warehouse – 3%
  - Tennis Courts – 2%
  - Human-Hunting Ground – 1%



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# Traits and Entertainment DTC Testing

Eye color

Asparagus urine

Wine preference

Fast twitch muscles

Can choose option to select DNA Products

Option to download your raw data for free

rsid	chromosome	position	genotype
r312564887	1	734462	AA
r43131972	1	752721	GG
r148822841	1	768998	CC
r312124819	1	776546	AA
r5115893985	1	787173	GG
r511248777	1	790059	AG
r75338385	1	824398	AA
r44978383	1	838555	CC
r4475691	1	846888	CT
r7537756	1	854258	AG
r51380282	1	861888	GG
r55678698	1	864498	CC
16819299	1	871267	CC
r5110852	1	873558	GT
r3147226514	1	878697	GG
16819302	1	881643	GG
r52727256	1	882933	GG
r487274836	1	884767	GG
16819303	1	888534	CC
r113382945	1	889159	CC
16819304	1	891182	GG
16819305	1	891343	GG
r113383186	1	891645	AG

Traits Reports 0 highlighted reports of 27 reports available

Explore the genetics behind

Ability to Match Musical

Asparagus Odor Detection

Bitter Taste

Cheek Dimples

Cilantro Taste Aversion

Cleft Chin

Earlobe Type

Earwax Type

Eye Color



Likely little freckling  
hair photobleaching  
likely straight or wavy



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## Clinical Utility?



**Paulo**

"I always suspected I had brown eyes, but DNA Friend finally confirmed it!"



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## {Gwen's DTC Test Report: Traits}

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**Trait Report**

Contained in every human's DNA are clues to the traits they will exhibit over the course of a lifetime. Below is a breakdown of what you can expect from your body in the future, or what you are already remarkably familiar with.

- You require fewer napkins than the average person.
- Soap is more likely to taste like cilantro to you.
- You prefer sweet foods to poisoned ones.



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# Fun Family Gift!

**CAUTION:**



**Ancestry testing can reveal:**

- Non paternity
- Adoption
- Sperm/egg donor
- Long lost relatives
- Unexpected ancestry
- Rape
- Incest
- Other family secrets/drama



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# DTC: Wellness, Genetic Risks, Carrier Testing



Ancestry  
5 reports

PLUS



Genetic Health Risks\*  
5+ reports  
Meets FDA requirements



Wellness  
5+ reports



Carrier Status\*  
40+ reports  
Meets FDA requirements



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# Wellness Report Example Report

**Wellness Reports** 2 highlighted reports of 8 reports available

Find out how your DNA may affect your body's response to diet, exercise, and sleep. Consider talking to a healthcare professional before making any major lifestyle changes or if you have any concerns about your results.

Alcohol Flush Reaction	Unlikely to flush
Caffeine Consumption	Likely to consume less
Deep Sleep	Less likely to be a deep sleeper
Genetic Weight	Predisposed to weigh about average
Lactose Intolerance	Likely tolerant
Muscle Composition	Common in elite power athletes
Saturated Fat and Weight	Likely to weigh more on a high saturated fat diet
Sleep Movement	Likely more than average movement

Useful?      Accurate?      Still fun?




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# {Gwen's DTC Test Result: Wellness}

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## Disease Forecast

How sick will you get compared to others in our DNA database? How much will you scream, and how many people can your germs take down with you? The answers lie within your genetic code.




**86%**

MORE likely to find yourself in a series of increasingly sophisticated wheelchairs



**63%**

LESS likely to catch the cold going around your workplace later this week



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## Genetic Health Risks Example Report

Late-Onset Alzheimer's Disease	Slightly increased risk
Hereditary Thrombophilia	Slightly increased risk
BRCA1/BRCA2 (Selected Variants)	Variants not detected
Parkinson's Disease	Variants not detected
Age-Related Macular Degeneration	Variants not detected
Alpha-1 Antitrypsin Deficiency	Variants not detected
Celiac Disease	Variants not detected
G6PD Deficiency	Variant not detected
Hereditary Hemochromatosis (HFE-Related)	Variants not detected



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**Sophia**

“Looks like I’ve got a race between Alzheimer’s and Parkinson’s coming up. How exciting!”



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## DTC: Hereditary Cancer Susceptibility

### Example: DTC Breast Cancer Test

Genotyping for 3 mutations within the *BRCA1* and *BRCA2* genes

- Tests only for 3 variants common in the Eastern European (Ashkenazi) Jewish population
- 1 in 40 individuals with AJ Ancestry

Great test if you are Ashkenazi Jewish

### Concerns:

>1800 known pathogenic variants within *BRCA1* and *BRCA2* genes NOT INCLUDED

Other breast cancer genes that impact breast cancer risk (*TP53*, *ATM*, *PALB2*, *CHEK2*)

False reassurance with “negative” results



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## DTC: Hereditary Cancer Susceptibility

Worst Case Scenarios Happening

Woman gets 23and Me BRCA test while waiting for full breast cancer genetic risk. Celebrated when got “no variants” from DTC test; then got “pathogenic mutation” news on clinical test. Hadn’t realized first test looked at 3 of 1800 variants.

My family member had DTC breast cancer testing and thought she did not have the family variant because she tested negative. She was diagnosed with metastatic breast cancer and died a year later.



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## DTC: Genetic Testing Raw Data File generated via genotyping

DTC companies may analyze >600,000 genetic variants, even if only reporting on a small number of these

Some labs allow raw data of these SNPs to be downloaded for free

Can upload to 3<sup>rd</sup> Party Interpretation Service for a fee

- Promethease
- SNPedia

rsid	chromosome	position	genotype
rs12564807	1	734462	AA
rs3131972	1	752721	GG
rs148828841	1	760998	CC
rs12124819	1	776546	AA
rs115893985	1	787173	GG
rs11240777	1	798959	AG
rs7538305	1	824398	AA
rs4970383	1	838555	CC
rs4475691	1	846808	CT
rs7537756	1	854250	AG
rs13382982	1	861808	GG
rs55678698	1	864498	CC
rs110852	1	871267	CC
rs1110052	1	873558	GT
rs147226614	1	878697	GG
rs16019302	1	881843	GG
rs2272756	1	882833	GG
rs467274836	1	884767	GG
rs16019303	1	888554	CC
rs13382945	1	889159	CC
rs16019304	1	889182	GG
rs16019305	1	891343	GG
rs13383106	1	891945	AG



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## DTC: Accuracy

Genetics  
inMedicine

Original Research Article | OPEN | Published: 22 March 2018

False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care

Stephany Tandy-Connor MS, Jenna Gultinan MS, Kate Krempely MS, Holly LaDuca MS, Patrick Reineke BS, Stephanie Gutierrez BS, Phillip Gray PhD & Brigitte Tippin Davis PhD, FACMG

**Purpose:** There is increasing demand from the public for direct-to-consumer (DTC) genetic tests, and the US Food and Drug Administration limits the type of health-related claims DTC tests can market. Some DTC companies provide raw genotyping data to customers if requested, and these raw data may include variants occurring in genes recommended by the American College of Medical Genetics and Genomics to be reported as incidental/secondary findings. The purpose of this study was to review the outcome of requests for clinical confirmation of DTC results that were received by our laboratory and to analyze variant classification concordance.

**Methods:** We identified 49 patient samples received for further testing that had previously identified genetic variants reported in DTC raw data. For each case identified, information pertaining to the outcome of clinical confirmation testing as well as classification of the DTC variant was collected and analyzed.

Genetics  
inMedicine

Original Research Article | OPEN | Published: 22

False-positive result to-consumer genetic importance of clinical confirmation testing for appropriate

Stephany Tandy-Connor MS, Jenna Gultinan Reineke BS, Stephanie Gutierrez BS, Phillip Gray

**Results:** Our analyses indicated that 40% of variants in a variety of genes reported in DTC raw data were false positives. In addition, some variants designated with the "increased risk" classification in DTC raw data or by a third-party interpretation service were classified as benign at Ambry Genetics as well as several other clinical laboratories, and are noted to be common variants in publicly available population frequency databases.

**Conclusion:** Our results demonstrate the importance of confirming DTC raw data variants in a clinical laboratory that is well versed in both complex variant detection and classification.

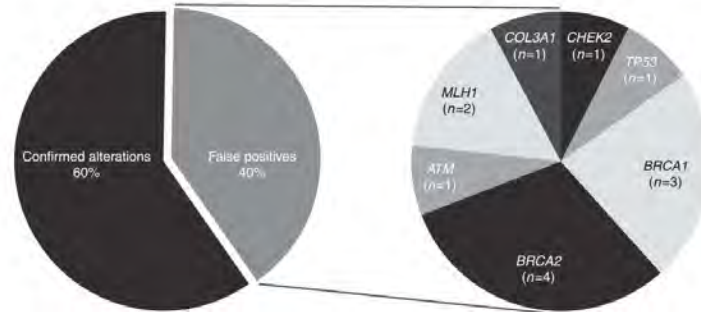
Genet Med advance online publication 22 March 2018

**Key Words:** classification discrepancy; clinical confirmation direct-to-consumer; false positive; raw data



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## False Positive Results



**Figure 1** False-positive variants in clinically actionable genes. The pie chart on the left indicates of the variants analyzed, 60% were confirmed and 40% were false positives. The pie chart on the right shows which genes were involved with the false-positive cases and how often those false calls were detected in this study.

**40% False Positive**



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## Misinterpretation of Variant

**Table 3** Classification discrepancies

Gene	Variant	DTC/third party <sup>a</sup>	Ambry <sup>b</sup>	ClinVar <sup>c</sup>
<i>ATM</i>	p.M1040V (c.3118A > G)	Increased risk	Benign	Benign
<i>BRCA1</i>	p.Q356R (c.1067A > G)	Increased risk	Benign	Benign
<i>BRCA2</i>	p.N372H (c.1114A > C)	Increased risk	Benign	Benign
<i>COL3A1</i>	p.A698T (c.2092G > A)	Increased risk	Benign	Benign
<i>COL5A1</i>	c.655-8689C > T	Increased risk	Deep intronic—benign	N/A
<i>COL5A1</i>	c.654+2749A > G	Increased risk	Deep intronic—benign	N/A
<i>COL5A1</i>	c.1827+399C > T	Increased risk	Deep intronic—VUS	N/A
<i>COL5A1</i>	c.1827+1142T > C	Increased risk	Deep intronic—benign	N/A

**19% Confirmed, but classified incorrectly**

DTC: Pathogenic variant

Diagnostic Lab: Benign or VUS



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## DTC: Confirmatory Testing

**FDA recommends confirmatory testing through clinical lab if positive on DTC testing**

### 2023 NCCN Guidelines:

Confirmatory germline testing through an appropriately certified laboratory (CAP, CLIA) is clinically indicated when a P/LP variant is identified through:

- Commercial entities providing ancestry and health information
- Commercial laboratory utilizing consumer-initiated or direct-to-consumer DTC marketing



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## DOT: Privacy Concerns

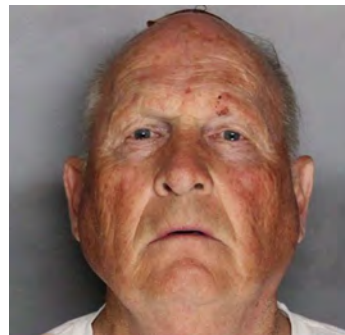
**Who owns the DNA and generated data?**

**Data may be sold or shared with 3<sup>rd</sup> parties**

- Pharmaceutical companies  
Development of drugs
- FBI and law enforcement  
2018 Golden State Killer
- Others?

### Golden State Killer

The Golden State Killer was a serial rapist turned serial killer who terrorized Californians in the 1970s and '80s. The killer was at large for decades until DNA evidence led to the arrest of Joseph DeAngelo in 2018, who pleaded guilty in June 2020.



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# {Gwen's DTC Test Results: Ancestry}

DISCLAIMER: DNA Friend is not a real genetic testing company. This is a parody website. DNA Friend does not collect anyone's DNA, nor does it receive, view, or keep any photos captured by users onsite.

## Possible Relatives

Family members support us, comfort us, and silently shoulder the same shameful hereditary burdens we do. By comparing your DNA results with those of other DNA Friend users, we have identified these likely relatives.



**George Clooney**

Relationship: None whatsoever  
Confidence: 100%



**Kendra Marsden**

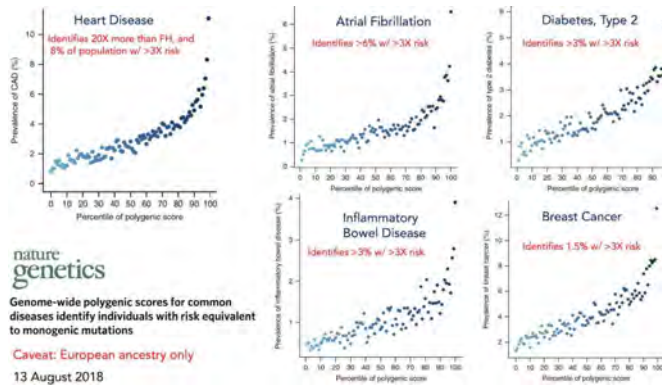
Relationship: Daughter. Well, she might not technically be your daughter, but Kendra really needs a steady adult presence in her life.  
Confidence: High



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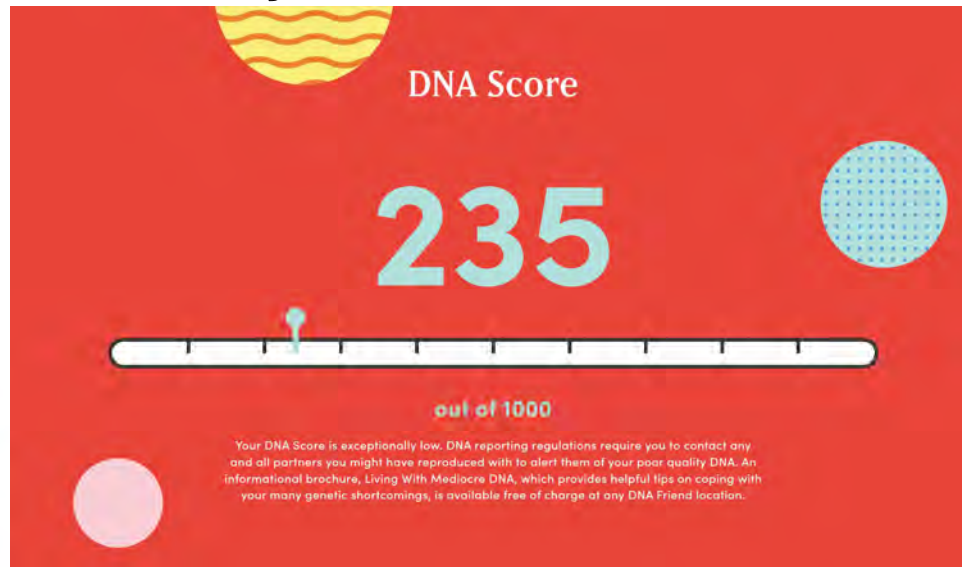
# DTC: Polygenic Risk Scores

- Most disease risk is not related to a single gene mutation
- Many diseases appear to be driven by several common genetic variants with small additive effects
- One genetic variant by itself may not have much effect
- Combined with 100 or more variants with small risks can combine to have a big effect



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## {Gwen's DTC Test Results: Genetic Health Risk}



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## DOT: Liquid Biopsies Circulating Tumor Cells ctDNA and cfDNA

**Examines blood to detect DNA fragments or methylation patterns from cancer cells**

**Used clinically to detect metastatic cancer for therapy and prognosis**

**Can also be found in early-stage cancer**

Clinical trials-ctDNA assays for early cancer screening test

GRAIL's commercial Galleri Multi-cancer early detection test

- uses cfDNA methylation patterns to detect 50 types of cancer
- ordered by HCP

Future Direction: Labs looking to use ctDNA technology and develop DTC tests

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## DOT Limitations and Concerns

- **Incomplete analysis of gene or genes**  
False negatives
- **3<sup>rd</sup> party analysis of raw data shown to be inaccurate**  
40% false positive rate
- **DTC positive test result need confirmatory testing**
- **Variable clinical utility and actionability**
- **Healthcare provider/team not required to be involved**  
Misinterpretation of results  
Screening and management lapses  
Lack of local support services
- **Potential for unexpected results/consequences**  
Discovery of non-paternity, adoption and other family secrets  
Unexpected ancestry  
Long lost relatives
- **Privacy/DNA protection issues**  
Who owns your DNA  
Who has access to your DNA



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## {Gwen's DTC Test Results: Summary}

DISCLAIMER: DNA Friend is not a real genetic testing company. This is a parody website. DNA Friend does not collect anyone's DNA, nor does it receive, view, or keep any photos captured by users onsite.

Now that you know all the most sensitive and intimate information there is to know about yourself, go ahead and share it indiscriminately on social media.

SHARE RESULTS

And be sure to tell your friends and family about DNA Friend so that they can receive their free genetic test results and we can complete our proprietary genome database. Thank you for being our DNA Friend!



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## Patient perceived Expectations/Benefits of DTC

Results are valid

Negative test results rule out risks

Results will be impactful for their healthcare

DNA data is “protected” from medical record systems and insurers

DTC cheaper than doctor visits and traditional lab tests

Marzulla et al. Genetic counseling following direct-to-consumer testing: Consumer perspectives. *J Genet Couns*



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## Summary

- Genotyping ≠ Gene sequencing
  - DTC ≠ Diagnostic Genetic Testing
- DTC positive results should have confirmatory testing through a clinical laboratory
- DTC testing is not comprehensive, so a negative DTC result is not an absolute negative
- If there is a family history of a genetic condition, a referral to Genetics is highly recommended to ensure:
  - the most informative testing is ordered
  - accurate risk assessment/medical management recommendations
  - **Hereditary Cancer Clinic (402-559-3602 for appointments)**



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