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# Direct-to-Consumer Genetic Testing: Opportunities and Challenges

Linnea M. Baudhuin, Ph.D., DABMG
Mayo Clinic

 

# Disclosures/COI

- Disclosures: none
- Conflicts of interest: none

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# Objectives

- Outline trends in DTC genetic testing
- Elaborate on role of regulatory bodies in ensuring appropriate validity and utility of DTC genetic tests
- Detail shortcomings of DTC genetic tests that may not be apparent to non-geneticists

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# Direct-to-Consumer Genetic Testing

- Traditionally, genetic testing has been available only through healthcare providers
- DTC genetic tests are becoming increasingly available and do not require input from a healthcare provider (in most cases)
- Process:
  - Consumer purchases test kit (at store or online)
  - Consumer submits sample to company
  - Consumer notified of results by mail, phone, or online
- UBS has estimated the global opportunity in the DTC genomics space as $2-7 billion per year
- Market is nascent and the utility is evolving

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# Evolution of DTC genetic tests

- Historically began as more of a health assessment with often questionable associations
  - e.g. Sports-related, health risks/associations, nutrition


- Usually based on variants in two genes, *ACTN3* and *ACE*, which may be related to speed and skeletal muscle strength
- Promoted as a test that may help spot athletic talent in children
- Evidence to support these links are weak and results are often over-interpreted
- May interfere with a child's ability to choose a sport and may narrow their interest unnecessarily

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# …Evolution of DTC genetic tests

- Other types of DTC genetic tests have been for paternity, zygosity, blood type, pharmacogenetics, ancestry
- Now evolving to move away from "health risks" and be more focused on inherited disorders
  - Evolution largely due to FDA regulation of tests
- Tests also evolving to be more comprehensive
  - Largely due to decreased costs and increased efficiency of technology

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# The FDA and 23andMe

- In 2012, 23andMe filed for FDA 510K clearance for their Personal Genome Service (PGS) test
- $99 saliva-based DNA test that analyzed 254 "health conditions and traits"
  - Inherited disorders (e.g. *BRCA1/2*)
  - PGx (e.g. warfarin sensitivity)
  - 120+ "Health Risks"
    - Disorders of known polygenic/multifactorial etiology
      - E.g. atrial fibrillation, celiac disease, restless legs syndrome
    - Algorithm utilized to establish a risk score



 

# The FDA and 23andMe

- FDA had questions about the validity of the uses of the PGS test and stated that 23andMe had failed to respond to those questions
  - 23andMe and the FDA had been in continuous negotiations, but in May 2013, 23andMe stopped communicating with the agency.
- 11/22/2013 letter from FDA to 23andMe
  - "… even after these many interactions with 23andMe, we still do not have any assurance that the firm has analytically or clinically validated the PGS for its intended uses, which have expanded from the uses the firm identified in its submission".
  - FDA ordered 23andMe to cease marketing its PGS test

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# The FDA and 23andMe

- The decision by the FDA was met with mixed review
- Green and Farahany (Nature 2014, 505:286-7) argued that the FDA's actions were "unwarranted without evidence of harm"
  - Objected that this action by the FDA was violating First Amendment rights by
    - Disallowing advertising ("commercial speech")
    - Preventing individuals from their right to receive information
- FDA expressed concern that consumers would incorrectly self-manage their health based on test results
  - Should the FDA presume that consumers are unable to understand their own genomic information?
- FDA expressed concern about the clinical validity and limitations of DTC tests like the PGS test
  - Their role is not to prevent consumers from receiving information, but rather to prevent them from receiving potentially invalid or misleading information

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Baudhuin LM, Clin Chem 2014, 60:835-7

# 23andMe International PGS Tests

- In late 2014, 23andMe rolled out two modified versions of its original PGS test:
  - Canada and UK (approx $160-190): 40+ inherited conditions, 10+ PGx tests, 10+ Genetic risk factors, 40+ traits (e.g. lactose intolerance, male pattern baldness)
  - Since rolled out to other European countries: Denmark, Finland, Ireland, Sweden, and Netherlands
- 23andMe: "After consulting with a number of the most respected stakeholders in the scientific community and professional associations, 23andMe has focused on individual genetic markers with well-established associations that have clinical validity"

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# 23andMe Receives FDA Approval for PGS Carrier Screening Test for Bloom Syndrome

- Feb 19, 2015- FDA approved 23andMe DTC test
- Analysis for single variant for Bloom syndrome – carrier status only
  - Intended for detection of autosomal recessive disease carrier status in adults
  - Not for diagnosis of Bloom syndrome
  - 23andMe performed extensive accuracy, usability, and user studies
- FDA press announcement: "The FDA believes that in many circumstances it is not necessary for consumers to go through a licensed practitioner to have direct access to their personal genetic information. Today's authorization and accompanying classification, along with FDA's intent to exempt these devices from FDA premarket review, supports innovation and will ultimately benefit consumers," Alberto Gutierrez, Ph.D.
  (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435003.htm)

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# 23andMe – Re-launch of U.S. PGS test in Oct., 2015

- $199
  - 35+ Carrier Status Reports
  - 3 Ancestry reports (Ancestry composition, maternal and paternal lineage, Neanderthal)
  - 5+ Wellness reports (Deep sleep, lactose intolerance, saturated fat and weight)
  - 19+ Traits (hair loss, sweet vs salty, unibrow, cheek dimples, eye color, red hair, photic sneeze reflex)
- "We've worked with the FDA for nearly two years to establish a regulatory path for direct-to-consumer genetic testing. We are a better company with a better product as a result of our work with the FDA," said 23andMe co-founder and CEO Anne Wojcicki.
- In addition to the new reports, the test allows customers the opportunity to participate in research (by consent)


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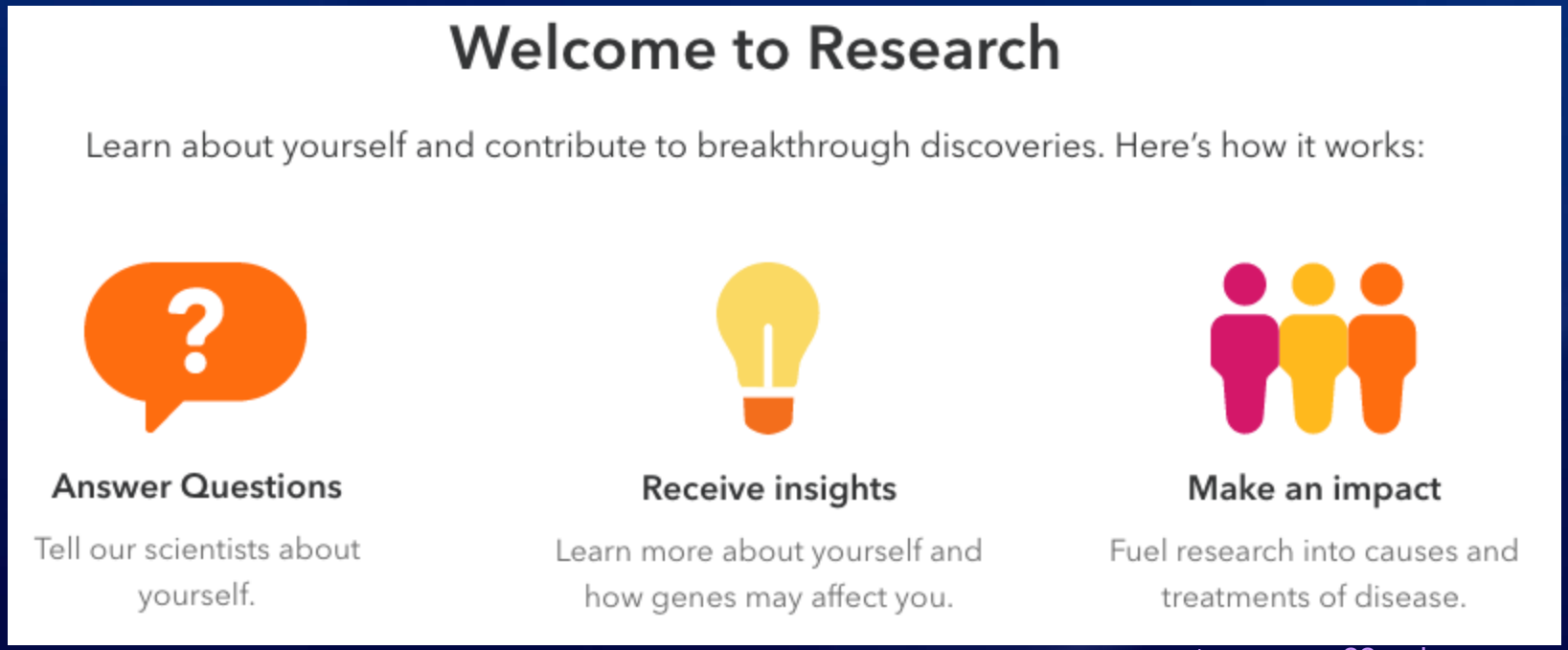
# 23andMe – Research

- 23andMe valued at $1 billion
- Largely based on selling its database
  - Largest database of DNA samples accompanied by health and survey information
  - In 2015, 23andMe sold access to its data to a dozen drug companies




customercare.23andme.com



# 23andMe – Parkinsons Disease Study

- Genentech $60 million deal - Parkinsons disease study
  - WGS 3000 customers to search for drug target
  - Questions about informed consent, incidental findings, privacy
  - Adams and Freidman, "23andMe sells DNA and health information", Genetics in Medicine, April, 2016:
    - "Do the patients and family members who are participating in 23andMe's research understand the extent of the information that these studies will provide that may not be returned to them?"
    - "Do the subjects know that their DNA is being used to profit others and that the data obtained may not be openly shared within the scientific and medical community?"
    - "Is this research being done with appropriate genetic counseling and the full informed consent of the subjects?"

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# Concerns about DTC Genome Services

**Genetic Gatekeepers:**
**Regulating Direct-to-Consumer Genomic Services in an Era of Participatory Medicine**

JESSICA ELIZABETH PALMER*

Food Drug Law J, 2012; 67:475-524

1. Misleading DTC Service Advertising
   - Consumers may expect a service to be more comprehensive than it is
   - Non-Caucasian customers may be unaware of the limitations of the test
2. Lack of Expert Gatekeepers
   - Health professional's role as gatekeeper and mediator of complex health technologies may be undermined
   - However, many physicians lack genetic gatekeeping abilities
3. Burdening Health Care Systems
   - "Cascade effect" of unnecessary diagnostic, pharmacologic, and surgical interventions
   - Increased demands on clinicians' times
   - Most medical providers admit that they are ill-prepared to understand DTC genetic test reports

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# ….Concerns about DTC Genome Services
## (Palmer, 2012)

4. Inaccurate Results
   - Genotype is likely accurate
   - Estimated risk predictions and interpretation of data may not be accurate
5. Misleading Results
   - Consumers may not understand their results
6. Collateral Results
   - Unanticipated or unwanted results
7. Consumer Distress
   - Psychological distress from adverse genetic results
8. Harmful Consumer Action
9. Lack of Genetic Counseling
10. Unanticipated Harms
    - Potential exploitation of consumers' genetic data
    - Security of personal data
    - Privacy concerns
    - Family may be exposed to information unwillingly

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Food Drug Law J, 2012;67(4):501-524

# Consumers' Understanding of Genetic Test Results

- Studies have indicated that DTC genetic information may only lead to transient, if any, anxiety in the consumer
- Furthermore, studies have shown that most consumers will not self-prescribe or change healthcare action based on DTC genetic information
- Significant limitations to studies
- Most studies have been conducted on early adopters
  - Caucasian
  - Better educated
  - Better physical and mental health

**The hidden harm behind the return of results from personal genome services: a need for rigorous and responsible evaluation**

A. Cecile J.W. Janssens, PhD[1,2]

Genetics in Medicine, 2015; 17(8): 621-2

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## Disclosure of *APOE* Genotype for Risk of Alzheimer's Disease

**Robert C. Green, M.D., M.P.H., J. Scott Roberts, Ph.D., L. Adrienne Cupples, Ph.D., Norman R. Relkin, M.D., Ph.D., Peter J. Whitehouse, M.D., Ph.D., Tamsen Brown, M.S., Susan LaRusse Eckert, M.S., Melissa Butson, Sc.M., A. Dessa Sadovnick, Ph.D., Kimberly A. Quaid, Ph.D., Clara Chen, M.H.S., Robert Cook-Deegan, M.D., and Lindsay A. Farrer, Ph.D. for the REVEAL Study Group***

*N Engl J Med*. 2009 July 16; 361(3): 245–254. doi:10.1056/NEJMoa0809578.

- Responses to receiving *APOE* results associated with risk for Alzheimer disease
- Conducted in offspring whose parents had Alzheimer disease
- 301 asymptomatic adults consented
  - 162 randomized to receive results from *APOE* genotyping
- No significant difference between two groups (disclosure vs non-diclosure) in time-averaged measures of anxiety, depression, or test-related distress
- Study that is often cited that DTC genetic tests may not increase harm
- Criticisms
  - Participants already well aware of their risk
  - They received genetic counseling
  - Of the 301 people who originally consented, 139 declined participation (46%)
  - Therefore the other half of people who participated may have brought bias
  - Authors themselves cautioned: "If *APOE* genotyping had been provided without genetic counseling or to subjects who had no family history of AD, the results might have been different"

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PeerJ
2013; 1:38

# Dealing with the unexpected: consumer responses to direct-access *BRCA* mutation testing

Uta Francke[1,2], Cheri Dijamco[1], Amy K. Kiefer[1], Nicholas Eriksson[1], Bianca Moiseff[1], Joyce Y. Tung[1] and Joanna L. Mountain[1]

[1] 23andMe, Inc., Mountain View, CA, USA
[2] Department of Genetics, Stanford University School of Medicine, Stanford, CA, USA

- *BRCA1/2* results in 23andMe customers who tested positive
- Invited 136 mutation-positive; 32 agreed to participate; 25 received an "unexpected" positive result (7 already knew they were carriers)
- None of the 25 reported extreme anxiety, 4 reported moderate anxiety; 11 described their responses as neutral
- Criticisms
  - Were these results really "unexpected"?
  - 81% AJ
  - 2/3 had first or second degree relative with breast or ovarian cancer
  - Low participation rate (24%)
    - Authors stated "relied on volunteers willing to share their experiences. The emotional responses reported by the 16 men and 16 women…. May differ from those experienced by the 61 male and 43 female mutation-positive ...who did not reply to our invitation"
  - What about the individuals who tested negative? They all were either "neutral' or "relieved" by their result. Did they understand the limitations to their results?

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# Summary of Limitations of Studies on Consumer's Responses to DTC Genetic Tests

- Included participants who were already aware they may be at increased risk
- Tests with limited or no demonstrated utility – noninformative test results
- Highly educated, Caucasian early adopters
- Low participation rates
- Small sample size
- Short follow-up
- Self-reported behavioral change
- Janssens (Genet Med, 2014): "What these studies do show is that early adopters can handle noninformative test results, that relatives of patients who choose to receive the test results can handle highly predictive results as well, and that genetic testing might be confusing for people from underserved populations. But their generalizability is otherwise limited"
- "Well-designed studies that investigate both benefits and harms are desperately needed if we are to ultimately realize the promise of genomic medicine"

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# The Future of DTC Genomic Tests

- Newer tests are emphasizing privacy and ownership of genomic data
- Genos test: $399 for WES
  - Customers enabled to share their data with researchers and receive compensation
- Tests are becoming more comprehensive because of technology
  - Whole exome/Whole genome
    - Informed consent
    - Incidental findings
    - Limitations of technology/quality of data

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# GUARDIOME

YOUR PERSONAL GENOME VAULT & ANALYZER


- $3100 WGS test
- Provides personal device that is not connected to the internet
- Emphasizes data security and consumer privacy
- Guardiome does not store or keep consumer data

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# Sure Genomics

## DTC WGS Test


**2 Blood, Heart, and Circulation 21 286 7**

Bad 21 | Good 7 | Not Set 286

| SNP Risk | Category | Description | Gene | Marker | Risk Factors |
|---|---|---|---|---|---|
| High Risk | Circulatory | Deep Vein Thrombosis | F9 | rs6048 | 2.1x increased risk of deep venous thrombosis |

# FDA and Sure Genomics

- Feb 18, 2016
- FDA sent a letter to Sure Genomics asking the company about clearance for its SureDNA test
- FDA stated that the SureDNA test appears to meet the definition of a device under the Federal Food Drug & Cosmetic Act and therefore might need clearance
- June, 2016: Sure Genomics stated that it is "in active communication with the FDA to show compliance as we gear up for public availability in the late summer"

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# Professional organization recommendations for DTC genetic tests

- Be clinically meaningful and scientifically evidence-based with robust association
  - ACMG
  - CPIC guidance - Level A (Genetic information should be used to change prescribing of affected drug)
- Include transparent limitations of test
  - What is included, what is missing
  - Accurate comparisons between consumer and population for risks
  - Results/interpretation should be as personalized as possible
- Have clear and understandable lay language in reporting
  - Visual results
- Be validated and interpreted by certified molecular laboratory professionals
- Be CLIA- and regulatory-compliant

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# Summary

- DTC genetic testing is here and will likely continue to increase in the marketplace
  - Expanded genetic testing
  - Data privacy
  - Research
- Regulatory landscape for DTC genetic testing is uncertain, but likely to continue to focus on
  - Ensuring clinically useful and valid tests
  - Preventing misleading or incorrect information
- Important to recognize
  - Responsible DTC genetic testing
  - Clinical utility is key
  - Transparency
  - Clear communication
  - Beneficial to engage and educate healthcare professionals

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