

The ELSI of DTC

*Duke University Institute for Genome
Science & Policy: Genomic &
Personalized Medicine Forum*

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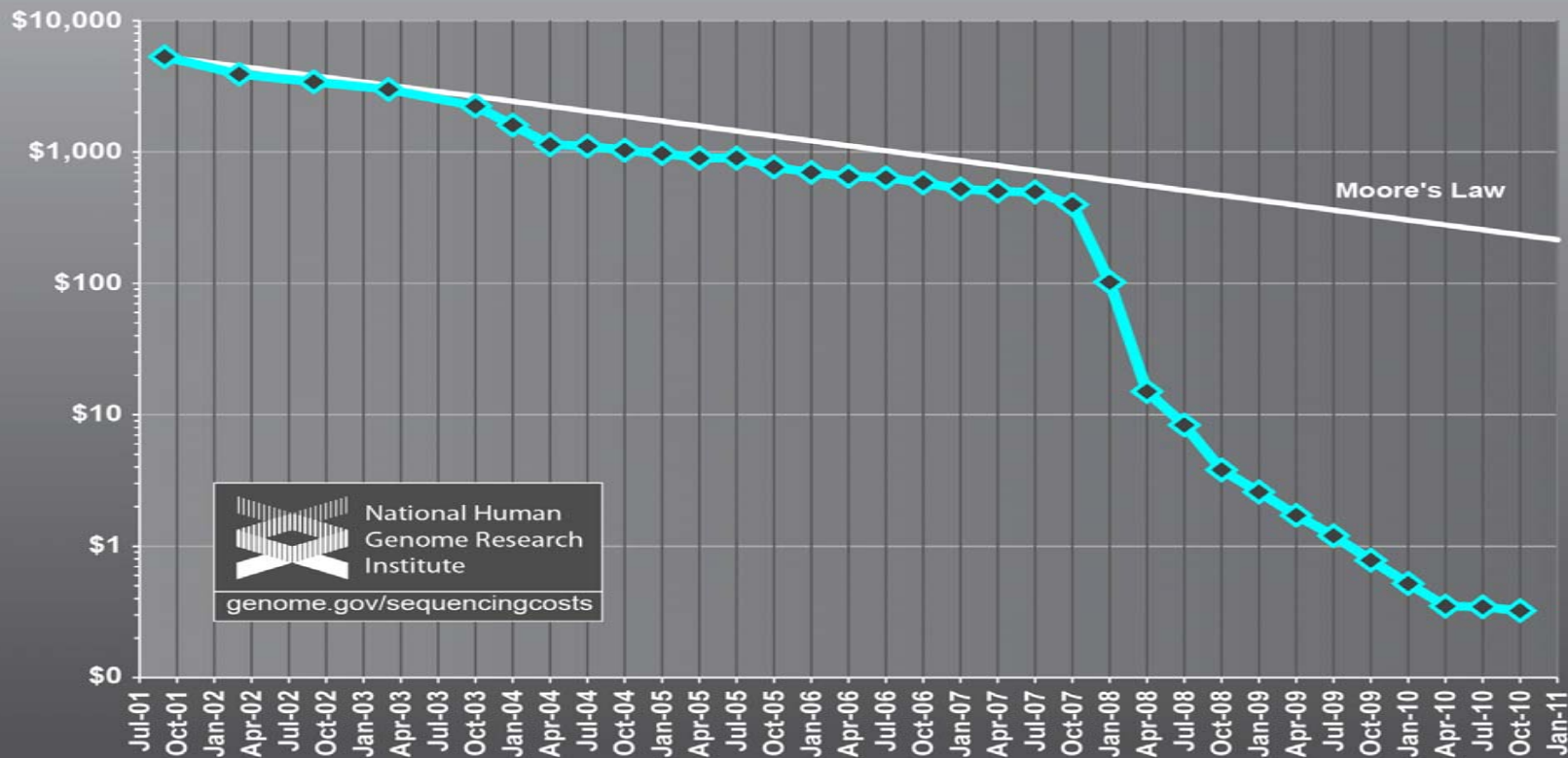
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Charlotte ■ Research Triangle ■ Rock Hill [rbh.com](#)

**Robinson
Bradshaw**

Why we are here: data

Cost per Megabase of DNA Sequence

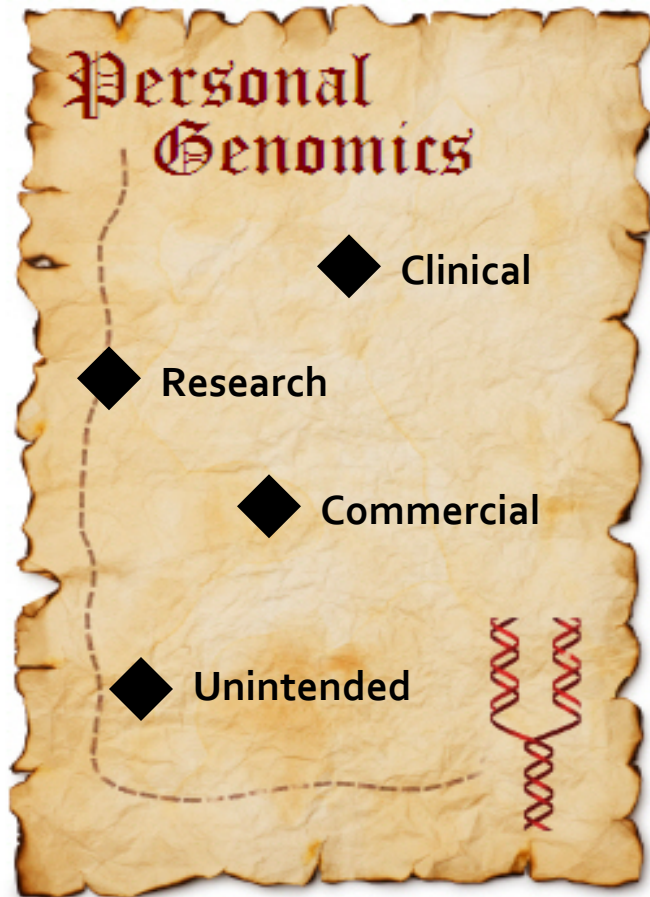


Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Large-Scale Genome Sequencing Program Avail. at: www.genome.gov/sequencingcosts. Accessed 3/5/11.

Why we are *really* here: personal genomics

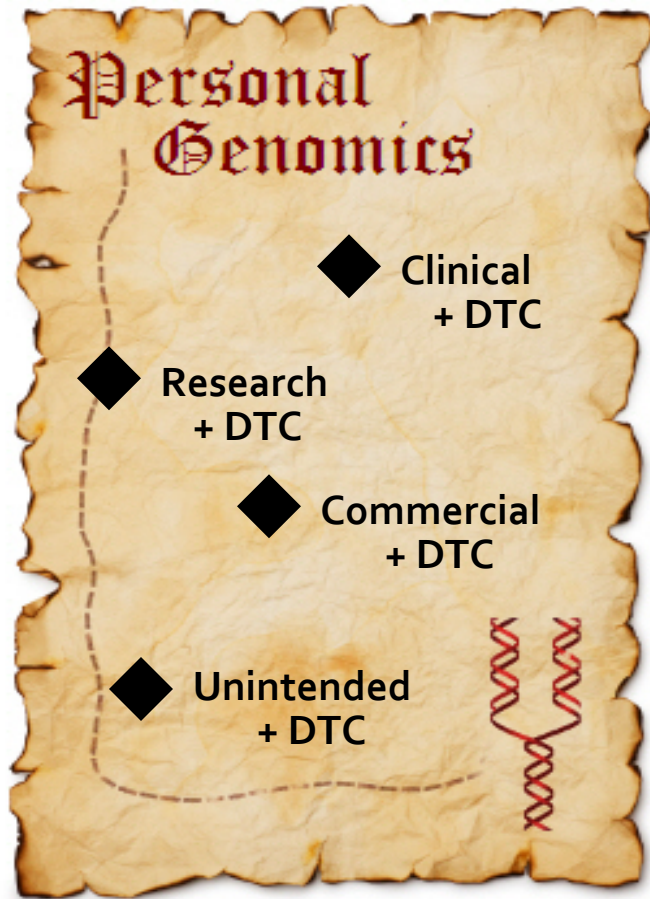


The personal genomics landscape



- ◆ **Clinical**
Target: patients
Purpose: therapeutic
Data Control: licensed healthcare provider
- ◆ **Research**
Target: subjects (specific traits or control)
Purpose: improved understanding
Data Control: varies – typically researchers with no subject access
- ◆ **Commercial**
Target: people (not just patients)
Purpose: profit motive
Data Control: depends on model, regulation
- ◆ **Unintended**
Common Feature: unintended exposure to genetic information

What about direct-to-consumer (DTC)?



◆ Clinical



BRCA^{Analysis}

A test for hereditary breast and ovarian cancer

◆ Research



RESEARCH ARTICLE

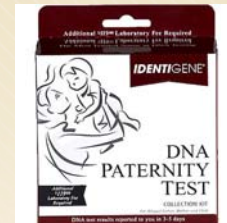
OPEN ACCESS

Web-Based, Participant-Driven Studies Yield Novel Genetic Associations for Common Traits

◆ Commercial



◆ Unintended



What does “DTC” mean?

- **Terminological Distractions:** “direct access” vs. “direct-to-consumer” vs. “over-the-counter” vs. “patient-authorized” vs. “home use” ...
- **Substantive Distinctions: for this genetic test, is there “direct”...**
 - Marketing: advertising directed at clinicians, laboratories vs. individual
 - Ordering: initiated by clinician (prescription) vs. individual
 - Payment: out-of-pocket by individual vs. reimbursement (whole or part)
 - Data Interpretation:
 - Provided by: nobody (raw data) vs. software vs. software + clinician (MD or GC?)
 - Included: no (raw data) vs. optional (add'l fee?) vs. mandatory (i.e., gatekeeper)
 - Data Receipt:
 - Type of data: all available data vs. subset (e.g., “clinically actionable”)
 - Recipient: direct to individual vs. by way of clinician (medical record inclusion?)
- **Additional Factors:**
 - Purpose of Testing: clinical vs. research vs. *commercial*
 - Mechanism of Ordering, Data Return: in-person/-store vs. online

DTC genetic testing: why bother?

- Self-exploration
- Public genomics
- Participatory health
- Novel research
- Personalized education
- **Autonomy & access:
"My Genome. My Right."**



nature.com

Collins hits the gym following genetic testing

RESEARCH ARTICLE

Web-Based, Participant-Driven Studies Yield Novel Genetic Associations for Common Traits



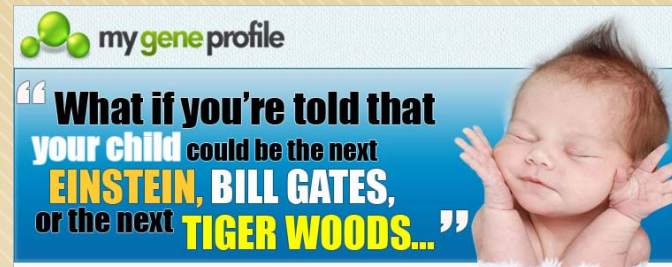
Genetic Bill of Rights Proposed in Massachusetts

DTC genetic testing: why worry?

- Anxiety, stress
- False or misleading claims (“snake oil”)
- Burden healthcare system
- Clinical harm
- Surreptitious testing
- Physician-patient relationship

Genetic testing mix-up reignites debate over degree of federal regulation needed

The Washington Post



“We know of reports of people who have found a test, found a doctor that is willing to order the test since they are so afraid of the disease, and even removed ovaries based on questionable results.” OIVD Director Alberto Gutierrez, *Washington Post*. July 17, 2010.



Current personal genomics ELSI debate

- **Genetic privacy** (e.g., DTC privacy policies; de-identification for research)
- **Acceptable uses** of genetic data (e.g., PGD or newborn screening; return of research results, incidental or otherwise; patenting genes)
- **Unacceptable uses** of genetic data (e.g., GINA/discrimination; surreptitious testing; genetic profiling)
- **Fundamental genetic rights** (e.g., Genetic Bill of Rights; commercial value of a genome; insurance coverage)
- **Federal oversight of DTC genetic tests**

The big non-question

- *Does clinical DTC genetic testing need **some** additional **oversight**?*
- That question has been affirmatively answered, again and again and again, including:
 - 1994: IOM Committee on Assessing Genetic Risks
 - 1997: Joint NIH-DOE HGP ELSI Working Group
 - 2000: SACGT (“Enhancing the Oversight of Genetic Tests”)
 - 2006: GAO report, FTC-FDA-CDC consumer fact sheet
 - 2008: SACGHS (“U.S. System of Oversight of Genetic Testing”)
 - 2009: DTC self-regulation efforts (PMC, S.B. 482)
 - 2010: Genetic Testing Registry, GAO report
- *Fundamental Tension: how do we enhance oversight to ensure public health and safety while still (1) promoting personal genomics innovation & (2) preserving autonomy?*

The regulatory pathway

Congress Legislates
(& Appropriates)



CLIA

HIPAA

Common Rule

Hatch?

FDCA

GINA

Patent Act

GPMA?



Agencies Interpret and Enforce



OPH?



Other sources of oversight

- State statutes
 - DTC genetic testing apparently restricted by ~50% of states, but inconsistent definitions, minimal enforcement, not up to date
 - Other state regulation: CLIA alternatives (NY), restrictions on surreptitious testing, genetic privacy protections
 - Recent legislative proposals (e.g., MA, VT)
- International legislation
 - DTC banned: Germany, South Korea? (enforcement?)
 - Varying restrictions on genetic testing: across most of Europe (many decades old, out of date), Australia, Japan
- Codes of practice, guidance (e.g., SACGHS, Human Genetics Commission – met the same fate)

DTC oversight to date






- 2006: GAO report, FDA-FTC-CDC consumer fact sheet
- 2008: state (NY, CA, etc.) “cease and desist” letters & (some) subsequent licensing; prompts shift to CLIA laboratories
- 2009: FDA & industry in private dialogue
- 2010:
 - May: Pathway/Walgreens “letter to industry”; House announces investigation
 - June: 5 more FDA letters (23andMe, Navigenics, deCode, Knome, Illumina); FDA announces LDT regulation (does this include LDTs?)
 - July: GAO report; House hearing; 14 more FDA letters; FDA public LDT meeting (FDA: “most DTCs not LDTs,” but DTC still invited)
- This week: FDA public meeting (Molecular & Clinical Genetics Panel) to provide recommendations to FDA re: clinical DTC genetic testing

Clearing a path for DTC oversight?

- **Terminological Distractions:** “direct access” vs. “direct-to-consumer” vs. “over-the-counter” vs. “patient-authorized” vs. “home use” ...we’ll use DTC
- **Substantive Distinctions: for this genetic test, is there “direct”...**
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What does “DTC” mean to the FDA?

- **FDA DTC Public Meeting:** “*This meeting is focused specifically on issues regarding **clinical** genetic tests that are (1) **marketed** directly to consumers (DTC clinical genetic tests), where a consumer can (2) **order** tests and (5) **receive** test results **without** the **involvement** of a **clinician**.*”
- **Key Additional Factor:** Test *must* be **clinical**
- **Interpretation?** Merges with data receipt. But *who* interprets? (GC vs MD; independent or company-provided?)
- **Intentionally excluded?**
 - Identity of (3) **payer**
 - **Mechanism** of ordering, data return

Test: Start-to-Finish	DTC?
(1) Marketing	
(2) Ordering	
(3) Payment	
(4) Data Interpretation	
(5) Data Receipt	

What question is the FDA considering?

Personal Genomics



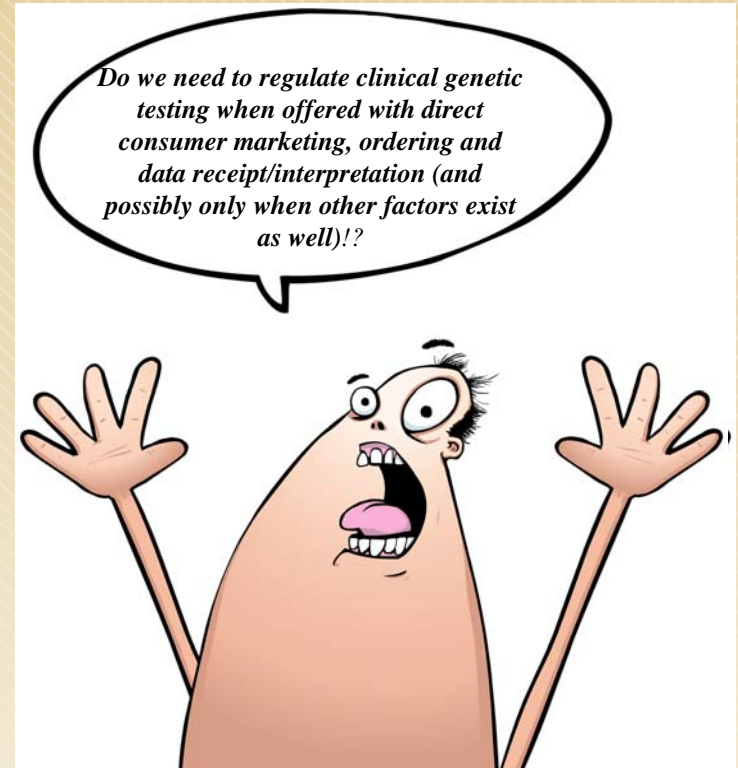
Genetic Testing



DTC Genetic Testing



Clinical genetic testing when offered with direct consumer marketing, ordering and data receipt/interpretation (and possibly only when other factors exist as well)



Questioning today's (and tomorrow's) DTC

- Risks and benefits of current clinical DTC genetic testing model(s). FDA requests “input on the following issues”:
 - Pros/cons of testing without clinician involvement (FDA Issue #1)
 - Risks/mitigations for incorrect, misunderstood test results (FDA Issue #2)
 - Appropriate scientific evidentiary standards for testing (FDA Issue #3)
- The *future* of DTC genetic testing model(s) in a climate of pervasive and inexpensive whole-genome sequencing (WGS):
 - Obliterates clinical/non-clinical distinction within a single test (if it is not already gone in current multiplex tests)
 - Divorces data acquisition from interpretation. Spit once and, after that, a browser (and maybe a credit card) is all you need to run a DTC genetic test
 - Geographic barriers significantly reduced, enforcement more difficult

Common ground in DTC oversight

- Clearer scientific evidentiary standards (FDA issue #3)
 - Clarify standards for demonstrating analytical & clinical validity
- Access to raw genetic / genomic data
 - “Free and open access to genome data has had a profoundly positive effect on progress.” (Francis Collins, *Nature*, April 2010)
- Greater transparency
 - GAO highlights “deceptive marketing and other questionable practices”
 - NIH Genetic Testing Registry, joint FTC/FDA oversight of advertising claims widely supported (e.g., GPPC/ASHG: 70%) – although authority is an issue
- Oversight between two extremes
 - Sensible oversight provides greater (but not perfect) clarity and assurance of quality to consumers, clinicians, companies and their investors

Contested ground in DTC oversight

Clinical DTC testing without clinician involvement (FDA issue #1)

- Concern: “[DTC] will have a significant adverse impact on consumers and undermine the physician-patient relationship.” (AMA)
- Key questions:
 - is a mandatory clinical consult for DTC a realistic possibility (today)?
 - who should decide when and whether a clinical consult is required – regulators, clinicians or consumers?
- Data:
 - “...several studies have reported that physicians find it difficult to keep up with the pace of genetic technology.” (AMA public comments)
 - Ex: Medco/AMA survey of PGx and MDs: 10,000 MDs, 26% had some PGx education; 10% believe they have sufficient education/training (presented ASHG, 2010)

Contested ground in DTC oversight

Danger of incorrect, misunderstood test results (FDA issue #2)

- Concern: consumers will undertake harmful or expensive self-directed actions as a result (e.g., unnecessary testing, worry/stress, detrimental changes in treatment, lifestyle, etc.)
- Key question: regulate in advance of demonstrated harms or continue gathering data?
- Data:
 - **GPPC** (n=1048): results easy to understand (88%) vs. vague (38%); 4-7% misinterpretation
 - **Scripps** (n=3639/2037): “...no indication of test-related distress in 90.3% of the subjects and no evidence of increased use of screening tests.” No physician, genetic counselor impact. (But 44% non-complete rate)
 - **Genomes Unzipped** (n=252): 166 DTC genetic tests, 1 direct negative experience
 - Other Items:
 - **REVEAL**: APOE genotyping does “not result in significant short-term psychological risks”
 - **23andMe “Sample Swap”**: Wrong data to 96 customers due to lab error. Evidence of risk or benefit of DTC model?

Additional issues for consideration

- Role of utility (clinical vs. personal) in evaluating benefits/harms
- Source of clinician, consumer information & education (DTC vs. gov't)
- Multiplex / WGS tests:
 - Regulation without constant resubmission (impossible FDA & industry burden)
 - Regulation of secondary interpretation-only “genetic tests”
- Coordination:
 - Other ongoing FDA efforts (particularly LDT, CMS/CLIA coordination)
 - Goal: integrate clinical DTC genetic testing oversight into personal genomics regulatory landscape given other potential federal (GPMA, Hatch), state (NY, MA, VT, CA) & int'l efforts.
 - **Avoid the band-aid approach.**



Next step: transparency, regulation or both?

- What don't we know about clinical DTC genetic tests?
 - How many there are & who offers them
 - How they are intended to be used vs. how they are actually used
- How could we collect this information?
 - Informational registry: voluntary (NIH) or mandatory (SACGHS, previous GPMA)
 - Via regulatory submissions (CDRH for devices or CADER for APDx)
 - Either way: cont. consumer/clinician engagement, monitor real-world use, outcomes
- How could we balance the innovation tension in clinical DTC genetic testing?
 - Pre-test: FDA regulatory approval/clearance, **gatekeeper model**
 - Post-test: oversight of marketing, interpretation, use/outcomes by regulators (FTC) and community (e.g., 23andMe sample swap)
- Fundamental Tensions:
 - Public health precautions vs. innovation
 - **"Route through clinician" vs. "My Genome. My Right."**

Uncertain impact: the cost of regulation

- Industry Costs
 - Pre-market clearance or approval (510(k) – difficulty of finding predicates – or PMA)
 - Informational disclosures (e.g., registry listing, algorithm publication)
 - Cost measured in out-of-pocket expense and product delays, although certain benefits associated with government approval (e.g., consumer/investor confidence, reimbursement?)
- Agency Costs
 - New products, technologies to regulate
 - Claim-by-claim, variant-by-variant regulation sustainable in WGS environment?
 - Political costs, personnel costs (budget?), challenges to authority (absent Congr. action)
- Individual Costs
 - Loss of access to personal genomic information; autonomy
 - Delay to market of potentially valuable products & services
- Possible Responses
 - Change in commercial model (e.g., Counsyl, Navigenics, Pathway, *Agendia*) or not (*23andMe*, *Genomic Health*)
 - DIY personal genomics
 - Flight to or competition from overseas

What happens next?

- Starting Line or Finish Line?
 - DTC regulation tied to industry submissions, LDT regulatory framework
 - MCGP recommendations not surprising, or binding
 - Recall: GINA, IVDMIA
- Participation vs. Reaction
 - Additional opportunities to comment (pre-IDE, less formal/expensive options)
 - Self-Regulation: tailor product development, intended use, marketing
 - Prepare for highly likely developments (e.g., registry, demonstrated analytical, clinical validity)
- Regulation in Context
 - A regulatory spectrum based on use, risk, etc.
 - Benefits of regulation (consumer / payer confidence, barriers to entry, risk mitigation)
- Long Term: (Genomic) Information Wants to be Free



Questions or Comments?

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