Direct-to-Consumer Genetic Testing: Providing Personalized Medicine

STEPHANIE BYERS ASHER, MS, CGC
SENIOR GENETIC COUNSELOR

1

Disclosures

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

2

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.

3

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

4

Presentation Outline

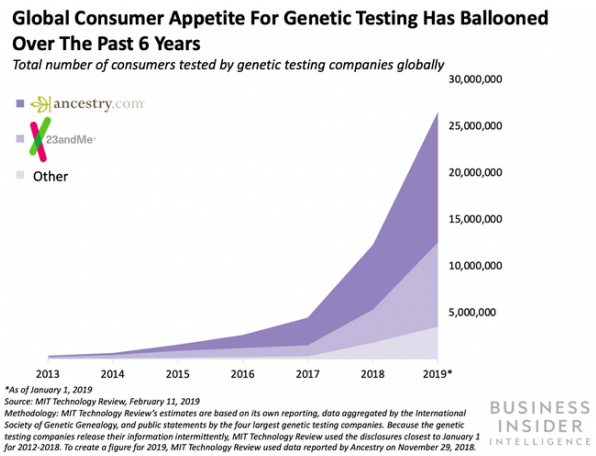
- Introduction on DTC genetic tests
- Interpreting DTC genetic tests
- Available resources and next steps for patients
- The future of DTC genetic test
- Q&A

5

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



6

VINOME

Helix

Veritas
The Genome Company

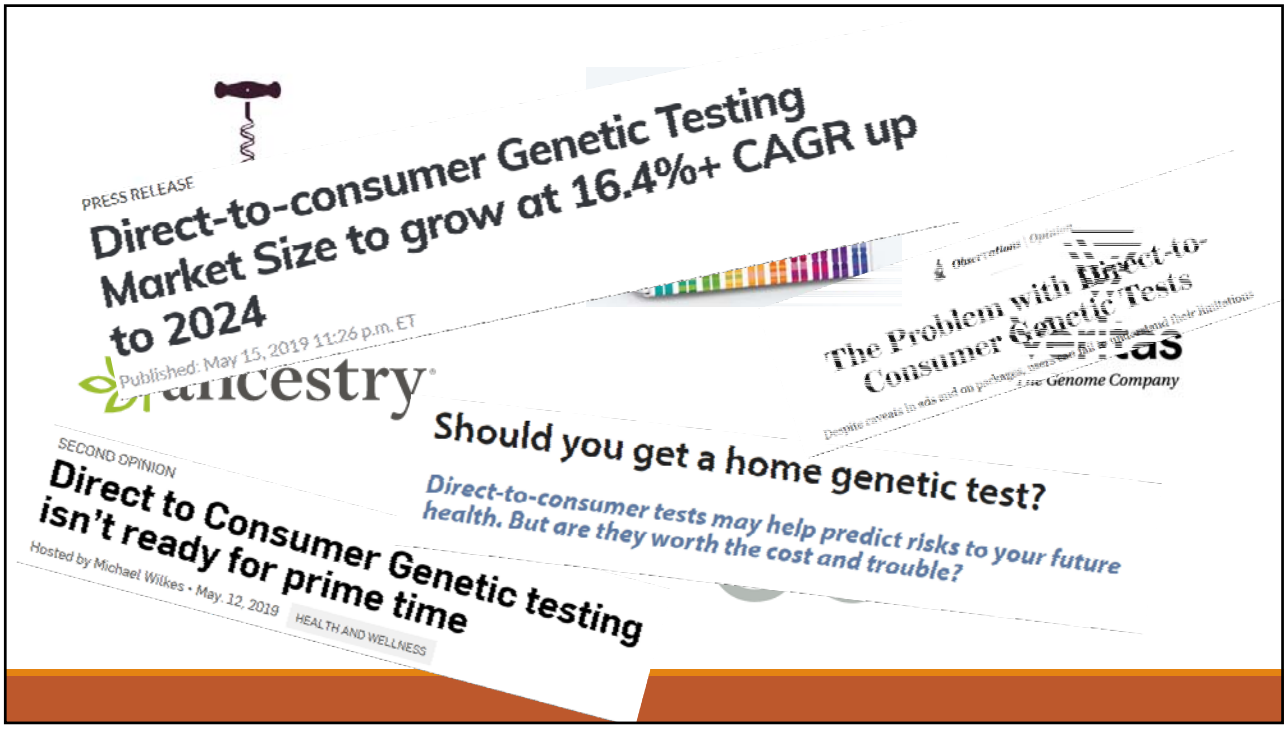
ancestry

INVITAE

FITNESS GENES

color

7



8

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

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

9

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

10

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

11

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

12

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

13

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

14

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

15

Wellness/Trait Markers

"Info-tainment" : Limited Clinical Utility

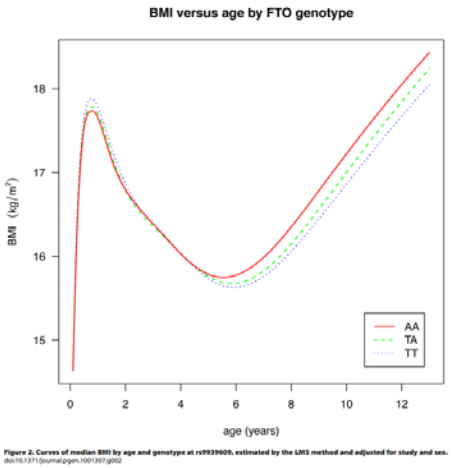
Helix Wellness

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

16

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

PMID 28664264

17

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

18

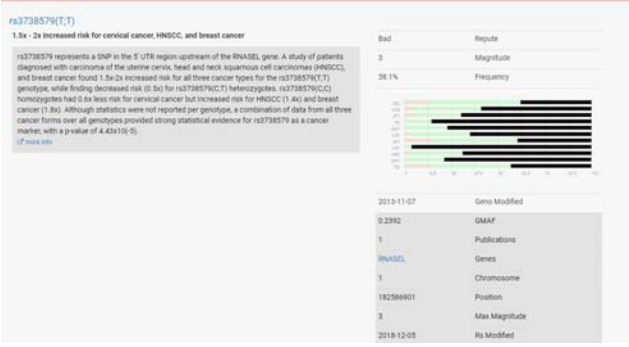
DTC Raw Data Analysis

- 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

19

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"



20

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"

21

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Open

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 Krempely, MS, Holly LaDuca, MS, Patrick Reineke, BS, Stephanie Gutierrez, BS, Phillip Gray, PhD and Brigette Tippin Davis, PhD, FACMG

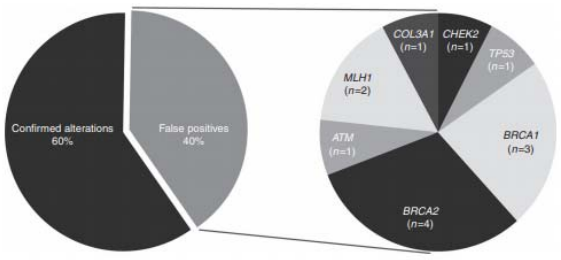


Figure 1 False-positive variants in clinically actionable genes. The pie chart on the left indicates of the variants analyzed, 60% were confirmed and 40% were false positives. The pie chart on the right shows which genes were involved with the false-positive cases and how often those false calls were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

PMID 29565420

22

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Open

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 Krempely, MS, Holly LaDuca, MS, Patrick Reineke, BS, Stephanie Gutierrez, BS, Phillip Gray, PhD and Brigette Tippin Davis, PhD, FACMG

Table 3 Classification discrepancies

Gene	Variant	DTC/third party[a]	Ambry[b]	ClinVar[c]	ESP[d]	1000 Genomes[e]	dbSNP[f]
ATM	p.M1040V (c.3118A > G)	Increased risk	Benign	Benign	1.36%	0.95%	1.48%
BRCA1	p.Q356R (c.1067A > G)	Increased risk	Benign	Benign	4.59%	2.81%	3.97%
BRCA2	p.N372H (c.1114A > C)	Increased risk	Benign	Benign	23.32%	24.26%	24.44%
COL3A1	p.A698T (c.2092G > A)	Increased risk	Benign	Benign	21.39%	21.16%	19.16%
COL5A1	c.655-8689C > T	Increased risk	Deep intronic—benign	N/A	N/A	N/A	N/A
COL5A1	c.654+2749A > G	Increased risk	Deep intronic—benign	N/A	N/A	N/A	N/A
COL5A1	c.1827+399C > T	Increased risk	Deep intronic—VUS	N/A	N/A	N/A	N/A
COL5A1	c.1827+1142T > C	Increased risk	Deep intronic—benign	N/A	N/A	N/A	N/A

DTC, direct to consumer; N/A, not available; VUS, variant of unknown significance.
aVariant classification provided by the DTC company or a third-party interpretation service. bVariant classification provided by Ambry. cVariant classification provided in ClinVar (clinical laboratory submissions only). dExome Sequencing Project population frequency database. e1000 Genomes population frequency database. fdbSNP population frequency database.

PMID 29565420

23

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

24

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

25

Web-Based Resources for Consumers

➢Genetics Home Reference:

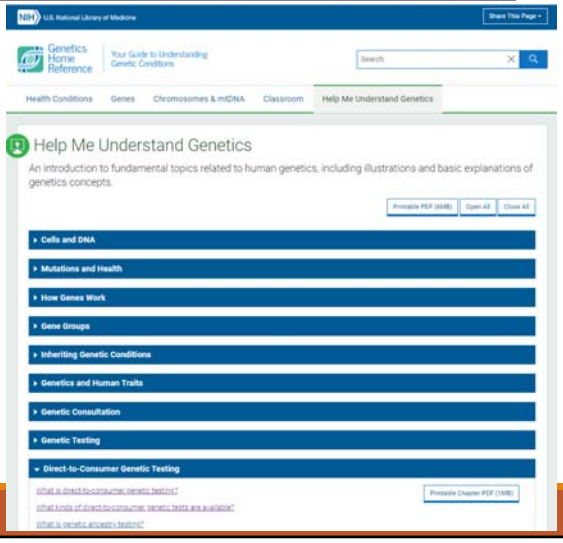
https://ghr.nlm.nih.gov/primer

➢National Human Genome Research Institute:

https://www.genome.gov/dna-day/15-ways/direct-to-consumer-genomic-testing

➢Questions about Genetic Discrimination:

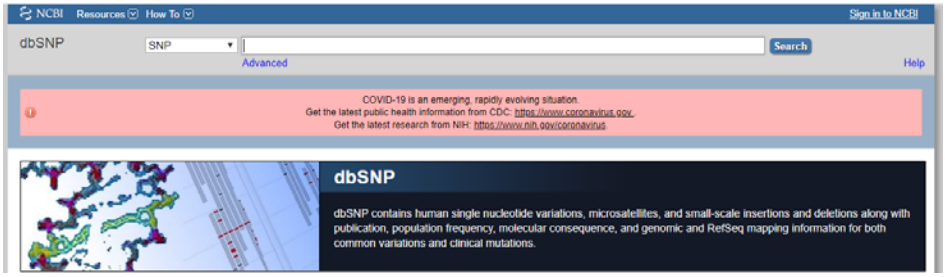
http://ginahelp.org/



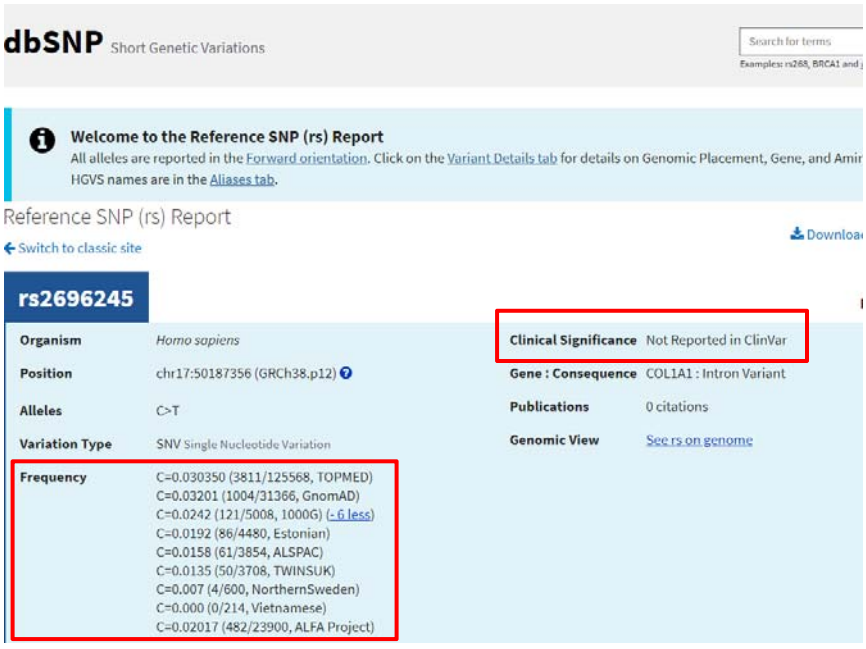
26

Variant Interpretation

- dbSNP: https://www.ncbi.nlm.nih.gov/snp/
- Reference SNP "rs" numbers



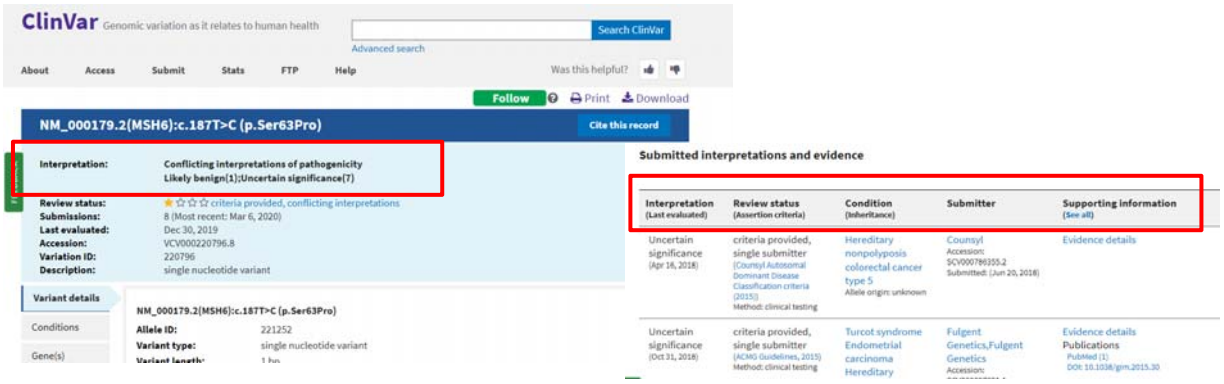
27



28

Variant Interpretation

- ClinVar: https://www.ncbi.nlm.nih.gov/clinvar/
  - Aggregate of information about genomic variation



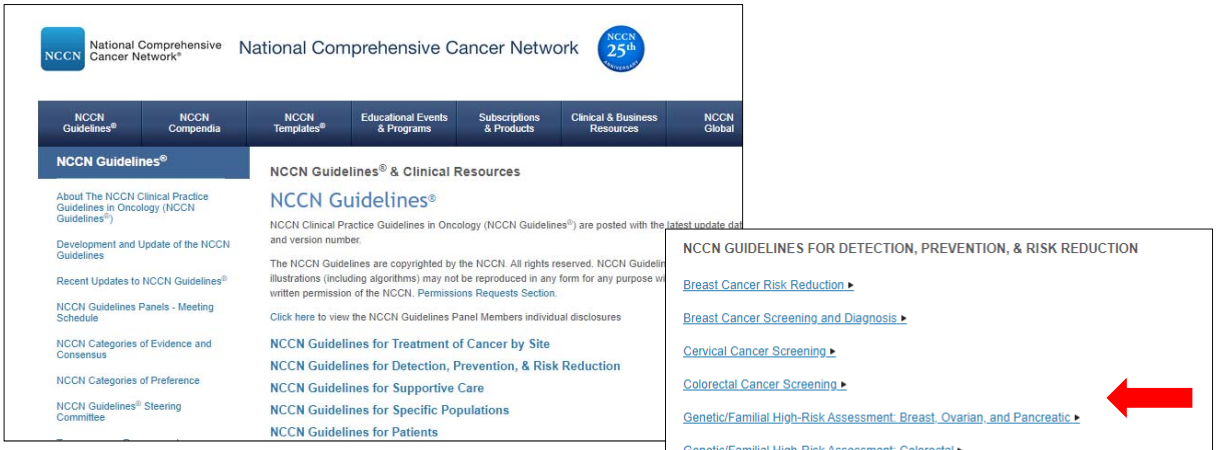
29

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

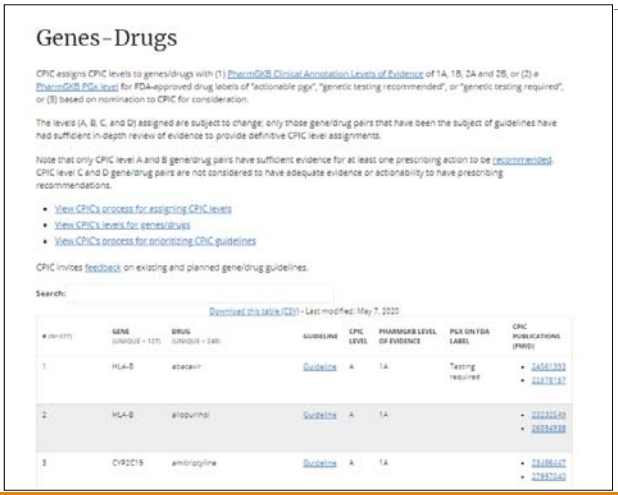
30

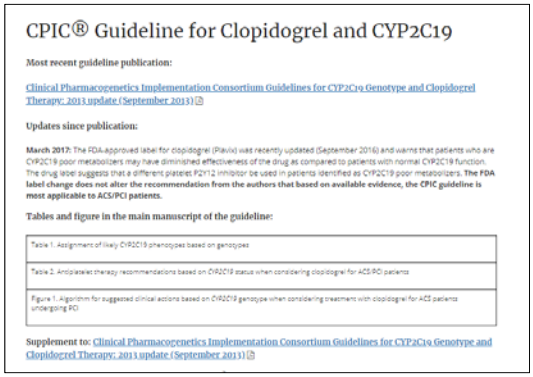
National Comprehensive Cancer Network



31

CPIC: Clinical Pharmacogenetics Implementation Consortium





32

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

33

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

34

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

35

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

36

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

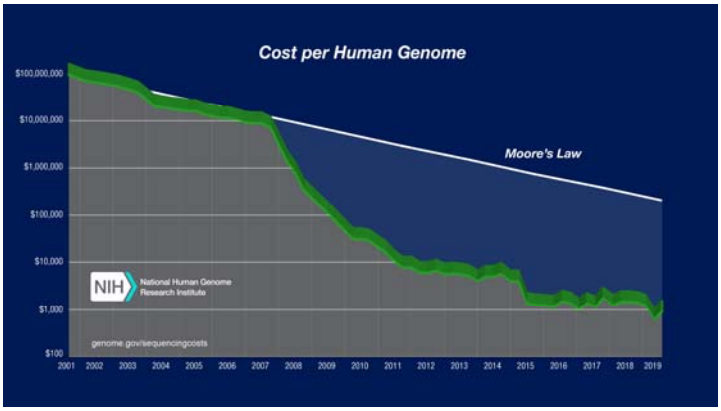
37

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

38

New Service Models

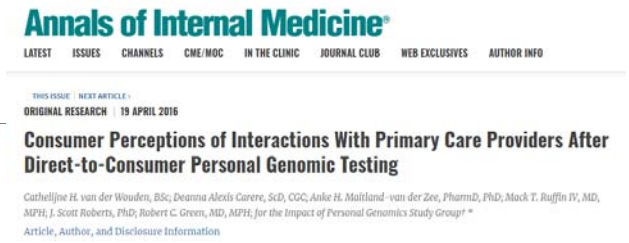
- Telehealth Services
  - COVID-19 pandemic has increased the availability of genetics telehealth services
  - Currently limited, though, as genetic counselors are not CMS-recognized providers
- New workflows to ensure that access isn't a barrier to care

39

Primary Care

Role of PCPs in ordering genetic testing

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



Annals of Internal Medicine

LATEST ISSUES CHANNELS CME/MOC IN THE CLINIC JOURNAL CLUB WEB EXCLUSIVES AUTHOR INFO

THIS ISSUE | NEXT ARTICLE ›

ORIGINAL RESEARCH | 19 APRIL 2016

Consumer Perceptions of Interactions With Primary Care Providers After Direct-to-Consumer Personal Genomic Testing

*Cathelijne H. van der Wouden, BSc; Deanna Alexis Carere, ScD, CGC; Anke H. Maitland-van der Zee, PharmD, PhD; Mack T. Ruffin IV, MD, MPH; J. Scott Roberts, PhD; Robert C. Green, MD, MPH; for the Impact of Personal Genomics Study Group† **

Article, Author, and Disclosure Information

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

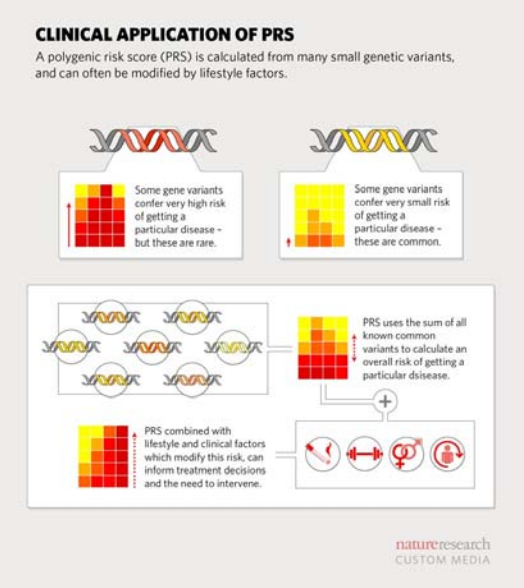
40

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)

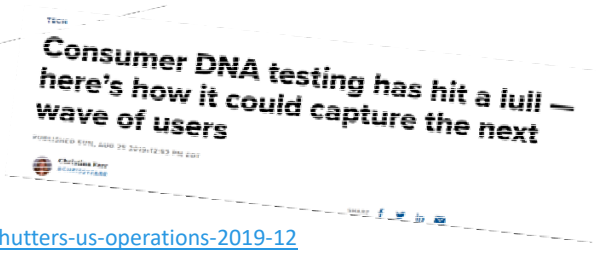
Big question: how to use these results in clinical care?



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

41

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



https://www.businessinsider.com/veritas-genetics-shutters-us-operations-2019-12
https://www.cnbc.com/2019/08/25/dna-tests-from-companies-like-23andme-ancestry-see-sales-slowdown.html

42

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

43

Summary of Resources

- For Consumers:
  - Genetics Home Reference: https://ghr.nlm.nih.gov/primer
  - 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/
  - ClinVar: https://www.ncbi.nlm.nih.gov/clinvar/
- 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/

44

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

45