Public Policy Challenges in Genetics

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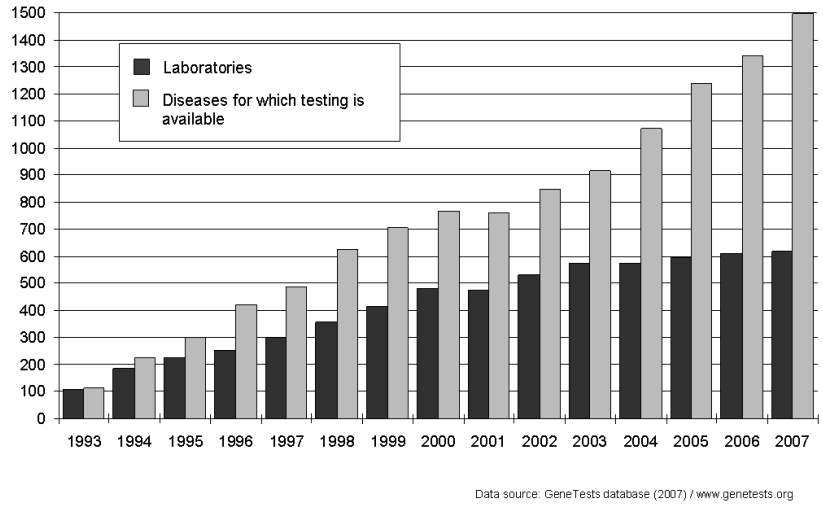
Key Prerequisites for Genetic Medicine

1. Robust and responsive research enterprise
2. Safe and effective tests and interventions
3. Improved guidelines development and adoption
4. Safeguards for genetic information

Growth of Genetic Testing

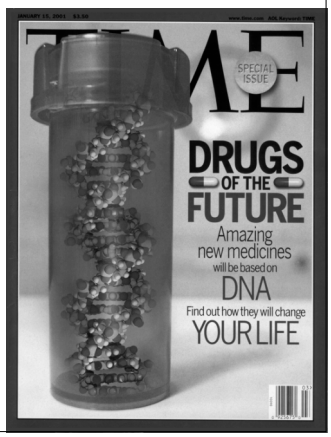


Clinical Genetic Tests To…

- Diagnose disease
  - e.g. Cystic Fibrosis, sickle cell disease
- Use in reproductive decision-making
- Determine prognosis
  - e.g. tumor profiling to determine recurrence risk for breast cancer
- Predict risk for future disease in asymptomatic individuals
  - e.g. Huntington disease, hereditary cancer

Clinical Genetic Tests To…

- Select optimal treatments
  - e.g. Herceptin treatment in Her2/neu positive breast cancer
- Identify risk for adverse drug reactions e.g.CYP450 testing



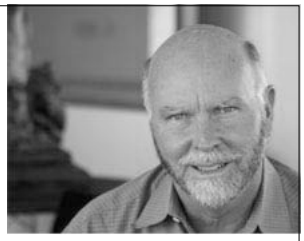
Newsweek Technology & Science

Reading the Book of Jim

The co-discoverer of the double helix is making his DNA public, pioneering the 'personal genome.'

By Sharon Begley
Newsweek
June 4, 2007 issue - It would be a mistake to think that reaching the age of 79 has mellowed James Watson. Fifty-four years after he discovered, with Francis Crick, the structure of DNA, and 45 years after sharing the Nobel Prize for it, he delights in provocation just as much as when he made his reputation as the bad boy of molecular biology, bulldozing colleagues and competitors (and

Technology Review
PUBLISHED BY MIT

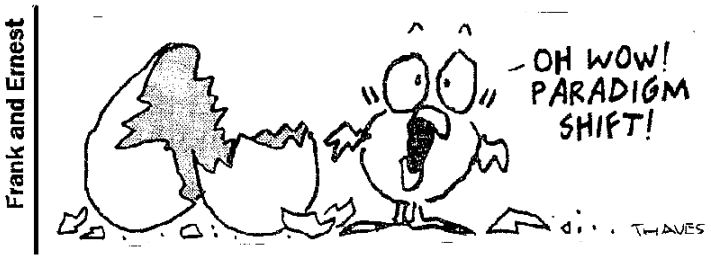


Tuesday, September 04, 2007

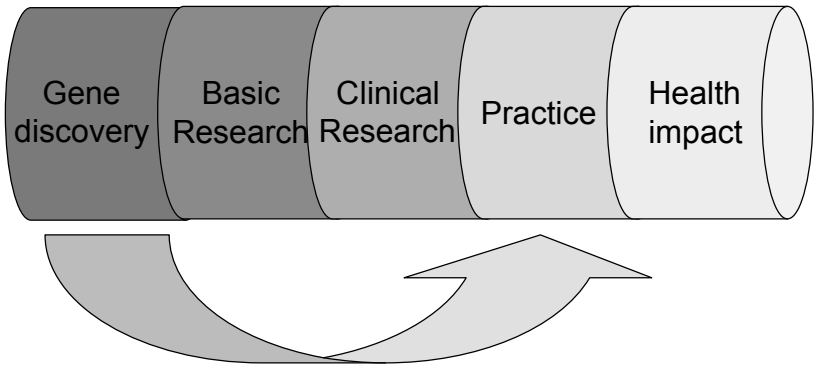
Craig Venter's Genome
The genomic pioneer bares his genetic code to the world.
By Emily Singer

Five years ago, Craig Venter let out a big secret. As president of Celera Genomics, Venter had led the race between his company and a government-funded project to decode the human genome. After leaving Celera in 2002, Venter announced that much of the genome that had been sequenced there was his own. Now Venter and colleagues at the J. Craig Venter Institute have finished the job, filling in the gaps from the initial sequence to publish the first personal genome.

New Paradigm in Genetics?



The Old Way



The New Way

Creative Destruction???

Joseph Schumpeter (1883-1950)

Transformation through radical innovation and entrepreneurship.

“process of industrial mutation that incessantly revolutionizes the economic structure from within, incessantly destroying the old one, incessantly creating a new one."

What is DTC?

(1) Direct access to testing by consumers without health care provider intermediary; OR

(2) Advertising about the availability of a genetic test to promote consumer demand. Test itself requires health care provider to order test and communicate results.

➢ Internet has been primary means of dissemination in both instances

Companies offering health-related tests DTC

Updated 4/2/08

Genetic Testing Company	Personal Genome Service	Addiction	Alzheimer	Amyotrophic Lateral Sclerosis	Arthritis	Ashkenazi Jewish Screening	Asthma	Athletic Performance	Bipolar / Depression	Cancer	Cardiovascular Disease	Celiac Disease	Cystic Fibrosis	Drug Response	Fanconi Anemia	Fetal Gender	Fragile X Syndrome	Gastrointestinal Disease	Gaucher Disease	General Nutrition	Glaucoma / AMD	Glycogen Storage Diseases	Hair Loss	Hemochromatosis	HIV Resistance	Infertility	Metabolic Health	Multiple Sclerosis	Narcolepsy	Obsessive-Compulsive Disorde	Osteoporosis / Bone Health	Parkinson's	Periodontal Disease	Recurrent Pregnancy Loss	Sickle Cell Disease	Skin Profile	Spinal Muscular Atrophy	Tay-Sachs Disease	Thrombosis	Type 1 / 2 Diabetes, Obesity
23andMe	X			X	X			X		X	X			X		X			X		X				X			X											X	X
Acu-gen Biolabs																X																									
Consumer Genetics														X		X																									
CyGene Direct								X													X					X					X								X		
DeCODE	X		X		X		X			X	X	X						X			X		X	X							X									X
DNA Direct	X					X				X			X	X					X					X		X								X			X	X	X	X
DNA Traits						X							X		X		X		X			X													X		X	X	X	
G-nostics		X																																						
GATC Biotech*	X																																							
Genelex											X	X		X						X				X					X		X		X							
GeneLink Biosciences											X									X										X		X			X					
Genetwist*	X																																							
Graceful Earth			X																																					
Hair DX																							X																	
Health Check USA												X												X															X	
Health Tests Direct												X	X																										X	
Holistic Heal																				X																				
Knome*	X																																							
MediChecks						X				X			X		X		X		X			X		X											X		X	X	X	
My Genome			X								X			X																	X			X				X	
Navigenics*	X																																							
Proactive Genomics										X																															
Psynomics									X																																
Quixtar - Interleukin Genetics											X									X																				
Salugen - DNA Services of America		X																		X																				
Scientific Match																																		X						
Sciona								X			X															X					X								
SeqWright*	X																																							
Smart Genetics			X																						X															
Suracell											X																														
*reported; not yet available																																								

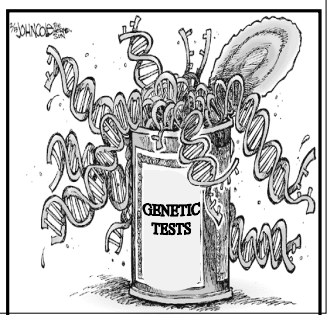
Promise of Personalized Medicine and Direct-to-Consumer Genetic Testing

- Source of information for consumers
- Direct access
- Personal control
- Opportunity for entrepreneurs

Concerns About DTC Marketing

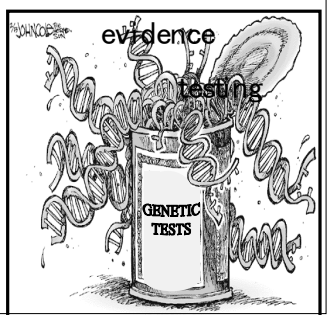
- Consumers can't understand genetic information; it is complicated.
- Consumers vulnerable to exaggerated claims.
- Consumers may get tested without adequately considering consequences to themselves and family members
- Consumers may forego standard treatments or make dietary or lifestyle changes without proven benefit

Need empirical data

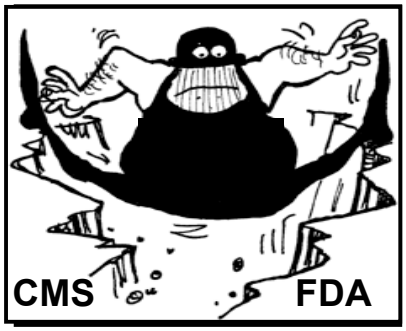


Concerns About DTC Marketing

- Companies may not adequately protect privacy of genetic information
- Test results may be used for discriminatory purposes
- The tests that are offered may not be valid
- The laboratories that perform the tests may not be competent
- Test claims unsupported by
- No legal barrier to surreptitious of another



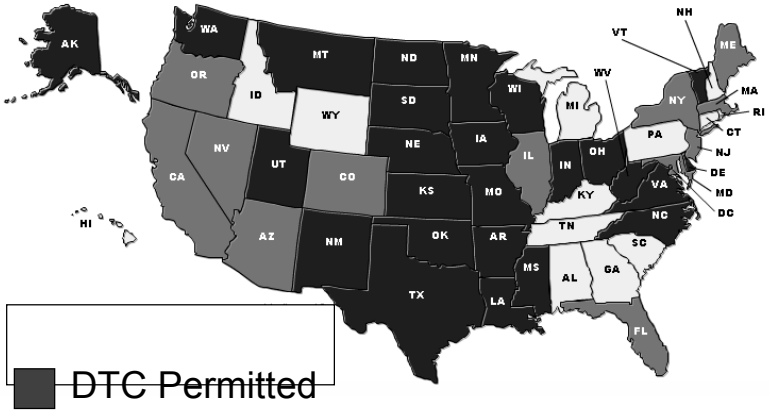
- Genetic tests have great potential to improve health.
- Quality genetic testing depends on quality oversight.
- Oversight of genetic testing is grossly inadequate.



Current Oversight of Genetic Testing

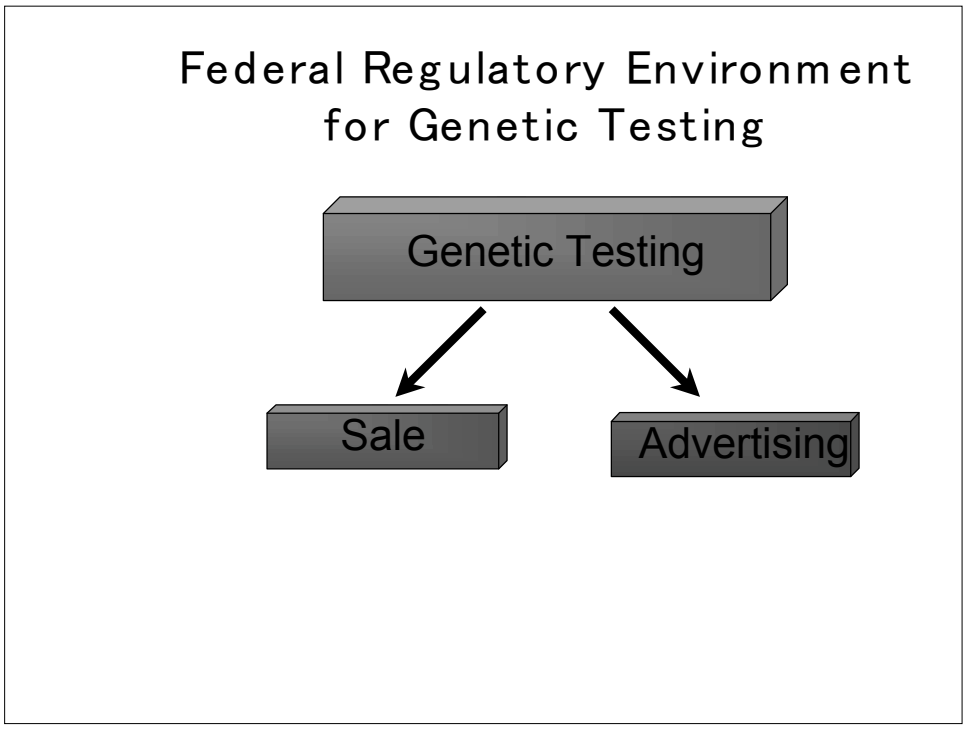
A fractured oversight system, with many cracks, that endangers the public's health

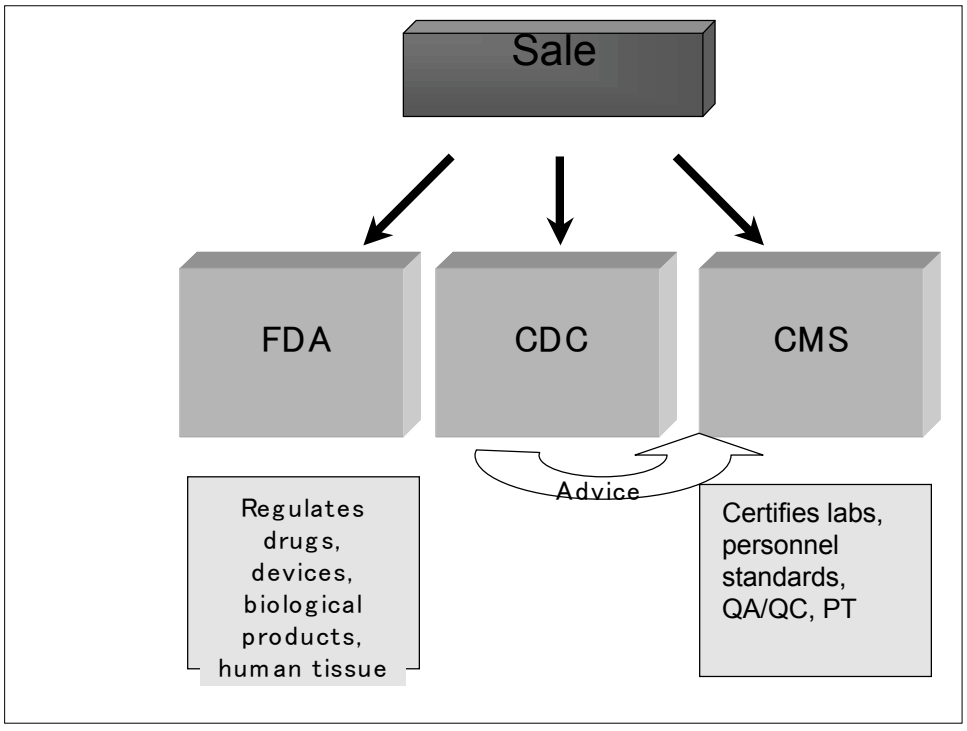
State DTC Testing Statutes and Regulations



DTC Permitted
Limited
DTC Not Permitted

Source: Genetics and Public Policy Center, http://www.dnapolicy.org/resources/DTCStateLawChart.pdf


Federal Regulatory Environment for Genetic Testing
Genetic Testing
Sale
Advertising


Sale
FDA
CDC
CMS
Advice
Regulates drugs, devices, biological products, human tissue
Certifies labs, personnel standards, QA/QC, PT

Oversight of Genetic Testing
The Two Path Problem

Non-FDA reviewed lab developed test.

FDA approved test "kit"

The Two Path Problem

- Adverse economic consequences
- Absence of public access to information
- Disparities in quality
- Risk to public health

Regulation of Clinical Laboratories in the United States

• Clinical laboratories are regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA)

• Law intended to "assure consistent performance by laboratories … of valid and reliable laboratory examinations"

• Standards must address:
- -quality assurance/quality control
- -record keeping
- -facilities and equipment
- -personnel
- -proficiency testing (*)

Regulation of Clinical Laboratories in the United States

- Proficiency testing (PT)
  - "a method of externally validating the level of a laboratory's performance"
  - Congress stated that PT "should be the central element in determining a laboratory's competence, as it provides a measure of actual performance on laboratory test procedures rather than only gauging the potential for accurate outcomes."

Regulation of Clinical Laboratories in the United States

- CLIA applies to labs doing clinical genetic tests
- No mandate to perform proficiency testing
- Voluntary proficiency testing (through CAP) for ~25 molecular genetic tests.
- CLIA does not evaluate clinical validity
- No public access to information
- No reach of CLIA to claims and labels

CMS Timeline of Inaction

- 1997 NIH/DOE Task Force Recommendations
- 2000 SACGT Recommendations
- 2000 CDC issues Notice of Intent
- April 2006 CMS puts genetic testing regulatory enhancement on regulatory agenda
- September 2006 CMS announces it will not issue revised regulations
- September 2006 GPPC files "petition for rulemaking" with CMS along with Genetic Alliance and Public Citizen
- August 2007 CMS denies petition, citing cost and other concerns

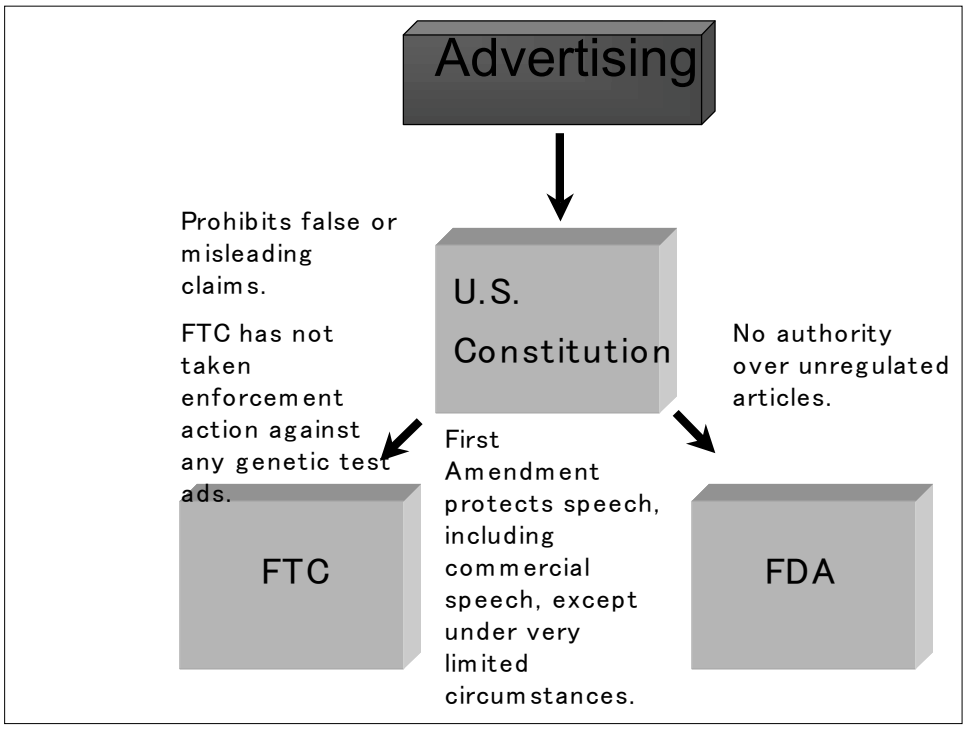
Oversight of Genetic Testing
The Two Path Problem

Non-FDA reviewed lab developed test.

FDA approved test "kit"

FDA Regulation of Genetic Testing

- Test kits
  - Clinical validity included in submission
  - Authority over manufacturer or distributor claims
  - Only a few genetic tests have been reviewed by FDA as kits
- Laboratory-developed tests
  - Enforcement discretion



POLICY FORUM

PUBLIC HEALTH

A Case Study of Personalized Medicine

Marketing of unproven tests shows the need for regulatory action to protect public health.

S. H. Katsanis, G. Javitt, K. Hudson*

Personalized medicine through pharmacogenetics promises to revolutionize health care by harnessing individual genetic information to improve drug safety and efficacy. Under a personalized medicine scheme, drug prescribing and dosing no longer would be "one size fits all" but would be carefully tailored to a patient's individual genetic variants. To date, there have been only a few genetic biomarkers whose clinical validity in predicting drug response has been clearly established, HER2-positive breast cancer as a predictor of response to the drug Herceptin being perhaps the best known. However, some foresee the emergence of many more such tests (*1*).

Pharmacogenetic testing presupposes the availability of validated genetic tests, i.e., tests for which there are data linking the presence or absence of specific variants with a specific outcome, such as improved therapeutic response or reduction in adverse events (see figure, right). Furthermore, it requires that information about the connection between genetic variation and drug response is accurately and truthfully communicated to both health-care providers and patients. As the case study below describes, several barriers currently impede the success of personalized medicine. Today, there is no mechanism to ensure that genetic tests are supported by adequate evidence before they are marketed or that marketing claims for such tests are truthful and not misleading. Misleading claims about tests mark[ed] health-care providers and both providers and patients to lose trust in the value of genetic testing to improve drug-prescribing decisions (*3*, *4*).

CYP450 Genetic Testing for SSRIs

Many drugs, including the commonly prescribed class of antidepressants, selective serotonin reuptake inhibitors (SSRIs), are either metabolized by CYP450 enzymes or inhibit the activity of these enzymes (*5*, *6*).

In Fall 2004, the Centers for Disease Control and Prevention (CDC) commissioned an independent, nonfederal expert panel, the EGAPP (Evaluation of Genomic Applications in Practice and Prevention) working group, to examine the validity and utility of genotyping for SSRI prescription. The review of the evidence found convincing data that SSRIs are metabolized by and inhibit the function of CYP450 enzymes and that polymorphisms in CYP450 enzymes are associated with the function and strength of SSRI metabolism (*7*, *9*). However, EGAPP found "no evidence was available showing that the results of CYP450 testing influenced SSRI choice or dose and improved patient outcomes…" (*9*). EGAPP's conclusion "discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed" (*9*).

Despite the EGAPP conclusions, at least 15 businesses currently offer CYP450 genotyping services, with four companies making specific claims about the benefit of such testing for SSRI prescribing or dosing. Seryx and DNADirect outsource the test to LabCorp and provide only interpretation of the genotypes, whereas

Problems with Genetic Testing Oversight

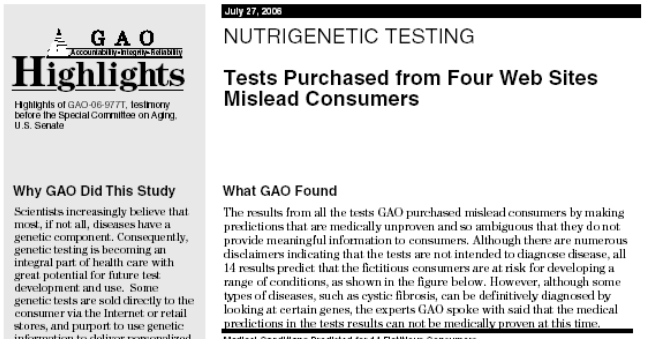
- No PT requirement under CLIA
- No review of clinical validity
- No HHS authority over false claims
- "Two paths" to market are disincentive to seek FDA review; lack of regulatory "level playing field"

Recent Policy Activity

- Government
- Professional Societies
- Industry

July 27, 2006:

Senate Hearing, Special Committee on Aging, "At Home DNA Tests: Marketing Scam or Medical Breakthrough"



GAO
Accountability • Integrity • Reliability

Highlights

Highlights of GAO-06-977T, testimony before the Special Committee on Aging, U.S. Senate

Why GAO Did This Study

Scientists increasingly believe that most, if not all, diseases have a genetic component. Consequently, genetic testing is becoming an integral part of health care with great potential for future test development and use. Some genetic tests are sold directly to the consumer via the Internet or retail stores, and purport to use genetic

July 27, 2006

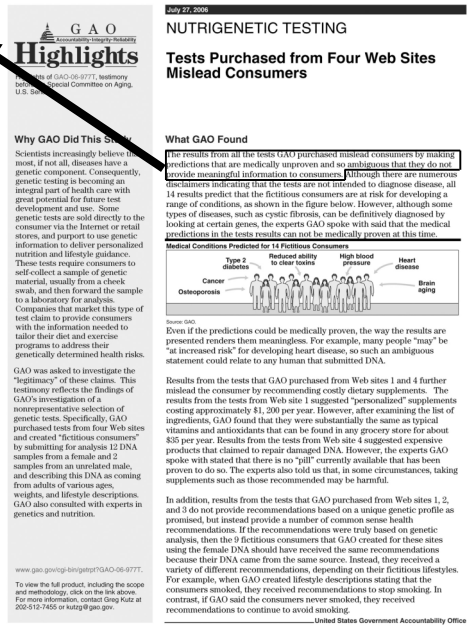
NUTRIGENETIC TESTING

Tests Purchased from Four Web Sites Mislead Consumers

What GAO Found

The results from all the tests GAO purchased mislead consumers by making predictions that are medically unproven and so ambiguous that they do not provide meaningful information to consumers. Although there are numerous disclaimers indicating that the tests are not intended to diagnose disease, all 14 results predict that the fictitious consumers are at risk for developing a range of conditions, as shown in the figure below. However, although some types of diseases, such as cystic fibrosis, can be definitively diagnosed by looking at certain genes, the experts GAO spoke with said that the medical predictions in the tests results can not be medically proven at this time.

"The results from all the tests GAO purchased mislead consumers by making predictions that are medically unproven and so ambiguous that they do not provide meaningful information to consumers."



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Why GAO Did This Study

Scientists increasingly believe that most, if not all, diseases have a genetic component. Consequently, genetic testing is becoming an integral part of health care with great potential for future test development and use. Some genetic tests are sold directly to the consumer via the Internet or retail stores, and purport to use genetic information to deliver personalized nutrition and lifestyle guidance. These tests require consumers to self-collect a sample of genetic material, usually from a cheek swab, and then forward the sample to a laboratory for analysis. Companies that market this type of test claim to provide consumers with the information needed to tailor their diet and exercise programs to address their genetically determined health risks.

GAO was asked to investigate the "legitimacy" of these claims. This testimony reflects the findings of GAO's investigation of a nonrepresentative selection of genetic tests. Specifically, GAO purchased tests from four Web sites and created "fictitious consumers" by submitting for analysis 12 DNA samples from a female and 2 samples from an unrelated male, and describing this DNA as coming from adults of various ages, weights, and lifestyle descriptions. GAO also consulted with experts in genetics and nutrition.

www.gao.gov/cgi-bin/getrpt?GAO-06-977T.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Greg Kutz at 202-512-7455 or kutzg@gao.gov.

July 27, 2006

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Medical Conditions Predicted for 14 Fictitious Consumers

Source: GAO.

Even if the predictions could be medically proven, the way the results are presented renders them meaningless. For example, many people "may" be "at increased risk" for developing heart disease, so such an ambiguous statement could relate to any human that submitted DNA.

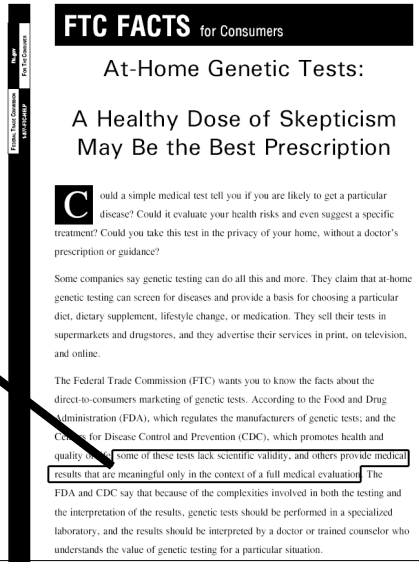
Results from the tests that GAO purchased from Web sites 1 and 4 further mislead the consumer by recommending costly dietary supplements. The results from the tests from Web site 1 suggested "personalized" supplements costing approximately $1, 200 per year. However, after examining the list of ingredients, GAO found that they were substantially the same as typical vitamins and antioxidants that can be found in any grocery store for about $35 per year. Results from the tests from Web site 4 suggested expensive products that claimed to repair damaged DNA. However, the experts GAO spoke with stated that there is no "pill" currently available that has been proven to do so. The experts also told us that, in some circumstances, taking supplements such as those recommended may be harmful.

In addition, results from the tests that GAO purchased from Web sites 1, 2, and 3 do not provide recommendations based on a unique genetic profile as promised, but instead provide a number of common sense health recommendations. If the recommendations were truly based on genetic analysis, then the 9 fictitious consumers that GAO created for these sites using the female DNA should have received the same recommendations because their DNA came from the same source. Instead, they received a variety of different recommendations, depending on their fictitious lifestyles. For example, when GAO created lifestyle descriptions stating that the consumers smoked, they received recommendations to stop smoking. In contrast, if GAO said the consumers never smoked, they received recommendations to continue to avoid smoking.

United States Government Accountability Office

Federal Trade Commission releases consumer advisory, "At Home Genetic Tests: A Healthy Dose of Skepticism May Be the best Prescription" (July 2006)

"…some of these tests lack scientific validity, and others provide medical results that are meaningful only in the context of a full medical evaluation."



FTC FACTS for Consumers

At-Home Genetic Tests:

A Healthy Dose of Skepticism May Be the Best Prescription

Could a simple medical test tell you if you are likely to get a particular disease? Could it evaluate your health risks and even suggest a specific treatment? Could you take this test in the privacy of your home, without a doctor's prescription or guidance?

Some companies say genetic testing can do all this and more. They claim that at-home genetic testing can screen for diseases and provide a basis for choosing a particular diet, dietary supplement, lifestyle change, or medication. They sell their tests in supermarkets and drugstores, and they advertise their services in print, on television, and online.

The Federal Trade Commission (FTC) wants you to know the facts about the direct-to-consumers marketing of genetic tests. According to the Food and Drug Administration (FDA), which regulates the manufacturers of genetic tests; and the Centers for Disease Control and Prevention (CDC), which promotes health and quality testing, some of these tests lack scientific validity, and others provide medical results that are meaningful only in the context of a full medical evaluation. The FDA and CDC say that because of the complexities involved in both the testing and the interpretation of the results, genetic tests should be performed in a specialized laboratory, and the results should be interpreted by a doctor or trained counselor who understands the value of genetic testing for a particular situation.

Legislation

- Laboratory Test Improvement Act (Kennedy-Smith)
- Genomics and Personalized Medicine Act (Obama-Burr)

Secretary's Advisory Committee on Genetics Health and Society (SACGHS)

- Secretary requested recommendations on genetic testing oversight
- Public draft release Nov. 2007
- Final recommendations February 2008
- Will be 4th set of recommendations on the issue

SACGHS Recommendations

- PT requirement for all non-waived tests
- Development of a mandatory registry for lab-developed tests
- Risk-based oversight of lab-developed tests by FDA
- Enhancement of enforcement actions for non-compliance
- Clinical utility assessment
- Creation of electronic health records

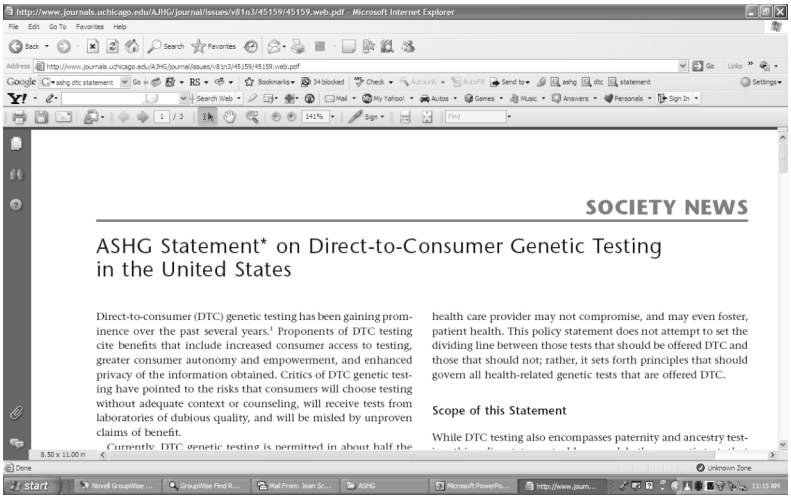
The Role of Professional and Industry Guidelines

More rapid and flexible than government

Have appropriate scientific expertise

- ACMG 2004 & 2008 Statements on DTC Genetic Testing
- ASHG Statement on DTC Genetic Testing
- Navigenics release of industry standards

ASHG Statement on DTC



SOCIETY NEWS

ASHG Statement* on Direct-to-Consumer Genetic Testing in the United States

Direct-to-consumer (DTC) genetic testing has been gaining prominence over the past several years.[1] Proponents of DTC testing cite benefits that include increased consumer access to testing, greater consumer autonomy and empowerment, and enhanced privacy of the information obtained. Critics of DTC genetic testing have pointed to the risks that consumers will choose testing without adequate context or counseling, will receive tests from laboratories of dubious quality, and will be misled by unproven claims of benefit.

health care provider may not compromise, and may even foster, patient health. This policy statement does not attempt to set the dividing line between those tests that should be offered DTC and those that should not; rather, it sets forth principles that should govern all health-related genetic tests that are offered DTC.

Scope of this Statement

**K. Hudson, G. Javitt, W. Burke, P. Byers, with the ASHG Social Issues Committee, Am. J.. Hum. Genetics, Sept. 2007*

ACMG Statement on DTC

- A knowledgeable professional should be involved in the process of ordering and interpreting a genetic test.
- The consumer should be fully informed regarding what the test can and cannot say about his or her health.
- The sceintific evidence on which a test is based should be clearly stated.
- The clinical laboratory must be accredited by CLIA, the state and/or other applicable accrediting agencies.
- ACMG 2004 & 2008 Statements on DTC Genetic Testing
- Privacy concerns must be addressed.

Approved by the Board of Directors, American College of Medical Genetics April 7, 2008

1. Validity

2. Accuracy and quality

3. Clinical relevance

4. Actionability

5. Access to genetic counseling

6. Security and privacy

7. Ownership of genetic information

8. Physician education and engagement

9. Transparency

10. Measurement

Navigenics

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NAVIGENICS PROPOSES STANDARDS FOR PERSONAL GENOMICS SERVICES, COUPLED WITH PROSPECTIVE OUTCOMES STUDIES, TO SAFEGUARD CONSUMERS

Company acts to 'ensure the integrity of this critical step toward personalized health care'

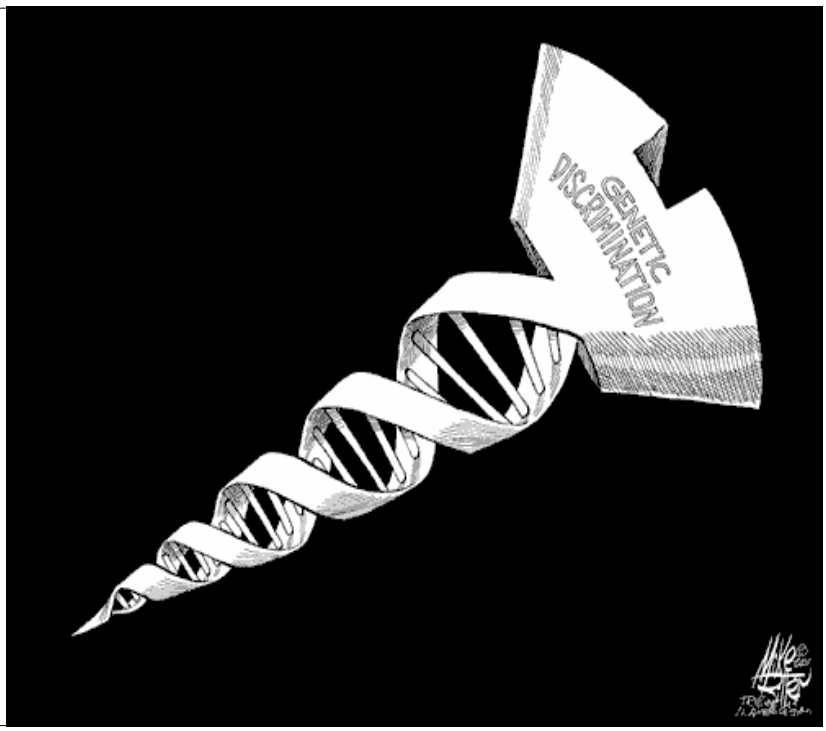
Redwood Shores, Calif. – April 8, 2008 – Navigenics, a personalized genetic health services company, today announced that it will develop a set of industry standards for consumer genomic testing services, and that it will seek broad, multi-stakeholder input and endorsement of these or similar criteria. Further, the company announced it will also support prospective health outcomes studies, involving leading medical centers and other partners, designed to examine the impact that consumer access to personal genetic information has on behaviors and health outcomes.

Goals of Genetic Testing Oversight

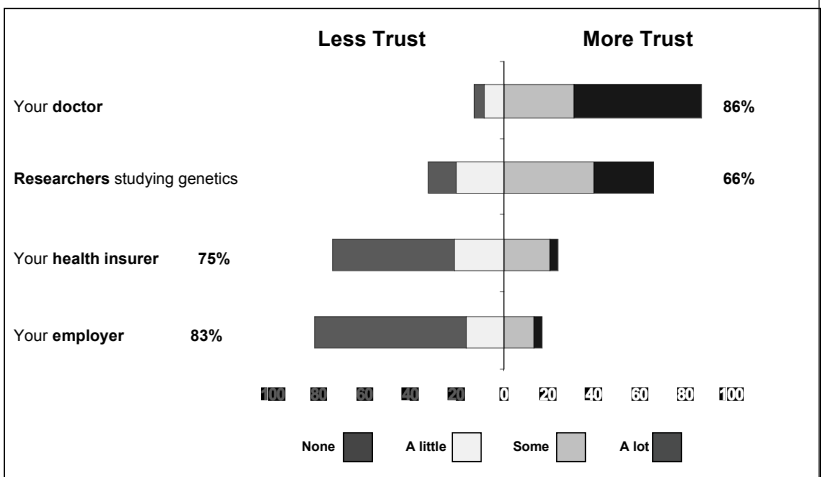
- Appropriate laboratory oversight
- Level regulatory playing field that incentivizes development of validated tests
- Test regulation based on risk
- Mechanism for evidence development and translation into clinical practice
- Truthful, non-misleading claims about test benefits and limitations

Key Prerequisites for Genetic Medicine

1. Robust and responsive research enterprise
2. Safe and effective tests and interventions
3. Improved guidelines development and adoption
4. Safeguards for genetic information



How much do you trust each of the following to have access to your genetic test results?



Genetics and Public Policy Center. http://www.dnapolicy.org. 2/27/07-3/4/07, N=1199 adults 18 years of age or older

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

- Group health plans may not establish eligibility, enrollment, continuation or premium requirements based on health status-related factors.
- Factors include medical conditions, claims experience, receipt of health care, medical history, genetic information, evidence of insurability, disability

Americans with Disabilities Act

Provides protections against discrimination to those with:

1) a physical or mental impairment that substantially limits one or more of the major life activities of such individual;

2) a record of such an impairment; or

3) being regarded as having such an impairment.

Clinton Signs Executive Order Banning Genetic Discrimination in the Federal Workplace

"By signing this executive order, my goal is to set an example and pose a challenge for every employer in America, because I believe no employer should ever review your genetic records along with your resume."
February 8, 2000

The Genetic Information Nondiscrimination Act

Prohibits group and individual health insurers from using genetic information in setting eligibility or premium or contribution amounts.

Prohibits health insurers from requesting or requiring that a person undergo a genetic test.

Prohibits employers from using genetic information in making employment decisions such as hiring, firing, job assignments, and promotions.

Prohibits employers from requesting, requiring, or purchasing genetic information about an employee or family member.

Status Report

Introduced in 1995

Passed Senate in 2003

Passed Senate in 2005

Blocked in House by Employer Groups

2006 Election

Passed House April 25, 2007

Senate passage expected

Bush has said he will sign

Department of Defense Personnel Policy

- Provides medical coverage for enlisted men/women
- Provides medical & disability benefits for retired service men/woman

Department of Defense Personnel Policy

- Served in the Marines for 14 years
- Diagnosed with renal cell carcinoma & cerebellar nodules
- Diagnosed with von Hippel-Lindau disease
- Requested medical discharge

DOD Instruction 1332.38

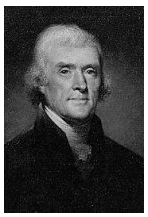
E3.P4.5.2.2.1. Presumption. Any injury or disease discovered after a service member enters active duty -- with the exception of congenital and hereditary conditions -- is presumed to have been incurred in the line of duty;

Key Prerequisites for Genetic Medicine

1. Robust and responsive research enterprise
2. Safe and effective tests and interventions
3. Improved guidelines development and adoption
4. Safeguards for genetic information

Public confidence

"Laws and institutions must go hand in hand with the progress of the human mind. As that becomes more developed, more enlightened, as new discoveries are made, new truths disclosed and manners and opinions change with the change of circumstances, institutions must advance also and keep pace with the times."



Thomas Jefferson to Samuel Kercheval
1816

Thanks to the Pew Charitable Trusts