Direct-to-Consumer Genetic Testing: Providing Personalized Medicine

STEPHANIE BYERS ASHER, MS, CGC
SENIOR GENETIC COUNSELOR

Disclosures

• I received gratis genetic testing for personal use from Color Genomics prior to being asked to give this talk.
A Note

• Specific products and laboratories will be discussed in this talk. This does not imply endorsement by myself, my employer or the providers of the activity.

Presentation Outline

• Introduction on DTC genetic tests
• Interpreting DTC genetic tests
• Available resources and next steps for patients
• The future of DTC genetic test
• Q&A
Presentation Outline

• Introduction on DTC genetic tests
• Interpreting DTC genetic tests
• Available resources and next steps for patients
• The future of DTC genetic test
• Q&A

Direct to Consumer Testing

About 30 million people are estimated to have had some type of DTC testing

Within a 4-day timespan (“Black Friday” through “Cyber Monday,” November 2017), Ancestry.com sold an estimated 1.5 million DNA kits
Two Major Categories of Testing

- Direct to Consumer Genetic Testing (DTC-GT)
  - Genetic tests ordered by an individual without the involvement of a health care professional

- Consumer-Initiated Genetic Testing (CI-GT)
  - Genetic tests ordered by an individual but require a health care professional to sign off

Direct to Consumer Genetic Testing

- Type of tests: Ancestry, genetic traits, some disease risk, entertainment

- Methodology: Generally uses genotyping of predefined single nucleotide variants

- Many give back raw data which can be interpreted through 3rd party websites

- Lab Examples:
  - 23andMe, Ancestry.com, FamilyTreeDNA, Genos, MyHeritage, Helix (some tests)

Weissman, Scott. “DTC Genetic Testing 201.”
https://www.nsgc.org/p/bl/et/blogid=59&blogaid=1057
Consumer-Initiated Genetic Testing

- Type of tests: genes known to cause a hereditary risk of disease, which can include cancer, cardiac and carrier testing; pharmacogenetic testing

- Methodology: Uses “full” gene sequencing

- Raw data is not generally available

- Lab Examples:
  - Color, Invitae, OneOme, Veritas (closed), Helix (some tests), JScreen

Weissman, Scott. “DTC Genetic Testing 201.”
https://www.nsgc.org/p/bl/et/blogid=59&blogaid=1057

Benefits and Limitations of DTC-GT

**BENEFITS**
- Allows consumers access to their genetic information
- Possibly encourage consumers to change their behaviors
- Research opportunities through partnerships between the lab and other companies

**LIMITATIONS**
- Testing type/methodology is not the same as clinical testing
- Concerns about consumer misunderstanding of the utility/limitations of the testing
- Concerns about privacy protections
- Potential to find unexpected information
- Results require confirmation in a clinical lab prior to using for clinical management
Benefits and Limitations of CI-GT

**BENEFITS**
- Medical-grade test
  - Performed in a CLIA-certified lab
- Improved access compared to traditional testing
- Involvement of HCP who is familiar with test, often includes post-test genetic counseling

**LIMITATIONS**
- May only report pathogenic or likely pathogenic variants
  - Variants of uncertain significance may not be reported
- May have limited methodology
  - Gene sequencing only
- May not be the “complete” test
  - Only selected genes/variants may be included

Presentation Outline
- Introduction on DTC genetic tests
- Interpreting DTC genetic tests
- Available resources and next steps for patients
- The future of DTC genetic test
- Q&A
Step One (The Most Important Step)

- Determine what testing has been performed:
  - Wellness/trait association
  - FDA-approved testing from a DTC company
  - 3rd party analysis of raw data from DTC testing
  - Consumer-initiated testing

Wellness/Trait Markers

“Info-tainment” : Limited Clinical Utility

Helix Wellness

**Does my DNA really impact my weight and wellbeing?**

You might be surprised how much you can learn about your day-to-day from your DNA. Helix Wellness can get you started with some fascinating and personal genetic traits.

**Traits included:**
- Body mass index (BMI) introduction
  It's no secret that genetics plays a role in weight, since two people who eat the same foods can have very different responses. You'll learn about just one of the many genes that influences BMI, the FTO gene, and how it influences your weight.

![BMI versus age by FTO genotype](image)

*Figure 1: Scans of weight (BMI) by sex and genotype in individuals measured by the two methods described for study analysis.*
Wellness/Trait Markers

• Main benefit: Changing consumer behavior
  • 23% had a positive lifestyle change (specifically improved dietary and exercise practices, quit smoking)
  • 7% had subsequent preventive checks

Clinical testing from DTC Companies

23ANDME
(FDA-APPROVED, CLIA-CERTIFIED)
Health Predisposition Reports:
• Age-related macular degeneration (2 variants);
  Alpha-1 Antitrypsin deficiency (2 variants);
  BRCA1/2 (3 variants);
  Celiac disease (2 variants);
  Familial hypercholesterolemia (24 variants);
  G6PD Deficiency (1 variant);
  Hereditary amyloidosis (3 variants);
  Hereditary hemochromatosis (2 variants);
  Hereditary thrombophilia (2 variants);
  Late-onset Alzheimer's disease (1 variant);
  MUTYH-Associated polyposis (2 variants);
  Parkinson's disease (2 variants)
Carrier Status Reports*: 40+ disorders
  https://www.23andme.com/dna-reports-list/

ANCESTRY.COM
(CLIA-CERTIFIED)
Cancer Risk:
• BRCA1/2: 27 variants
• Lynch syndrome: 12 variants in 4 genes
Carrier status:
• Selected variants for cystic fibrosis, sickle cell anemia, Tay-Sachs disease
Heart and Blood Health
• MYBPC3 and MYH7- associated cardiomyopathy (9 variants)
• Familial hypercholesterolemia (9 variants)
• Hereditary Hemochromatosis (2 variants)
• Hereditary Thrombophilia (2 variants)

https://www.ancestry.com/health/variants
DTC Raw Data Analysis

- Many DTC companies, such as Ancestry.com and 23andMe give users the option to download their raw data.
- Raw data can then be analyzed through a 3rd party site, such as:
  - Promethease
  - GenomeGenie
  - LiveWello

Promethease

- “Literature retrieval system that builds a personal DNA report based on connecting a file of DNA genotypes to the scientific findings cited in SNPedia”
Promethease

- "Literature retrieval system that builds a personal DNA report based on connecting a file of DNA genotypes to the scientific findings cited in SNPedia"

A study of patients diagnosed with carcinoma of the uterine cervix, head and neck squamous cell carcinoma (HNSCC), and breast cancer found a 1.6–2.1 times increased risk for all three cancer types for the rs738579 (C) genotype, while the finding decreased risk (0.5–0.4) for rs738579 (T) heterozygotes. However, these genotypes had no increased risk for cervical cancer but increased risk for HNSCC (1.4–1.6) and breast cancer (1.2–1.4). 

Although statistics were not reported per genotype, a combination of data from all three cancer forms and all genotypes provided a strong statistical evidence for rs738579 as a cancer marker, with p-value of 0.01 and PMID 29565420.

Note that the research cited above was published over a decade ago, and there has been no follow-up or replication to our knowledge. It would be best to consider the research preliminary and perhaps of little to no clinical significance (until it is confirmed or replicated in a larger sample).

ORIGINAL RESEARCH ARTICLE

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 Guiltinan, MS, Kate Krempe, MS, Holly LaDuca, MS, Patrick Reineke, BS, Stephanie Gutierrez, BS, Phillip Gray, PhD and Brigitte Tippin Davis, PhD, FACMG

Figure 1: false-positive variants in clinically actionable genes. The pie chart on the left indicates the variants analyzed, 62% were confirmed and 4% were false positives. The pie chart on the right shows which genes were involved in the false-positive cases and how often those false calls were detected in this study.

PMID 29565420
Consumer Initiated Genetic Testing

- Hereditary Cancer Syndromes:
  - Hereditary breast and ovarian cancer, Lynch syndrome, prostate cancer, thyroid cancer, etc.
- Cardiovascular Disease:
  - Aortopathies, arrhythmias, cardiomyopathies, familial hypercholesterolemia
- Carrier testing:
  - Testing to determine the chances of having a child with a condition due to the parent being a carrier for the disorder
- Pharmacogenomic testing
- Newborn genetic screening
- Whole exome or whole genome sequencing:
  - Analysis of the coding portions of genes (exome) or entirety of genome for sequence variants
Presentation Outline

- Introduction on DTC genetic tests
- Interpreting DTC genetic tests
- Available resources and next steps for patients
- The future of DTC genetic test
- Q&A

Web-Based Resources for Consumers

- Genetics Home Reference:
- National Human Genome Research Institute:
- Questions about Genetic Discrimination:
  [http://ginahelp.org/](http://ginahelp.org/)
Variant Interpretation

- Reference SNP “rs” numbers
Variant Interpretation

  - Aggregate of information about genomic variation

Management Resources for Providers

- American College of Medical Genetics and Genomics
- American College of Cardiology
- American College of Obstetrics and Gynecology
  - Follow-up information for carrier testing
- National Comprehensive Cancer Network: www.NCCN.org
  - Recommendations for screening for hereditary cancer syndromes
- Pharmacogenomics:
  - Clinical Pharmacogenomics Implementation Consortium (CPIC)
  - PharmGKB
National Comprehensive Cancer Network

CPIC: Clinical Pharmacogenetics Implementation Consortium

Genes - Drugs

CPIC® Guideline for Clopidogrel and CYP2C19

Update status: Published

Available Clinical Genetics Resources

- Laboratory Resources
  - Many labs performing testing offer genetic counseling as a service to users
  - 23andMeBlog: provides information on a variety of common topics
- National Society of Genetic Counseling (www.NSGC.org)
  - Traditional in-person genetic counseling
  - Telehealth genetic counseling
- American College of Medical Genetics and Genomics (www.ACMG.net)
- Personalized Genomic Medicine Clinics

Reasons for Referral to Clinical Genetics

- Provide disease-specific evaluation, counseling and recommendations
- Coordination of cascade testing for family members or testing for reproductive partners
- Tracking variant re-classification
Case Example

• 25 yo female undergoes DTC genetic testing due to multiple medical concerns
• DTC testing identifies a heterozygous pathogenic variant in the GBA gene associated with Gaucher disease
• Patient receives raw data and uses a 3rd party website to analyze her test results
  ◦ Identifies C677T and A1298C variants in the MTHFR gene
• Presents to her PCP with these results who refers her for a clinical genetics evaluation

Case Example (continued)

• Review of results with the geneticist and genetic counselor
  ◦ MTHFR variants: not likely clinically relevant
    ◦ These variants are present in up to 50% of individuals in some ethnic groups and have been linked to a variety of medical concerns. Studies are inconclusive or conflicting about the role of MTHFR in these disorders.
  ◦ GBA variant: carrier for Gaucher disease
    ◦ However, only 3 variants were included on the test.
• In the evaluation: history of anemia is shared, and splenomegaly is appreciated on physical exam
• Genetic testing is ordered for full analysis of GBA, which identifies a second variant, thus confirming a diagnosis of Gaucher disease in the patient
• Treatment with enzyme replacement therapy is initiated
Presentation Outline

- Introduction on DTC genetic tests
- Interpreting DTC genetic tests
- Available resources and next steps for patients
- The future of DTC genetic testing
- Q&A

Increased Access to Genetic Testing

Decreasing Cost
- 2007: $1000
- 2010: $300-400
- Now: $99

Broadening test menu
Insurance coverage for tests

https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data
New Service Models

- Telehealth Services
  - COVID-19 pandemic has increased the availability of genetics telehealth services
  - Currently limited, though, as genetic counselors are not CMS-recognized providers
- New workflows to ensure that access isn’t a barrier to care

Primary Care

Role of PCPs in ordering genetic testing

Increased expectations that PCPs will understand and utilize test results in clinical care

- 1026 participants
- 63% planned to share results with PCP
- At 6 months, only 27% reported having done so
- Among participants who discussed the results, 35% were very satisfied with the encounter and 18% were not satisfied at all

PMID 26928821
New Testing Options

Polygenic Risk Scores
- Summation of many common variants to derive an overall risk of developing a particular disease
- Currently available:
  - 23andMe (diabetes)
  - Color (CAD)
  - Helix (prostate cancer)

Big question: how to use these results in clinical care?

https://www.nature.com/articles/d42473-019-00270-w

However, has the public’s interest already started to decrease?

Take Home Points

- Not all “direct-to-consumer” genetic testing is created equal
- Important to determine what type of testing has been performed prior to taking action
  - Consider whether the results need to be confirmed in a clinical lab
- Providers have many resources available to help patients interpret their results
- When in doubt, clinical genetics experts are available to help

Summary of Resources

- For Consumers:
  - National Human Genome Research Institute: https://www.genome.gov/dna-day/15-ways/direct-to-consumer-genomic-testing
  - Questions about Genetic Discrimination: http://ginahelp.org/
- Variant Interpretation:
- Clinical:
  - National Society of Genetic Counselors
  - American College of Medical Genetics and Genomics
  - American College of Cardiology
  - American College of Obstetrics and Gynecology
  - National Comprehensive Cancer Network: www.NCCN.org
  - Clinical Pharmacogenomics Implementation Consortium (CPIC): https://cpicpgx.org/
  - PharmGKB: https://www.pharmgkb.org/
- Miscellaneous:
  - 23andMe Blog: https://blog.23andme.com/
Presentation Outline

- Introduction on DTC genetic tests
- Interpreting DTC genetic tests
- Available resources and next steps for patients
- The future of DTC genetic test
- Q&A