Direct-to-Consumer Genetic Testing: Providing Personalized Medicine

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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
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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

Global Consumer Appetite For Genetic Testing Has Ballooned Over The Past 6 Years

Total number of consumers tested by genetic testing companies globally

*As of January 3, 2019
Source: ART Technology Review, February 25, 2019
Ancestry, ART Technology Review (estimates and data) aggregated by the International Society of Genetic Counseling, and publicly available for the four largest genetic testing companies. Because the genetic testing companies release their information intermittently, ART Technology Review used the disclosures shared in January 1 for 2015-2016. To make a figure for 2019, ART Technology Review used data reported to Ancestry in December 26, 2018.
Direct-to-consumer Genetic Testing Market Size to grow at 16.4%+ CAGR up to 2024

Published: May 15, 2019 11:28 p.m. ET

Direct-to-consumer genetic tests may help predict risks to your future health. But are they worth the cost and trouble?

Should you get a home genetic test?

Second Opinion
Direct to Consumer Genetic testing isn’t ready for prime time

Hosted by Michael Williams - May 12, 2019 (Health and Wellness)
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)
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

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 may be included

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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 eight 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.

PMID 21379325
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

<table>
<thead>
<tr>
<th>23ANDME</th>
<th>ANCESTRY.COM</th>
</tr>
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<tbody>
<tr>
<td>(FDA-APPROVED, CLIA-CERTIFIED)</td>
<td>(CLIA-CERTIFIED)</td>
</tr>
<tr>
<td>Health Predisposition Reports:</td>
<td>Cancer Risk:</td>
</tr>
<tr>
<td></td>
<td>- BRCA1/2: 27 variants</td>
</tr>
<tr>
<td></td>
<td>- Lynch syndrome: 12 variants in 4 genes</td>
</tr>
<tr>
<td></td>
<td>Carrier status:</td>
</tr>
<tr>
<td></td>
<td>- Selected variants for cystic fibrosis, sickle cell anemia, Tay-Sachs disease</td>
</tr>
<tr>
<td></td>
<td>Heart and Blood Health</td>
</tr>
<tr>
<td></td>
<td>- MYBPC3 and MYH7- associated cardiomyopathy (9 variants)</td>
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<tr>
<td></td>
<td>- Familial hypercholesterolemia (9 variants)</td>
</tr>
<tr>
<td></td>
<td>- Hereditary Hemochromatosis (2 variants)</td>
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<tr>
<td></td>
<td>- Hereditary Thrombophilia (2 variants)</td>
</tr>
<tr>
<td>Carrier Status Reports*: 40+ disorders</td>
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</tbody>
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https://www.23andme.com/dna-reports-list/  
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”

Promethease™ is a SNP retrieval system that builds a personal DNA report based on connecting a file of DNA genotypes to the scientific findings cited in SNPedia. This system allows users to access comprehensive information about genetic variants and their implications for health and disease.

Promethease™ can be used to:
- Identify genetic variants associated with specific health conditions
- Understand the scientific basis for genetic findings
- Personalize genetic information for more accurate medical advice

Promethease™ is designed to help users make informed decisions about their health by providing them with detailed and reliable genetic information.
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
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Web-Based 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

- Reference SNP “rs” numbers
**Variant Interpretation**

  - Aggregate of information about genomic variation

**ClinVar**

Genomic variation as it relates to human health

![ClinVar excerpt]

- **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](http://www.NCCN.org)
    - Recommendations for screening for hereditary cancer syndromes
  - Pharmacogenomics:
    - Clinical Pharmacogenomics Implementation Consortium (CPIC)
    - PharmGKB
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
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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:
  • dbSNP: https://www.ncbi.nlm.nih.gov/snp/

• 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/
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