First Do No Harm: Regulation and Clinical Integration of DTC Genetic Testing

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**Single Gene Tests**

- **DTC Advertising**
- **Personal Genome Testing**

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**GeneDx**

- **DNA Diagnostic Experts**
- **About GeneDx**
  - Meet Our Experts
  - News
  - Licensing
  - FAQs
  - Employment
- **Tests Offered**
  - Diagnostic Tests
    - By Gene
    - By Disease
    - Mitochondrial Disorders

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**Concerned about your personal or family history of cancer?**

**Wondering if genetic testing is right for you?**

**We can help.**

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**Diseases for which GeneDx offers tests**
Challenge with DTC PGT: Multiple Test Purposes
What kind of test/product/service is this?

- Ancestry
- Recreational traits (earwax, bitter taste)
- Disease risk, Drug response
  - Associations with varying levels of risk

Solution: Stratified regulatory approach (SACGHS)

Need for risk stratification criteria!
Primary Goal of Regulation

Consumer Protection: First, Do No Harm [Also: Enable innovation]
Regulatory Concerns

- Analytic validity
- Clinical validity
- Clinical utility
- Access to accurate and truthful information
- Physician involvement
Analytic Validity

Accuracy and reliably of test result

Sample swaps at 23andMe: a cautionary tale

Category: 23andme • decodeme • direct-to-consumer genetic testing • errors
Posted on: June 7, 2010 6:00 AM, by Daniel MacArthur

“Personal genomics company 23andMe revealed that a lab mix-up resulted in as many as 96 customers receiving the wrong data.”
Clinical Validity

Ability to detect or predict the associated disorder

A Critical Appraisal of the Scientific Basis of Commercial Genomic Profiles Used to Assess Health Risks and Personalize Health Interventions

A. Cecile J.W. Janssens,1,* Marta Gwinn,2 Linda A. Bradley,2 Ben A. Oostra,3 Cornelia M. van Duijn,4 and Muin J. Khoury2

The American Journal of Human Genetics 82, 593–599, March 2008

“There is insufficient scientific evidence to conclude that genomic profiles are useful in measuring genetic risk for common diseases or in developing personalized diet and lifestyle recommendations for disease prevention.”
Clinical Utility

Likelihood that test will produce more benefit than harm

• Genuine gap in evidence regarding the risks and benefits of DTC genetic testing!
• Concerns:
  – Psychosocial harm: anxiety, distress, stigmatization, discrimination
  – False sense of security from negative results
  – Iatrogenic harm from unnecessary follow-up
• Despite disclaimers, results contained health-related predictions
• Results based more on lifestyle questionnaire than DNA analysis
• Recommended expensive dietary supplements ($1200/year) that could be bought in grocery store for $35
Physician Involvement

May help avoid misinterpretation of test results

- ACMG, AMA, FTC call for qualified health care provider to supervise genetic testing
- Some companies employ physicians/genetic counselors
Integration with Clinical Care

• **Advice to consumers:**
  
  “If you have concerns or questions about what you learn through 23andMe, you should contact your physician or other appropriate professional.”

  23andMe Consent Form

• **Advice to physicians:**

  *Provide “a general statement about the poor sensitivity and positive predictive value” of results.*

  Concern: validity; utility

Patient Expectations
Online survey: Facebook.com users

- Demographics (n=1087)
  - Age: 35 (12)
  - Race: 83% Caucasian
  - Gender: 73% Female
  - Education: 60% College Grad

Potential Use

Wouldn't use 30%

Would use 64%

Have used 6%
Reasons for Use

- General curiosity
- See if specific disease runs in family or is genetic
- Learn about genetic make-up without going through doctor
Reasons for Non-Use

- Don't think information will be useful
- Cost
- Concerns about privacy
- Potential return of unwanted information
Considered Medical Diagnosis

![Bar chart showing PGT result considered medical diagnosis]

- Blue: Did use
- Red: Would use
- Green: Wouldn't use

PGT result considered medical diagnosis
Professional Obligations

- Discussed results with physician (of those who have used PGT)
- Would ask DTC company to help interpret results (of those who would use PGT)
- Would ask physician for help interpreting results (of those who would use PGT)
- Physicians have professional obligation to help individual understand results
Medical school to offer course that gives students option of studying their own genotype data
At-Home Genetic Tests: A Healthy Dose of Skepticism May Be the Best Prescription
With an increasing number of genetic tests available, the National Institutes of Health (NIH) recognizes the importance of making information about these tests easily accessible to researchers, patients, consumers, health care providers, payers, and others. Therefore, NIH is initiating the development of the Genetic Testing Registry (GTR), an online resource that will provide a centralized location for test developers and manufacturers to voluntarily submit test information such as indications for use, validity data, and evidence of the test’s usefulness.

The overarching goal of the GTR is to advance the public health and research into the genetic basis of health and disease. As such, the Registry will have several key functions:
• CLIA regulations address quality of lab testing services
  – Ensures labs are properly staffed and follow proper testing procedures
• CLIA does not provide external data-driven review to substantiate claims (FDA does this)
FDA Oversight of Genetic Tests

~ 1500 Genetic Tests Available  A Few Dozen FDA Cleared/Approved


Slide provided by Barbara Evans
23andMe, Inc.
c/o Ms. Anne Wojcicki
President and Co-Founder
2606 Bayshore Parkway
Mountain View, CA 94043

RE: 23andMe Personal Geno

Dear Ms. Wojcicki:

United States Food and Drug Admi.
23andMe Personal Geno
section 201(h)
extend

Knome, Inc.
c/o Mr. Jorge Conde
Co-Founder & CEO
1 Main Street, Suite 530
Cambridge, MA 02142

JUN 1 0

RE: KnomeCOMPLETE™
FDA Regulation

Upstream
Basic Science

Precalinal Research
Clinical Trials

FDA approval of product, labeling, warnings

Postmarket Research/Surveillance

Premarket Review: requires data to substantiate test’s safety and effectiveness; precise data requirements depend on risk classification

Post-market Period: limited postmarket surveillance; focus on adverse event reporting

Slide adopted from Barbara Evans
Premarket Review: Limitations

Goal: Predict and Prevent

Time (lifetime)

Start
(Predictive Genetic Test)

Event
(Disease)

Outcome (Death, Recurrence)

• Delaying consumer access would inhibit product development and regulate DTC companies out of existence
Potential Solution

- Premarket review: focus on test validity and accuracy of claims made
- Enhanced postmarket data collection and regulation: focus on utility (“wait (collect data) and see”)

Medical Practice Laws

• US state law regulates against the unlicensed practice of medicine (includes diagnosing disease or disorder, developing treatment plan, or providing treatment)

• Germany requires all tests to be provided by licensed health care provider
Physician Involvement

- Company-employed physician (knows the test best but no history or physical)
- Referral to geneticist (not enough of them)
- Rely on consumer’s own PCP (already help patients understand and manage health risks but lack of knowledge about genetic testing and not enough time)

Need for educational reform (informatics/statistics); decision support tools (to prevent inappropriate follow-up); reimbursement reform in US (won’t happen until we have evidence of utility)
Industry Standards

- Informed consent
  - Risks (including privacy risks) and benefits
  - Research use of samples/data

- Privacy Protections
  - Beyond GINA
  - Bankruptcy/Sale of company

- Issue for storage and use of all genetic information (e.g., newborn screening program)

- Testing children
• The internet has no national borders and regional regulation can only do so much

• Need for international collaborative efforts!
  • Must take into account international laws, local norms, and implications for stakeholders from diverse health systems.
Key Collaborators:
Barbara Evans, Tim Caulfield, Wylie Burke

Funders:
NHGRI-ELSI, Greenwall Foundation
References


• Food and Drug Administration, *Overview of Device Regulation* (2010); [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm)


• United States Food and Drug Administration, *Letters to Industry*; [http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm111104.htm](http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm111104.htm)


• GAPP Knowledge Base; http://www.hugenavigator.net/GAPPPKB/home.do
