Direct-to-Consumer (DTC) Testing and Early Onset Breast Cancer

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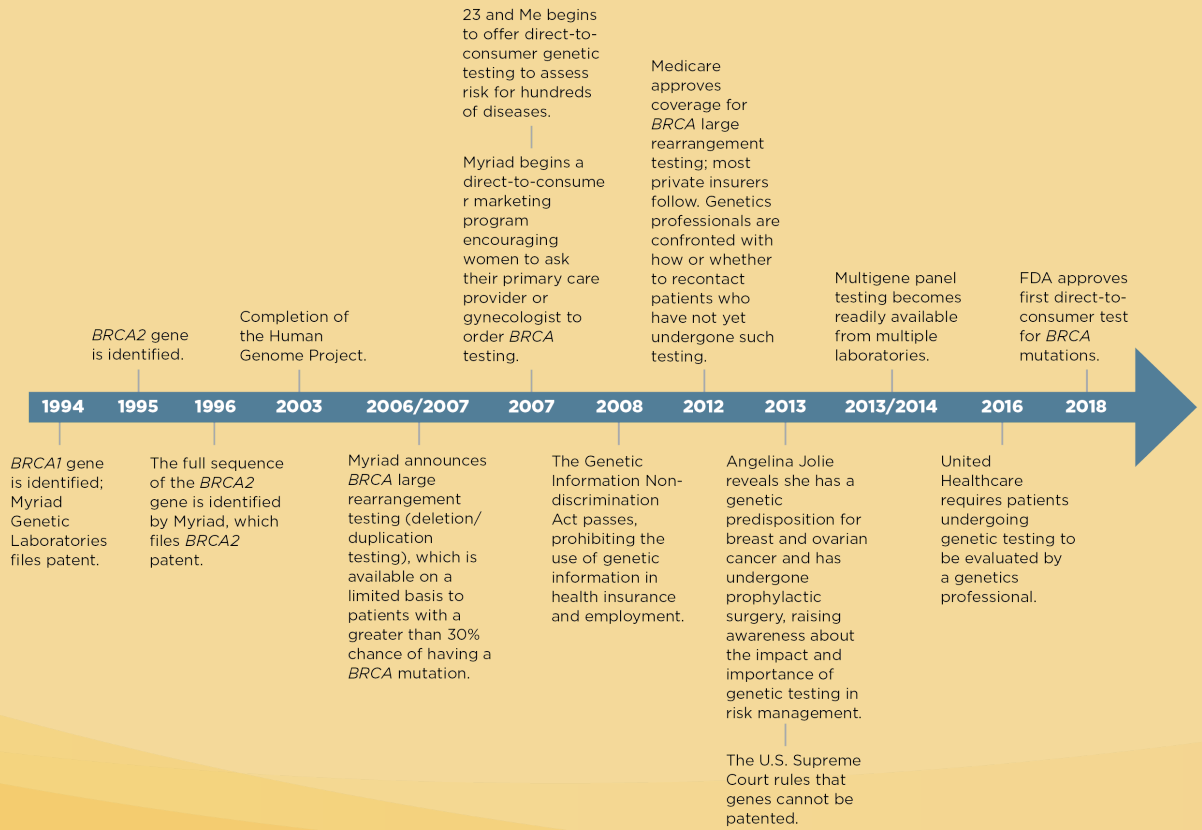
Outline

- History of Genetic Testing for Hereditary Cancer
- Overview of DTC Testing for BRCA
- DTC Tests and Regulatory Pathways
- Cost of DTC Tests
- Research about DTC Tests
- Advantages and Disadvantages about DTC Tests
- Case Presentation
- Implications for Patients and Providers

FIGURE 1.
HISTORY OF GENETIC TESTING FOR HEREDITARY CANCER SYNDROMES



- In 2007, the first DTC tests did not use comprehensive sequencing technology, but rather SNPs (variations in a single base pair.

Adapted from King, E. & Mahon, S. (2017). *Clinical Journal of Oncology Nursing*, 21(5), 590.

DTC Testing

- Genetic testing that consumers can purchase and interpret without necessarily involving a healthcare provider

- March 6, 2018- FDA granted the first marketing authorization to 23andMe for a DTC testing for 3 *BRCA1* or *BRCA2* mutations to identify women at increased lifetime risk of breast cancer.

What Variants are tested?

- The 185delAG variant in *BRCA1*
- The 5382insC variant in *BRCA1*
- The 6174delT variant in *BRCA2*

- Founder mutations found in approximately 2% of women in the Ashkenazi Jewish population
- More than 1000 mutations exist in *BRCA* genes

DTC Tests & Regulatory Pathways

- In general, DTC tests for non-medical, general wellness, or low risk medical purposes are not reviewed by the FDA

- DTC tests for moderate to high risk medical purposes are generally reviewed for the following:
  - Analytical Validity
  - Clinical Validity
  - Claims about the test and how well it works

DTC Tests & Regulatory Pathways

Type of Test	FDA Review
Carrier Screening Tests	Exempt from pre-market review, but must follow specific requirements
Genetic Health Risk Tests	Required to obtain FDA clearance prior to first test
Pharmacogenetics Tests	Required to obtain FDA clearance (none currently approved)
Cancer Predisposition Tests	Required to obtain FDA clearance prior to first test
Low Risk General Wellness Tests	Not reviewed
Ancestry Tests	Not reviewed

https://www.fda.gov/medical-devices/vitro-diagnostics/direct-consumer-tests

What are the costs?

- 23andMe - $199
  - Consumers mail a salivary swab
  - Results take 6-8 weeks

- Color- $249
  - 30 genes, salivary sample, physician review, genetic counseling
- Invitae- Proactive Test- $250
  - 60 genes, salivary sample, physician review, genetic counseling

color

INVITAE

U.S. Preventative Services Task Force

Population	Recommendation	Grade
Women who have family members with breast, ovarian tubal, or peritoneal cancer	The USPSTF recommends that primary are providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one of several screening tools designed to identify family history associated with increased risk of mutations in *BRCA1/2*. Women with positive family history should receive genetic counseling and, if indicated, genetic testing	B
Women whose family history is not associated with an increased risk	The USPSTF recommends against routine genetic counseling or testing for women whose family history is not associated with an increased risk of *BRCA1/2* mutations	D

Key Criteria for Hereditary Cancer Risk Evaluation (Personal History)

- Female breast cancer diagnosed ≤50 years
- Triple-negative breast cancer diagnosed ≤60 years
- Two or more primary breast cancers
- Invasive ovarian or fallopian tube cancer, or primary peritoneal cancer
- Male breast cancer
- Any HBOC-associated cancers, regardless of age at diagnosis, and of Ashkenazi (central or eastern European) Jewish ancestry
- Breast cancer and either a relative with breast cancer diagnosed ≤50 years or ovarian cancer, or two relatives with breast, prostate, and/or pancreatic cancer, diagnosed at any age
- Metastatic, regional, or high to very high risk clinically localized prostate cancer
- *BRCA* pathogenic variant identified from tumor genomic analysis, regardless of tumor type

Key Criteria for Hereditary Cancer Risk Evaluation (Family History)

- A pathogenic variant in *BRCA1* or *BRCA2* in a biological relative, usually a first- or second-degree relative
- At least two individuals with breast cancer primaries on the same side of the family with at least one diagnosed ≤50 years
- A first- or second-degree relative with any of the following: breast cancer ≤45 years, ovarian cancer, male breast cancer, pancreatic cancer, metastatic prostate cancer, or ≥2 breast cancer primaries in a single individual or on the same side of the family with at least one diagnosed ≤50 years
- Family history of three or more cancers linked to hereditary cancer syndromes

Major Concerns about DTC Testing for Breast Cancer

1

The 3 mutations in the 23andMe test occur in 2% of women of Ashkenazi Jewish descent, but occur rarely among other populations (0%-0.1%)

2

Negative results of DTC testing are not definitive; additional testing may be needed if there is a clinical indication of increased risk

3

Clinical decisions about DTC test results should not be made until results are confirmed in a clinical lab on a new specimen

4

Testing may appeal and be overpromoted to low-risk populations

Research about DTC Tests for Breast Cancer

- April 2019- Study led by investigators at Invitae, Dana-Farber, Yale, and Georgetown presented preliminary results about the limited clinical utility of DTC tests (n=125,000):
  - 119,000 were referred because of a personal history
  - 5200 without personal or family history
  - 100 individuals who were referred for confirmatory testing after a positive DTC test result

Research about DTC Tests for Breast Cancer

- Results identified that a DTC examining the three founder mutations:
  - Indication based cohort- 11% had a pathogenic mutation (n=13,000)
    - 4700 had a pathogenic mutation in BRCA1/2, but only 12% had one of the founder mutations (n=564)
  - 19% of women who self-reported they were AJ had a mutation other than the 3 founder mutations
  - Only 12% of individuals who had no personal or family history were found to have a mutation in the 3 founder mutations; 88% had a different mutation

Research about DTC Tests for Breast Cancer

- In the 100 patients who were referred for confirmatory testing, the lab was only able to confirm a positive result in 50% of individuals

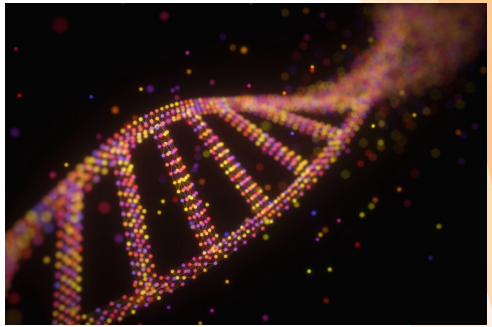
OVERALL

- The DTC missed almost 90% of BRCA mutation carriers
- The DTC missed almost 20% of BRCA mutations in those who self-reported Ashkenazi Jewish descent

Other Relevant DTC Research

- European Breast Cancer Council (2018)
  - Manifesto on genetic testing among healthy people to establish risk amidst fragmented regulatory standards
  - Call to policy makers, healthcare professionals and advocates to ensure genetic testing is carried out according to EBP guidelines
- Hamilton et al. (2017). Primary care provider (PCP) attitudes about genetic testing were generally favorable, but PCPs were more skeptical about DTC testing.

Advantages of DTC Testing



- Patient empowerment
- Sample collection is non-invasive
- Increased accessibility to BRCA testing
- Results have prompted adoption of healthier lifestyle changes
- Increased awareness of diseases that have a genetic component; increased patient engagement may lead to improved genetics literacy among consumers

Additional Disadvantages of DTC Testing

- A DTC containing 3 founder mutations does not achieve improved access to those with barriers to access for genetic risk assessment and testing
- Availability of test does not provide assurance that health outcomes will change for patients
- Unintended psychosocial consequences
- Important decisions about treatment and disease management may be made based on incomplete, inaccurate, or misunderstood information
- Genetic privacy may be compromised if companies use results in an unauthorized way

Case Study- Direct to Consumer

- Natalie
  - 26 year-old female, self-referred to clinic
  - Mother diagnosed with breast cancer at 49
  - Sister diagnosed with ovarian cancer at 44
  - Maternal grandmother diagnosed with breast cancer at 55
  - DTC testing revealed ”No Variants Detected.”

I feel so relieved that I did not have any mutations in BRCA1 and BRCA2 and I can live my life without this worry. Now I can focus on marrying my partner and having children.

Case Study- Direct to Provider

- Breanna- 37 year-old female, self-refer
- Paternal grandmother diagnosed with breast cancer at 67
- Father with lung cancer at 60 (occupational history of working in coal mines)
- Provider-initiated testing
- Breast Cancer High Risk Extended Panel Plus *(BRCA1, BRCA2, CDH1, PTEN, TP53, STK11, ATM, CHEK2, PALB2, BARD1, BRIP1, MUTYH, RAD51C, RAD51D)*
  - VUS in *ATM*

I've been told that I have a mutation in ATM and that I needed to see you to determine what surgery I need so I don't get cancer.

Case Study- Direct to Provider, continued

- Confirmatory testing did not reveal any deleterious mutations or VUS
- “The scientists at the lab let us know that we detected the same variant (ATM, c.4578C>T), but that we classify it as benign. Our lab has chosen not to report likely benign or benign variants.”

Implications for Patients

- Test results can often be confusing
- Conflicting information from multiple companies
- Communication with providers regarding testing and subsequent results may not be happening
- Costs of genetic testing (DTC or provider-initiated are not well-understood
- Family implications resulting from testing

Implications for Providers

- The implications for patients are inherently the implications for providers
- Landscape of genetic and genomic testing is rapidly evolving
- Providers of all types must be informed about all of these tests and take the time to seek resources for their practices and for their patients

How can we achieve balance?

Patient Autonomy

Technological Innovation

Clinical Utility & Ensuring Patient Safety

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

Thanks!

Any questions?

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