

Health-Related Direct-to-Consumer Genetic Tests: A Public Health Assessment and Analysis of Practices Related to Internet-Based Tests for Risk of Thrombosis

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Key Words

Direct access testing · Factor V Leiden · Nutrigenomics · Pharmacogenomics

Abstract

Background: Recent years have seen increased concern about direct-to-consumer (DTC) genetic testing (i.e., the sale and use of genetic tests without involving a health care provider). Numerous professional organizations have developed policies in this area. However, little systematic evidence exists to inform public policy about these tests. **Methods:** We conducted a systematic search to identify genetic tests that are sold DTC without involving a health care provider. We evaluated the practices of companies offering DTC genetic tests for risk of thrombosis using criteria from multiple sources and a minimal set of key practices. **Results:** We identified 84 instances of currently available health-related DTC genetic tests sold on 27 Web sites; the most common were for pharmacogenomics (12), risk of thrombosis (10), and nutrigenomics (10). For the DTC genetic tests for risk of thrombosis, we found low adherence to recommendations. Online information was frequently in-

complete and had low agreement with professional recommendations. **Conclusion:** Our findings document the rapid growth in the availability of health-related DTC genetic tests and highlight the need to improve the delivery of DTC genetic tests. A major implication of this study is the need for the scientific and medical community to develop consistent recommendations to increase their impact.

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Direct-to-consumer (DTC) genetic testing is the sale and use of genetic tests without the involvement of a health care provider. This activity has recently gained the attention of many professional organizations [1–3]. Some of the concerns fueling the growing debate about DTC genetic tests [4–7] are the perception of rapid increases in their availability over the Internet and the sale of questionable products that have received widespread atten-

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

tion in the popular media [8, 9]. In addition, investigations on the impact of DTC advertisements of pharmaceuticals and medical products suggest that such advertisements may be more harmful than beneficial to consumers [10–13].

Although anecdotal evidence suggests that the concerns raised may be valid in at least some instances, systematic research is needed to document the extent of the problem and the areas requiring particular scrutiny. In 2003 Gollust and coworkers [14] provided the most current assessment of health-related DTC genetic tests; these investigators identified 14 distinct health-related genetic testing products. The recent recommendations published in the ASHG policy statement [3] provide an important tool or yardstick to measure the performance of these tests and provide valuable and much-needed information about their delivery. In addition, an evaluation of DTC genetic tests in the context of recommended practices will inform us about the extent to which current recommendations are followed, if they exist, and it will provide insight into the comprehensiveness and utility of available recommendations.

To inform the public policy debate surrounding these tests, we collected observations on Web sites offering health-related DTC genetic tests to assess the content, quality, and quantity of DTC advertising and sale of health-related genetic tests. We examined to what extent current practices adhere to related professional recommendations or federal regulatory requirements. To document this adherence, we evaluated the content of 5 Web sites that distributed a genetic test for assessment of the risk of thrombosis. This subset was selected because the genetic tests were relatively uniform in terms of the genes and polymorphisms that were included as part of the test, and therefore could be more accurately compared with each other. We evaluated practices such as providing pre- and post-test counseling, laboratory accreditations, methods of reporting test results, privacy policies, and cost. We compared indications for testing, presentation of risks and benefits, and the limitations of testing with existing practice recommendations from professional organizations for risk of thrombosis.

Material and Methods

Resources Used to Identify Health-Related DTC Genetic Tests

To identify health-related genetic tests that were sold DTC (vs. advertised DTC) (table 1), we used 3 sources of information: the scientific literature, gray literature, and professional contacts. We used PubMed to identify sources through the scientific literature

using key search terms including *direct to consumer* and *direct access* in combination with terms such as *DNA/gene/genetic/test/testing*. To search the gray literature, we followed the strategy of Gollust and colleagues [14] by employing Google to identify genetic tests sold DTC; we used key search terms including *genetics* or *DNA* and *test* or *testing* combined with *home*, *kit*, *disease*, or *service*. Because so many documents (over a million) were identified by this method, we reviewed only a subset of those documents (approximately the first few 100 at the top of the list), which is a limitation of our study. This search yielded news articles, Web sites maintained by consumer advocacy groups, diagnostic manufacturer, laboratory, or test distributor Web sites, and scientific articles. Documents were read to extract potential novel health-related DTC genetic tests. Based on a report by Chin et al. [15], we also used Lexis-Nexis® (www.lexisnexis.com) which they deemed high-utility or very productive in identifying genetic tests. Finally, we solicited information from professional contacts. These searches were conducted in spring 2007.

Definition of Health-Related DTC Genetic Tests

Using the sources identified above, we applied several definitions, conventions, and criteria to compile a final list of health-related DTC genetic tests. First, we used the definition of genetic test developed by the Secretary's Advisory Committee on Genetic Testing (SACGT): 'A genetic test is an analysis performed on human DNA, RNA, genes, and/or chromosomes to detect heritable or acquired genotypes, mutations, phenotypes, or karyotypes that cause or are likely to cause a specific disease or condition. A genetic test also is the analysis of human proteins and certain metabolites, which are predominantly used to detect heritable or acquired genotypes, mutations, or phenotypes' [16].

Thus, a genetic test could refer to an inherited or a somatic genetic alteration, and it could include a test that detects the alteration using either molecular or biochemical biomarkers in the assay. Furthermore, it could be a test of a single alteration, or it could refer to a panel of markers within the same gene or in different genes. We designated a genetic test as health related if its purpose was to predict risk of disease, screen for disease, direct clinical management, identify carriers, or establish prenatal diagnoses, clinical diagnoses, or prognoses in individual people or families.

We designated a genetic test as available DTC if we were able to identify an online mechanism to order the test (e.g., Web site, phone number or address, or a form to be printed and faxed or mailed) by consumers in the US without the involvement of a health care professional. We excluded all instances where the test was not yet available, where the Web site link no longer existed (as of May 2007), and where we could not determine how to order the test. Our search criteria were specifically designed to exclude tests sold through some other mechanism (e.g., drugstore, grocery store, spa, exercise facility, or catalog), but not available for sale over the Internet. Each element we identified was a unique combination of a test distributor (i.e., a company providing a Web site where the test could be purchased) and a health-related DTC genetic test. Thus, a test that was offered by more than one distributor was included more than once. If a test distributor offered more than one genetic test that could be ordered individually or in a bundle, we included only the individual tests and did not include the bundle separately. We did not include companies that manufactured a test but did not provide a method to directly order the

Table 1. Eighty-four instances of health-related DTC genetic tests sold over the Internet in the US as of August, 2007

Application	Company name	Test name	Cost (USD)
Fetal sex (5)			215–390
	Acu-Gen Biolab	Baby Gender Mentor	
	Consumer Genetics	Pink or Blue Test	
	GeneTree	Pink or Blue Test	
	DNAplus	Fetal Cell/DNA Prenatal Gender Test	
	Paragon Genetics	Non-Invasive Baby Gender Predictor	
Pregnancy complications (3)			350–995
	DNA Direct	Infertility - Male/Female	
	DNA Direct	Recurrent Pregnancy Loss Male/Female	
	MyGenome	Pregnancy Risk	
Lifestyle factors (6)			100–258
	Consumer Genetics	Heart Attack Risk	
	CyGene Direct	Athletic Performance	
	Genetic Technologies	Athletic Performance	
	Dermagenetics	Dermagenetics	
	GeneLink	Dermagenetics	
	G-nostic	Smoking Cessation	
Nutrigenomics (10)			100–625
	Carolyn Katzin	The DNA Diet	
	Genelex	DNA Diet	
	Genelex	Nutritional Genetic Panel	
	GeneLink	GeneLink Nutrigenetic Profile	
	Interleukin Genetics	Gensona General Nutrition Genetic Test	
	MarketAmerica	GeneSNP	
	Quixtar	Gensona General Nutrition	
	Salugen	Genoscore DNA Test	
	Sciona	MyCellf	
	Suracell	Personal DNA Analysis Profile	
Pharmacogenomics (12)			250–2,500
	DNA Direct	Drug Metabolism	
	Genelex	Extended DNA Drug Reaction Panel	
	Genelex	Drug Reaction Panel	
	Genelex	Warfarin (Coumadin) Target Dose Safety Test	
	DNA Direct	Tamoxifen (CYP2D6)	
	Kimball Genetics	Warfarin DoseAdvise Genetic Test	
	MyGenome	Drug Sensitivities	
	PGxHealth	PGxPredict: CLOZAPINE	
	PGxHealth	PGxPredict: RITUXIMAB	
	PGxHealth	PGXPredict: WARFARIN	
	Signature Genetics	The All Inclusive Report	
	Signature Genetics	The Drug Gene Report	
Thrombosis (10)			90–380
	CyGene Direct	Thrombosis DNA Analysis	
	DNA Direct	Factor V Leiden	
	Health Tests Direct	Factor V Leiden	
	HealthCheckUSA	Factor V DNA Test	
	HealthCheckUSA	Factor V R2 DNA Test	
	HealthCheckUSA	Prothombin (Factor II) DNA Test	
	Kimball Genetics	Factor V Leiden DNA Test	
	Kimball Genetics	Factor V R2 DNA Test	
	Kimball Genetics	Prothrombin (Factor II) DNA Test	
	MyGenome	Thrombosis	

Table 1 (continued)

Application	Company name	Test name	Cost (USD)
Hemochromatosis (5)	DNA Direct	Hemochromatosis	195–560
	Genelex	Hemochromatosis DNA Test	
	Health Tests Direct	Hereditary Hemochromatosis	
	HealthCheckUSA	Hereditary Hemochromatosis	
	Kimball Genetics	Hemochromatosis DNA Test	
Chronic diseases (14)	Graceful Earth	Alzheimer Test/ApoE	90–3,456
	Kimball Genetics	ApoE Genotype Test	
	MyGenome	Alzheimer Disease/ApoE	
	DNA Direct	Breast and Ovarian Cancer/BRCA1 & BRCA2	
	Health Tests Direct	Breast Cancer/HER2	
	DNA Direct	PreGen-Plus Colon Cancer Screening	
	Kimball Genetics	Coronary Artery Disease/MTHFR DNA Test	
	DNA Direct	Diabetes/deCODE T2	
	CyGene Direct	Glaucoma & Macular Degeneration DNA Analysis	
	Interleukin Genetics	Gensona Heart Health Genetic Test	
	MyGenome	Cardiovascular Disease	
	Quixtar	Gensona Heart Health	
	CyGene Direct	Osteoporosis DNA Analysis	
	MyGenome	Osteoporosis	
Pediatric conditions (7)	DNA Direct	Cystic Fibrosis	260–1,266
	Health Tests Direct	CF Carrier Screen	
	Kimball Genetics	Cystic Fibrosis DNA Test	
	Kimball Genetics	Fragile X DNA Test	
	Kimball Genetics	Fragile X-Associated Tremor/Ataxia Syndrome Test	
	DNA Direct	Ashkenazi Jewish Carrier Screening	
	Kimball Genetics	Tay-Sachs Disease DNA Test	
Immune-related conditions (6)	Kimball Genetics	Ankylosing Spondylitis/HLA-B27 DNA Test	99–445
	Genelex	Celiac Disease DNA Test	
	HealthCheckUSA	Celiac Disease DNA Test	
	Kimball Genetics	Celiac Disease DNA Test	
	DNA Direct	α 1-Antitrypsin Deficiency	
	HIVmirror	HIV-1 Progression/CCR5 and HIV-1 Progression	
Other health-related tests (6)	PGxHealth	The Familion Test/Cardiac Channelopathies	160–5,400
	CyGene Direct	Metabolic Health Assessment	
	Genelex	Narcolepsy DNA test	
	Kimball Genetics	Narcolepsy DNA Test	
	Genelex	Periodontal Disease DNA Test	
	Kimball Genetics	PST Genetic Test: Susceptibility to Periodontal Disease	

test from their Web site. We also excluded laboratories that performed the genetic test but did not provide a method for consumers to directly order the test.

Evaluation of Web Site Practices

Previous reports of laboratory practices in the area of genetic testing, especially those including questions about DTC services and quality of reporting, were used as a starting point to develop

survey questions [17–19]. We created data collection forms to systematically abstract information from each Web site. Two abstractors (K.G., J.R.) independently collected data via the data collection forms using the information provided on each Web site. The information from the data collection forms was coded (typically as present or absent) and entered into an electronic file, and it was compared for consistency across abstractors. Items that were inconsistent were resolved through discussion with a third

Table 2. Interpretation of recommendations presented in supplementary table 1 with respect to the sets of practices evaluated in this study

	ASHG	ACMG (2008)	NSGC	FDA/FTC ^a	Set 1 practices	Set 2 practices
General information						
disclose which genes are tested					+	+
disclose which polymorphisms are tested					+	
Pre-test counseling						
provide guidance on indications for testing		+			+	+
describe benefits of testing	+	+		+	+	+
describe risks of testing	+			+	+	+
Laboratory						
laboratory is CLIA certified	+	+	+	+	+	+
Post-test counseling						
provide information on test limitations	+	+	+	+	+	
provide information on clinical validity	+		+		+	
allow consumer to call with questions					+	
refer consumer to their doctor			+	+	+	+
assist consumer with obtaining a doctor			+		+	
refer to another source of information			+		+	
Privacy protections						
provide written privacy policy	+			+	+	+
Total practices	6	4	6	6	13	7

^a Recommendations in the FTC fact sheet were consumer-oriented rather than company-oriented.

evaluator (C.M.). Our report of company practices refers to companies by code only. Data collection was approved by the human research protection offices at the Centers for Disease Control (CDC) as public health practice (and not research) after review for determination of research status.

Identification of Recommended Practices and Guidelines

We used several published and professional sources to establish 2 sets of criteria for the analysis of the practices of test distributors. Because there are no definitive standards of practice for DTC genetic testing, the first set of criteria was based on a group of published recommendations: ASHG (American Society of Human Genetics) recommendations, ACMG (American College of Medical Genetics) recommendations [1], a position statement of DTC genetic testing from the National Society of Genetic Counselors (NSGC) [2], and a publication by Reich and coworkers [20] that specifically addresses recommendations for counseling for inherited thrombophilia in the traditional medical framework. In the absence of publications from the Food and Drug Administration (FDA) and Federal Trade Commission (FTC) explicitly relating to regulation of DTC genetic testing, we considered publications on broadcast [21] or print [22, 23] advertisements aimed directly to consumers for prescription medications or for dietary supplements [24]. We also considered a FTC fact sheet on DTC genetic testing, although these recommendations were consumer-oriented rather than company-oriented [25]. From these sources, we identified 13 potential practices (Set 1) for health-related DTC genetic test distributors (we should note that no

single source recommends all 13 practices) (table 2). Because this set of practices was subjective, we used a minimal set of 7 practices (Set 2) as the second set of criteria (table 2). The practices in Set 2 were identified as (1) typical requirements for disclosure of information, according to FDA regulations on DTC print advertisements for prescription medications [22, 23] or for dietary supplements [24], and (2) practices that were observed for at least 4 of the 5 test distributors evaluated in our analysis. Further details regarding the practices recommended by these organizations are provided in supplementary table 1 (for online supplementary material, see www.karger.com/doi/10.1159/000176794) and table 3.

In the context of genetic tests for thrombophilias (tests that relate genetic variations to blood clotting disorders), 2 consensus-based recommendations (vs. evidence-based recommendations) outline accepted indications for testing, one published by the ACMG [26] and the other presented at the College of American Pathologists (CAP) Consensus Conference XXXVI [27]. These recommendations, in addition to other statements by the ACMG [1, 26], provided direction on accepted indications for testing, risks and benefits of testing, and reporting guidelines.

Statistical Analysis

Data was coded and tabulated, and inter-rater agreement was assessed by computing the proportion agreement and kappa statistics using SAS (SAS Institute, Cary, N.C., USA).

Table 3. Logistics and practices of direct-to-consumer companies offering genetic tests for thrombosis

	Set 1 practices ^a	Set 2 practices ^b	DTC company				
			A	B	C	E	F
<i>Logistics</i>							
Method of sample collection			cheek	cheek	blood	blood	blood
Length of time to obtain test result (in days)			NA	7–10	1	NA	4–10
How is report delivered?			Web site	Web site	letter	letter	letter, fax, or Web site
Who is report delivered to?			consumer	consumer	consumer and doctor	consumer	consumer
<i>Practices</i>							
<i>General information</i>							
disclose which genes are tested	+	+	yes	yes	yes	yes	yes
disclose which polymorphisms are tested	+		yes	no	yes	yes	no
<i>Pre-test counseling</i>							
provide guidance on indications for testing	+	+	yes	yes	yes	no	yes
describe benefits of testing	+	+	yes	yes	no	no	no
describe risks of testing	+	+	no	yes	no	no	no
<i>Laboratory</i>							
laboratory is CLIA certified ^c	+	+	yes	yes	yes	yes	no
<i>Post-test counseling</i>							
provide sample report of test result			yes	yes	no	no	no
provide information on test limitations	+		no	no	no	no	no
provide information on clinical validity	+		no	no	no	no	no
allow consumer to call with questions	+		no	yes	yes	no	no
refer consumer to their doctor	+	+	yes	yes	yes	no	no
assist consumer with obtaining a doctor	+		no	no	no	yes	no
refer to another source of information	+		yes	no	no	yes	no
<i>Privacy protections</i>							
provide written privacy policy	+	+	yes	yes	no	yes	yes
Total Set 1 practices	13	–	8	8	6	6	3
Total Set 2 practices	–	7	6	7	4	3	3

^a Set 1 practices identified from recommendations including the ASHG policy statement, the NSGC position statement, the ACMG policy statement, FTC recommendations for DTC advertisements, and a publication by Reich and co-workers [20].

^b Set 2 practices are defined as (1) required by FTC recommendations for DTC advertisements or (2) practices used by most test distributors.

^c We assessed whether there was a statement that a CLIA certified laboratory was used, but we could not confirm these statements.

Results

Scan for Health-Related DTC Genetic Tests

We identified 84 instances of health-related DTC genetic tests that were being sold on 27 distinct test distributor Web sites as of August 2007 (table 1). These instances corresponded to 53 unique tests, because some were sold by more than one distributor. Each Web site contained between 1 and 15 health-related DTC genetic testing products. These estimates should be considered a lower bound on the number of currently available health-

related DTC genetic tests, as although we carefully confirmed each observed instance, our scans could have missed some sites.

Most of the test distributors were located in the US, with 3 from Canada, the United Kingdom, and Australia (online supplementary table 2). The most common health-related DTC genetic tests were for pharmacogenomics (tests that relate genetic variations to the response to drugs) (12), thrombosis (tests that relate genetic variations to clotting disorders) (10), nutrigenomics (tests using information on diet, lifestyle, and genetics to inform recom-

Table 4. Genes and polymorphisms evaluated in DTC genetic tests for thrombosis

DTC company	Gene (polymorphism) ^a			
	factor V Leiden (R506Q)	factor V R2 (H1299R)	prothrombin (factor II)	<i>MTHFR</i> ^b
A	+ (G1691A)		+ (G20210A)	+ (C667T, A1298C)
B	+ (G1691A)		+	
C	+ (G1691A)	+	+	+ (C667T, A1298C)
E	+ (G1691A)			
F	+ (G1691A)	+	+	

^a + indicates that a genetic test for this gene is present on the website. If the + is followed by parentheses, this indicates that the specific polymorphisms were also mentioned on the Web site. Otherwise, the Web site only mentions the gene, without indicating which polymorphisms within that gene are tested.

^b *MTHFR* = Methylene tetrahydrofolate reductase.

recommendations on changes in behaviors, diet, or specific nutritional supplements) (10), fetal sex (5), and hereditary hemochromatosis (5). Prices ranged from USD 90 to 5,400.

About one-third of health-related DTC genetic tests were offered in both the DTC and typical clinical settings. Tests offered in both settings include those for pediatric conditions (such as Tay-Sachs disease, fragile X syndrome, and cystic fibrosis) and for chronic disorders (such as *BRCA1/2* testing for risk of breast or ovarian cancer, *HER2* testing for recurrence of breast cancer, thrombosis risk, and hereditary hemochromatosis). In contrast, the majority (~66%) of the tests was offered primarily outside the framework of traditional clinical medicine and included genetic tests such as prediction of fetal sex, dermatogenetics (tests using genetic information to inform recommendations on skin care products), nutrigenomics, and prediction of smoking cessation.

Survey of Company Practices

Company practices were evaluated for only a subset of health-related genetic tests that included those for thrombosis risk. This subset was selected because (1) the genetic tests were relatively uniform in terms of the genes and polymorphisms that were included as part of the test, (2) there are existing professional recommendations regarding their use, and (3) thrombosis risk is a potentially serious and life-threatening condition. These factors improve our ability to compare the company practices with each other. Thrombosis is a multifactorial disease with both genetic and acquired risk factors. The factor V Leiden (R506Q) mutation (OMIM (Online Mendelian

Inheritance in Man): 227400), associated with increased resistance to the anticoagulant effects of activated protein C, is the most common prothrombotic variant. About 5% of Caucasians are carriers, and the increase in risk for venous thromboembolism is 3–8% and 50–80% for heterozygous and homozygous carriers, respectively [28, 29]. Anecdotally, the genetic test for the factor V Leiden mutation is one of the tests most commonly ordered by clinicians. A G-to-A transition at position 20210 of the prothrombin gene (OMIM: 176930), present in 2–3% of Caucasians, is associated with elevation in blood prothrombin concentrations and with a 3-fold increased risk for venous thromboembolism [30]. Some studies have demonstrated that polymorphisms in other genes in coagulation pathways, including the methylenetetrahydrofolate reductase (*MTHFR*) C677T mutation (OMIM: 607093), are associated with small elevations in risk of thrombosis [31].

The 10 tests for risk of thrombosis that were offered in the DTC setting were relatively homogeneous, including 7 tests for the same mutation, factor V Leiden (R506Q). The other 3 tests included evaluation of prothrombin (G20210A), the factor V R2 (H1299R or A4070G) mutation, and *MTHFR* (C677T) (table 4). The 10 tests were offered DTC by 6 different companies (table 1). One of the tests (and companies) was eliminated from further consideration because the information provided on the Web site was inadequate to include in this analysis and we did not receive a response to an e-mail query for more information.

The test distributors that we evaluated generally used fewer than 9 of the 13 practices in Set 1, ranging between

Table 5. Indications of factor V Leiden or prothrombin (factor II) genetic testing

Indications ^a	ACMG ^b	CAP ^c	DTC company ^d				
			A	B	C	E	F
A first VTE before age 50 years	S	S	-	S	-	-	-
A first unprovoked VTE at any age	-	S	-	-	-	-	-
A history of recurrent VTE	S	S	-	S	-	-	-
Venous thrombosis at unusual sites	S	S	-	S	-	-	-
VTE during pregnancy	S	S	-	S	-	-	-
VTE during the puerperium	-	S	-	S	-	-	-
VTE associated with use of OC	S	S	-	S	-	-	-
VTE associated with HRT	-	S	-	M	-	-	-
Relatives of individuals with venous thrombosis under age 50	S	-	-	-	-	-	-
A first VTE in an individual with a first degree family member with VTE before age 50	S ^e	S	-	S ^e	-	-	-
Women with unexplained fetal loss after 10 weeks gestation	M	S	-	-	S	-	-
Female smokers younger than age 50 years with an MI or stroke	S	M	-	-	-	-	-
Selected women with unexplained severe preeclampsia, placental abruption, or intrauterine growth restriction	M	M	-	-	-	-	-
A first VTE related to the use of tamoxifen or other SERMs	-	M	-	-	-	-	-
Individuals >50 years with a first provoked VTE in the absence of malignancy or an intravascular device	M	M	-	M	-	-	-
Asymptomatic adult relatives of probands with a known factor V Leiden mutation	M	-	-	M	-	-	-
Asymptomatic adult relatives of probands with a known factor V Leiden mutation, especially those with a strong family history of VTE at a young age (<50 years)	-	M	-	-	S	-	-
Asymptomatic female relatives of probands with a known factor V Leiden mutation who are pregnant or are considering pregnancy or OC use	M	M	-	-	-	-	-
Women with recurrent pregnancy loss	M	-	-	M	S	-	-
Individuals with any family member with VTE	-	-	S	M	S	-	S
Anyone	-	-	M	-	-	-	-
Personal history of VTE	-	-	-	-	S	-	S
Personal history of pulmonary embolism	-	-	-	-	S	-	S
Personal history of TIA or premature stroke	-	-	-	-	S	-	S
Personal history of peripheral vascular disease	-	-	-	-	S	-	-
Personal history of cerebral vein thrombosis	-	-	-	-	S	-	S
Women with premature MI	-	-	-	-	S	-	S
Prior to major surgery, pregnancy, OC use, or HRT if there is a personal or family history of thrombosis	-	-	-	M	S	-	-
Presence of another known genetic hypercoagulability in an individual with a history of thrombosis	-	-	-	-	S	-	-
Previous finding of activated protein C resistance by lab analysis	-	-	-	-	S	-	-

^a HRT = Hormone replacement therapy; MI = myocardial infarction; OC = oral contraceptives; SERMs = selective estrogen receptor modulators; TIA = transient ischemic attack; VTE = venous thromboembolism.

^b American College of Medical Genetics consensus recommendation published in Grody et al. [26].

^c College of American Pathologists consensus recommendation published in Press et al. [27].

^d S = Testing should be performed; M = testing may be considered; - = the indication was not specifically mentioned.

^e The wording of the recommendation specified a 'strong family history', which was not defined.

3 and 8 (table 3). The practices least likely to be used were (1) disclosure of the risks and limitations of testing and (2) information on the clinical validity of the test. The practices in Set 2 contain disclosures typically required by the FDA for products other than genetic tests (in the absence of FDA guidance explicitly for DTC genetic tests),

including risks and benefits of testing and 'adequate provision ... for dissemination of the approved or permitted package labeling', such as referral to a physician for more information. Furthermore, the FDA typically requires 'fair balance' in the portrayal of risks and benefits of the product. Of the 7 practices in Set 2, only company B im-

Table 6. Risks, benefits, and limitations of factor V Leiden testing

	ACMG ^b	CAP ^c	DTC company ^d					
			A	B	C	E	F	
Benefits of factor V Leiden testing^a								
identification of high-risk patients who could benefit from long-term anticoagulant therapy	+	+	-	-	-	-	-	
identification of high-risk patients who could benefit from aggressive prophylaxis in temporary periods of high thrombotic risk	+	+	-	-	-	-	-	
opportunity to counsel at-risk family members about risks, signs, and symptoms of VTE	+	+	-	-	-	-	-	
future decisions regarding HRT could depend on genotype	-	+	-	+	-	-	-	
future decisions regarding management of pregnancy complications could depend on genotype	+	+	-	+	-	-	-	
future decisions regarding OC use could depend on genotype	+	+	-	+	-	-	-	
to have greater control over your health care	-	-	+	+	-	-	-	
to provide you with tools to live a longer, healthier life	-	-	+	-	-	-	-	
future decisions regarding health-enhancing strategies could depend on genotype	-	-	+	-	-	-	-	
future decisions regarding lifestyle changes could depend on genotype	-	-	+	+	-	-	-	
provide a customized risk assessment	-	-	+	+	-	-	-	
Risks and limitations of factor V Leiden testing								
test does not predict thrombosis with certainty	-	+	-	-	-	-	-	
implications for other family members	+	-	-	-	-	-	-	
possibility of genetic discrimination	+	+	-	+	-	-	-	
positive test results could lead to overly aggressive anticoagulation in situations with relatively low thrombotic risk	-	+	-	-	-	-	-	
individual could have increased risk for thrombophilia from another cause not detected by this test	-	-	-	-	-	-	-	
individuals could have psychological, medical, social, and reproductive implications due to testing, but counseling is not needed	-	-	+	-	-	-	-	
the cost of testing may not be covered by insurance	-	-	-	+	-	-	-	
the results of testing may not change the medical care or lifestyle of the subject	-	-	-	+	-	-	-	
results of test could reveal non-paternity	-	-	-	+	-	-	-	
^a HRT = Hormone replacement therapy; OC = oral contraceptive; VTE = venous thromboembolism. ^b American College of Medical Genetics consensus recommendation published in Grody et al. [26]. ^c College of American Pathologists consensus recommendation published in Press et al. [27]. ^d + = The risk or benefit was specifically mentioned; - = the risk or benefit was not mentioned.								

plemented all 7 (table 3), with the other companies implementing between 3 and 6. Only company B provided information on both risks and benefits of testing. Information on test limitations and information on clinical validity were the least likely practices to be implemented. We note that this information is also frequently unavailable for genetic tests that are marketed to providers. We evaluated the presence or absence of particular practices on the Web sites, but that does not speak to the accuracy of the information provided. Therefore, we evaluated the accuracy of information provided on the sites on indications for testing, risks, and benefits by using published guidance documents for these tests.

The 2 professional organizations (ACMG, CAP) had good agreement for the recommended indications for

testing (proportion agreement = 0.73) (table 5). In contrast, the company Web sites demonstrated relatively poor agreement with the recommended indications from the professional organizations. In general, the Web sites used simplified language that tended to broaden the class of persons for whom testing was indicated. Some examples of this pattern include ‘individuals with any family member with venous thromboembolism (VTE)’ (from the Web site) vs. ‘relatives of individuals with venous thrombosis under age 50’ (from the recommendation), or ‘women with premature MI’ (myocardial infarction) (from the Web site) vs. ‘female smokers younger than age 50 years with a MI or stroke’ (from the recommendation), or ‘a personal history of VTE’ (from the Web site) vs. ‘a first VTE before age 50 years’ (from

Table 7. Inter-rater agreement on initial classification in each table

	Proportion agreement	Kappa statistic (CI)	Class-specific proportion agreement ^b		
Table 3 ^a	0.676				
Table 4 – Genes	0.917	0.86 (0.67, 1.00)	0.86 (Y)	0.75 (N)	1.00 (NA)
Table 4 – Polymorphisms	0.933	0.89 (0.75, 1.00)	0.92 (Y)	0.60 (N)	0.93 (NA)
Table 5 – Recommendations	0.917	0.86 (0.75, 0.98)	1.00 (S)	0.64 (M)	0.85 (–)
Table 5 – Web sites	0.933	0.81 (0.70, 0.92)	0.80 (S)	0.50 (M)	0.92 (–)
Table 6 – Benefits, Recommendations	0.962	0.92 (0.77, 1.00)	0.91 (Y)	0.94 (N)	
Table 6 – Benefits, Web sites	0.846	0.55 (0.30, 0.79)	0.87 (Y)	0.96 (N)	
Table 6 – Benefits, Web sites A & B only	0.615	0.23 (0.00, 0.61)	0.87 (Y)	0.85 (N)	
Table 6 – Risks, Recommendations	0.722	0.21 (0.00, 0.89)	0.17 (Y)	0.71 (N)	
Table 6 – Risks, Web sites	0.956	0.78 (0.48, 1.00)	0.67 (Y)	0.95 (N)	
Table 6 – Risks, Web sites A & B only	0.889	0.73 (0.38, 1.00)	0.67 (Y)	0.86 (N)	

CI = 95% Confidence interval.

^a Statistics were not computed for Table 3 because there were different response categories for each line in the table.

^b Y = Yes; S = should; N = no; M = maybe; NA = not available; – = the indication was not specifically mentioned.

the recommendation). In some instances, the Web sites provided little or no guidance about who should receive testing (e.g., companies A and E), and in 3 out of 5 instances there was no overlap between the recommended indications from the professional organizations and the indications from the Web sites. Company C included only 3 of the 19 indications from the professional recommendations, and it included 10 additional indications that were not in the professional recommendations. Overall, company B had the highest agreement with the recommended indications of testing (proportion agreement = 0.6 with ACMG and 0.7 with CAP). We note, however, that the indications for testing were difficult for us to find on this Web site, which might be a point for a future study.

We found strong agreement between the ACMG and CAP recommendations on the risks and benefits of testing (proportion agreement = 0.81) (table 6). Three of the distributors, however, did not mention any risks and benefits of testing, and only one (company B) mentioned risks and benefits that overlapped with the professional recommendations. We should note that in some instances the differences in the portrayal of benefits and risks may be related to the DTC delivery mode, as the focus of the professional recommendations is the traditional delivery of genetics services through medical settings. For example, the DTC Web sites emphasized having ‘greater control over your health care’ and making ‘lifestyle changes’, which do not depend on interaction

with a physician. In other instances, however, the benefits of testing mentioned by the distributor may be misleading, such as ‘provide you with tools to live a longer, healthier life.’

The lack of initial classification agreement between 2 independent raters in some categories could suggest that in many instances the information provided by the distributors was not clear or easy to find, or could indicate a need to further define the criteria (table 7). There was good agreement ($\kappa > 0.8$) in the initial classification for disclosure of the genes and polymorphisms tested (table 4), for the indications of testing (table 5), and for the benefits of testing identified by professional organizations (table 6). In contrast, the initial classification by the 2 raters had poor agreement ($\kappa < 0.8$) for the risks and benefits identified on the Web sites and for the risks identified by the professional organizations (table 6). The level of inter-rater agreement depended on the response category. For the indications for testing (table 5), the proportion agreement was lowest when testing might be indicated (category M in the table). For the risks and benefits of testing (table 6), the proportion agreement was lowest in the ‘yes’ category (+ in the table), indicating that when statements of risks and benefits were present, they were not always clear, while it was clear when statements on risks and benefits were absent. All of the information reported in the tables reflects the consensus after review of the discrepancies by the 2 raters and a third evaluator.

Discussion

Our results clearly demonstrate that the number of health-related DTC genetic tests is increasing at a fast pace, similar to the expansion of DTC advertising for other medical products. The availability of health-related DTC genetic tests grew from 14 tests in 2003 [14] to 84 instances (or 53 unique tests) as of August 2007. These results are not the whole story, however. Our study was restricted to health-related DTC genetic tests that were currently available, but we identified numerous products that were in the pipeline as well as products that were previously available but are no longer sold DTC (data not shown). In addition, our scans may have been incomplete, because the wealth of information on the Internet made it difficult to exhaustively search and identify these products. Finally, our analysis was restricted to health-related tests, while non-health-related genetic-based products may, in fact, represent the majority of DTC genetic testing that is currently available [14]. Nevertheless, our findings represent at least 53 well-documented examples of health-related DTC genetic testing products, and there could be more.

This study was also designed to evaluate the quality of information provided on the Web sites of test distributors. Compared to professional recommendations for DTC marketing of genetic tests, the information provided by the majority of distributors of thrombosis testing was either not present or uniquely different. All of the Web sites used fewer than half of the 13 practices in Set 1 identified from guidance documents by professional organizations, and only one company used all 7 practices in Set 2 (i.e., practices either typically required by the FDA or used by 4 or more Web sites). In addition, the presentation of indications for testing and of risks and benefits of testing did not generally agree with existing recommendations. The indications for testing on the Web sites tended to overstate the need for testing when viewed against the consensus-based recommendations, and most Web sites were silent regarding the risks and benefits of testing. Unfortunately, where these issues were addressed, there was not much overlap with the risks and benefits identified in the recommendations. This latter result may be at least partially explained by the DTC focus of the Web sites, which contrasts with the focus of the recommendations on the traditional medical genetics model. These results indicate discrepancies between the recommendations and current practice for some health-related DTC genetic tests, and they highlight potential problems that need further clarification

by the professional or federal organizations that conduct oversight activities.

In the absence of regulation of DTC genetic testing, mechanisms for oversight are important for establishing good practices in this area, such as the recently published ASHG policy statement on DTC genetic testing [3]. However, existing policy statements by professional organizations express a variety of opinions, ranging from banning all DTC genetic testing to requiring federal regulation of all such testing. These differences may reflect the diverse perspectives of the respective organizations that have proposed such recommendations. For example, ACMG's statement places a greater emphasis on requiring pre- and post-test counseling and referrals to genetics professionals. Because of this lack of consensus, we evaluated 2 sets of criteria (table 2) and found generally low compliance with both sets among the test distributors we evaluated. A recent report by the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) identified several gaps in existing oversight of genetic tests [32]. These recommendations include requiring proficiency testing for all non-waived laboratory tests for which materials are available to address the issue of analytic validity, that a mandatory, publicly available registry of laboratory tests should exist, that the FDA should address all laboratory tests, that a research agenda should be developed to address the issue of clinical utility, and that the educational needs of health professionals should be met, including the development of clinical decision support tools.

We should approach the interpretation of this study with caution for several reasons. First, the requirements for the type of information that should be provided by DTC genetic test distributors are not well defined, and indeed, the various professional recommendations on DTC genetic testing are inconsistent. Although we used several resources to identify recommended practices, the sets of criteria are subjective, maybe incomplete, and do not represent the view of any one organization. Second, in the case of risk for thrombosis in particular, the published recommendations are not based on a systematic review of the evidence and, instead, are based on consensus conferences and expert opinion (although a substantial literature review was included to develop the recommendations). Moreover, the recommendations may have preceded the era of DTC genetic testing to some extent, and they may not have carefully addressed all of the issues (especially risks and benefits) that are specific to the DTC mode of delivery. Therefore, the answer in terms of indications for testing, and risks, benefits, and limita-

tions of testing remains an open question. A final concern is that the practices of only a few DTC genetic test distributors were observed, and generalization to other Web sites or products may not be appropriate. However, these distributors tended to offer more tests (mean = 8.2; median = 5) than all 27 distributors identified in our search considered as a group (mean = 1.7; median = 1) and, as such, may represent the more established and experienced distributors.

A major implication of this study is the need to generate greater consensus within the scientific and medical community on recommendations to increase the impact of and compliance with the recommendations. Consensus recommendations may need to incorporate a broader range of stakeholders representing diverse perspectives. However, even if recommendations for DTC genetic testing were very clearly delineated today, implementation of such guidelines is still a problem. Until the evidence base for the validity and utility of genetic tests is well established and in the public domain, it will not be possible to ensure the accuracy of claims made about health-related DTC genetic testing products.

Achieving these goals will require greater investment in translation research for genetic discoveries in general [33] and better reporting mechanisms to include such information in the public domain. Evaluation and synthesis of the body of evidence supporting each genetic test will be critical given the lack of formal regulation and the inconsistent application of informal review for DTC genetic tests (e.g., by professional organizations, health insurers, expert opinion, consensus conference, or individual physicians) [34]. The complexity of the information means that such analyses need to be provided in a user-friendly format for both health professionals and consumers. Although neutral, respected groups already exist to commission systematic evidence-based reviews and assess the quality of evidence, such as the US Preventive

Services Task Force (USPSTF) or the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, these processes are non-regulatory, and given their limited resources, they must prioritize the review of the existing genetic tests. Development of clinical recommendations, whether evidence-based or expert/consensus, should consider potential differences in the balance of benefits and harms (clinical utility) based on the mode of test delivery. For example, access to interventions following testing may differ depending on whether the test is conducted in a clinical setting or in a DTC setting.

In summary, the field of health-related DTC genetic testing is rapidly growing. Until now, there has been very little concrete data on compliance with recommended practices for DTC genetic testing. As this example illustrates, measuring and maintaining compliance with recommended practices is complicated by inconsistent recommendations from professional organizations. Establishing greater agreement in recommendations could lead to a greater responsibility to comply with those recommendations and improvement in the oversight of DTC genetic testing. Our findings highlight the urgent need for oversight, for greater consensus in recommendations for health-related DTC genetic tests, for greater responsibility on the part of DTC companies to comply with recommended practices, and for the development of improved resources for health care providers and consumers to assess existing tests.

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References

- 1 American College of Medicine Genetics Board of Directors. ACMG statement on direct-to-consumer genetic testing. *Genet Med* 2004;6:60.
- 2 National Society of Genetic Counselors Position Statement on Direct to Consumer Genetic Testing. Available at www.nsgc.org/about/position.cfm#DTC. Accessed on March 10, 2008.
- 3 Hudson K, Javitt G, Buke W, Byers P, American Society of Human Genetics Social Issues Committee: ASHG statement on direct-to-consumer genetic testing in the United States. *Am J Hum Genet* 2007;81:635–637.
- 4 Wolfberg AJ: Genes on the Web—direct-to-consumer marketing of genetic testing. *N Engl J Med* 2006;355:543–545.
- 5 Gray S, Olopade OI: Direct-to-consumer marketing of genetic tests for cancer: buyer beware. *J Clin Oncol* 2003;21:3191–3193.
- 6 McCabe LL, McCabe ER: Direct-to-consumer genetic testing: access and marketing. *Genet Med* 2004;6:58–59.
- 7 United States Government Accountability Office. Nutrigenetic testing: Tests purchased from four Web sites mislead consumers. Testimony to the US Senate Special Committee on Aging. GAO Document GAO-06-977T. GAO-06-977T. 2006. Washington, D. C., US Government Accountability Office. Available at <http://www.gao.gov/new.items/d06977t.pdf>.

- 8 Javitt GH: Pink or blue? The need for regulation is black and white. *Fertil Steril* 2006;86:13–15.
- 9 Hull SC, Prasad K: Reading between the lines: direct-to-consumer advertising of genetic testing in the USA. *Reprod Health Matters* 2001;9:44–48.
- 10 Kessler DA, Levy DA: Direct-to-consumer advertising: is it too late to manage the risks? *Ann Fam Med* 2007;5:4–5.
- 11 Gilbody S, Wilson P, Watt I: Benefits and harms of direct to consumer advertising: a systematic review. *Qual Saf Health Care* 2005;14:246–250.
- 12 Stange KC: Time to ban direct-to-consumer prescription drug marketing. *Ann Fam Med* 2007;5:101–104.
- 13 Vastag B: US aims to tighten rules on direct-to-consumer drug ads. *Nat Biotechnol* 2007;25:267.
- 14 Gollust SE, Wilfond BS, Hull SC: Direct-to-consumer sales of genetic services on the Internet. *Genet Med* 2003;5:332–337.
- 15 Chin KM, Wessler B, Chew P, Lau J: Technology Assessment: genetic tests for cancer. 290-02-0022. Agency for Healthcare Research and Quality, 2006. Available at <http://www.ahrq.gov/clinic/ta/genests/genests.pdf>.
- 16 Secretary's Advisory Committee on Genetic Testing. Enhancing the oversight of genetic tests: recommendations of the SACGT. Bethesda, Md, National Institutes of Health, 2000. Available at http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf.
- 17 Quality assurance and proficiency testing for molecular genetic testing: summary results of a survey of 18 OECD member countries. OECD, 2005. Available at <http://www.oecd.org/dataoecd/25/12/34779945.pdf>.
- 18 Andersson HC, Krousel-Wood MA, Jackson KE, Rice J, Lubin IM: Medical genetic test reporting for cystic fibrosis (deltaF508) and factor V Leiden in North American laboratories. *Genet Med* 2002;4:324–327.
- 19 Krousel-Wood M, Andersson HC, Rice J, Jackson KE, Rosner ER, Lubin I: Physicians' perceived usefulness of and satisfaction with test reports for cystic fibrosis (DeltaF508) and factor V Leiden. *Genet Med* 2003;5:166–171.
- 20 Reich LM, Bower M, Key NS: Role of the geneticist in testing and counseling for inherited thrombophilia. *Genet Med* 2003;5:133–143.
- 21 Guidance for industry: Consumer-directed broadcast advertisements. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Veterinary Medicine (CVM), 1999. Available at <http://www.fda.gov/cder/Guidance/1804fnl.htm>.
- 22 Guidance for industry: Brief summary: Disclosing risk information in consumer-directed print advertisements. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER), 2004. Available at <http://www.fda.gov/cber/gdlns/consumad.htm>.
- 23 Guidance for industry: Industry-supported scientific and educational activities. U.S. Department of Health and Human Services, Food and Drug Administration, 1997. Available at <http://www.fda.gov/Cder/guidance/isse.htm>.
- 24 Dietary Supplements: An advertising guide for industry. Federal Trade Commission, 2001. Available at <http://www.ftc.gov/bcp/online/pubs/buspubs/dietsupp.pdf>.
- 25 Federal Trade Commission fact sheet on at-home genetic tests: A healthy dose of skepticism may be the best prescription. Available at <http://www.ftc.gov/bcp/edu/pubs/consumer/health/hea02.pdf>. Accessed October 15, 2007.
- 26 Grody WW, Griffin JH, Taylor AK, Korf BR, Heit JA: American College of Medical Genetics consensus statement on factor V Leiden mutation testing. *Genet Med* 2001;3:139–148.
- 27 Press RD, Bauer KA, Kujovich JL, Heit JA: Clinical utility of factor V Leiden (R506Q) testing for the diagnosis and management of thromboembolic disorders. *Arch Pathol Lab Med* 2002;126:1304–1318.
- 28 Koster T, Rosendaal FR, de Ronde H, Briet E, Vandenbroucke JP, Bertina RM: Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. *Lancet* 1993;342:1503–1506.
- 29 Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH: Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994;369:64–67.
- 30 Poort SR, Rosendaal FR, Reitsma PH, Bertina RM: A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* 1996;88:3698–3703.
- 31 Den Heijer M, Lewington S, Clarke R: Homocysteine, *MTHFR* and risk of venous thrombosis: a meta-analysis of published epidemiological studies. *J Thromb Haemost* 2005;3:292–299.
- 32 U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services, 2008. Available at http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf. Accessed on July 22, 2008.
- 33 Khoury MJ, Gwinn M, Yoon PW, Dowling N, Moore CA, Bradley L: The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genet Med* 2007;9:665–674.
- 34 Hudson KL, Murphy JA, Kaufman DJ, Javitt GH, Katsanis SH, Scott J: Oversight of US genetic testing laboratories. *Nat Biotechnol* 2006;24:1083–1090.