The on-line promotion and sale of nutrigenomic services

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Purpose: Nutrigenomic researchers hope to improve health through personalized nutrition, but many consider the sale of nutrigenomic services to be premature. Few studies have evaluated the promotion and sales practices of organizations hosting nutrigenomic websites. **Methods:** Systematic search and analysis of websites promoting nutrigenomic services in October 2006. **Results:** Of the 64 organizations hosting websites, 29 organizations offered (24 of 29) or promoted (5 of 29) at-home testing and 26 organizations sold services on-line (17 of 26) or provided a direct link to on-line sales (9 of 26). A lack of transparency made it difficult to identify unique tests; however, three organizations were linked to 56% of all test mentions. Most organizations were healthcare/wellness service providers (50%) or laboratories/biotech companies (27%). Few organizations provided on-line information about laboratory certifications (20%), nutrigenomic test or research limitations (13%), test validity or utility (11%), or genetic counseling (9%). Affiliation opportunities were offered by 15 organizations. **Conclusions:** Organizations did not provide adequate information about nutrigenomic services and at-home genetic testing. Affiliation opportunities and distribution agreements suggest the promotion and sale of nutrigenomic services will continue, increasing the importance of consumer and provider education. In absence of federal regulation, organizations promoting nutrigenomic services should equate websites to product labels and include information to facilitate informed decision-making. ***Genet Med* 2008:10(11):784–796.**

Key Words: *nutrigenomic services, at-home genetic testing, direct-to-consumer marketing, internet, policy*

Nutrigenomics (NG) examines relationships among genes, diet, and health. Specifically, NG research is "the study of how foods affect the expression of genetic information in an individual and how an individual's genetic makeup affects the metabolism and response to nutrients and other bioactive components in food."[1] Included among the aims of NG research are to: (1) identify genes and gene variants that may be significant in understanding genetic responses to diet, (2) identify genotypes associated with diet-related disease, (3) modify diet for the treatment or prevention of disease, and (4) improve dietary guidelines at group and individual levels.[2–5]

Although there is growing expectation that NG research will improve individual and group health through personalized nutrition,[6,7] the field faces several methodological challenges. Some of these challenges include: (1) defining and measuring dietary intake; (2) shifting outcomes of interest from actual disease to biomarkers indicating early stages of disease; (3) simultaneously analyzing genetic, molecular, clinical, phenotypic, and dietary data to account for the full effects of food; (4) conducting longitudinal studies with large, diverse populations for adequate statistical power; and (5) addressing bias toward positive findings in the publication of NG research.[8–11] These and other challenges contribute to inconsistent findings across genetic association studies and complicate the development of NG interventions to improve individual health.[12]

Despite these challenges, biotechnology companies and laboratories (here forward companies) are offering genetic services based on findings from NG research. These services include NG tests for variants in several genes associated with diet-related disease or other health conditions that have multiple causes, such as heart disease, diabetes, and osteoporosis. Companies also offer supplement, diet, and lifestyle recommendations based on NG test results and other health-related information (e.g., smoking status, exercise habits, family history of disease). Like the majority of commercially available genetic services, NG services are sold as laboratory services, whereby the laboratory uses an in-house protocol to analyze patient or consumer specimens and prepare a report of test results. Unlike in vitro diagnostic "test kits" that are manufactured and labeled with instructions for a specific clinical use by multiple laboratories, laboratory services are not currently regulated by the US Food and Drug Administration (FDA), including their validity, utility, branding, and marketing.[13] Furthermore, regulations and policies pertaining to laboratory and

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testding standards, informed consent, and direct-to-consumer (DTC) sale in the delivery of genetic services vary by state.[14,15]

The US Government Accountability Office (GAO) investigated the legitimacy of claims made by companies with DTC marketing of NG services in June 2006. The GAO reported that the NG services provided by four companies were "meaningless and potentially harmful to consumers."[16] This investigation prompted the US Federal Trade Commission (FTC) to release a fact sheet advising consumers and health practitioners to review advertisements for at-home genetic tests with "a healthy dose of skepticism."[17] The fact sheet noted that no at-home genetic tests have been reviewed by the FDA and discussed several important caveats to genetic testing as follows: (1) some genetic tests lack scientific validity, (2) genetic testing should be performed by specialized laboratories, (3) genetic test results are complex and require expert interpretation, and (4) genetic test results are meaningful only in the context of a complete medical evaluation. In addition, consumers were advised to review company privacy policies.

NG services are largely marketed on the internet. Results from four internet searches for websites selling health-related genetic (HG) services directly to consumers have been published to date.[18–21] These studies found websites to provide inadequate levels of information regarding the diseases tested, risks associated with genetic testing, efforts to protect consumer privacy, or the management or destroying of specimens post-testing. The lack of information was of particular concern given limited availability of genetic counseling services.

Studies to date have focused on the on-line DTC sale of HG tests by companies, some of which include NG services. Relatively less attention has been paid to the marketing and sales practices of other types of organizations that serve as intermediaries between consumers and companies or promote the use of NG services. In addition, previous studies have not focused on the types of NG services promoted on-line (e.g., conditions and traits, genes profiled, recommendations provided) and the frequency of their promotion.

Given the potential of NG research to improve health, the inadequate oversight of NG services, and gaps in information about the promotion and sale of NG services on-line, this study seeks to answer the following research questions: Who is involved in the on-line promotion and sale of NG services? What types of NG services are promoted? To what extent do websites provide information addressing important caveats about at-home genetic testing identified by the FTC?

MATERIALS AND METHODS

Search for organizations promoting NG services

The search strategy was designed to capture the population of organizations that promoted or sold NG services on-line in the months following release of the FTC fact sheet regarding at-home genetic testing. To be eligible for inclusion, organizations had to host at least one publicly-accessible website with a unique domain name (i.e., address that identifies a site on the internet) promoting or selling at least one NG service. An organization was considered to promote NG services on-line if services could be purchased from the organization, the primary content of its website included traditional advertising features (e.g., prominent product placement, cost information, persuasive messages, sponsor information), or its website directed readers to another website selling NG services. Organizations were considered to sell NG services on-line if consumers could purchase NG services by entering their contact, delivery, and payment information on its website (e.g., on-line shopping cart, order form).

A pilot study was conducted to identify a practical number of search terms, similar to previous studies.[22] As illustrated in Figure 1, 25 terms were used to search the web using Google. All uniform record locators (URLs) listed in the first five pages of results (10 URLs per page) for each search were followed. Web pages were coded for primary content and 26 promoted or sold at least one NG service. All 26 websites were captured by nine terms and selected for inclusion in a broader systematic search. To identify additional terms, the HyperText Markup Language (HTML) code for each relevant website was searched for metatags (i.e., optional codes that identify webpage content in search engine indexes). Eleven new terms related to genetics, diet, and testing were selected for inclusion in the final search.

The systematic search was conducted in October 2006 using 20 terms and the three most popular search engines by share of total visits: Google, Yahoo, and MSN.[23] For each of the 60 independent searches, all URLs appearing on the first three pages of results (up to 10 URLs per page) were followed and coded for web page content (including any sponsored links or advertisements). For each relevant URL, Internet Researcher by Zylox Software, Inc. was used to save web pages under the domain name. To determine how many websites continued to promote NG services when submitting this manuscript for review, relevant domains were search for on-line in March 2008.

Content analysis of websites

Methods proposed by Riffe et al.[24] for the content analysis of media messages were followed. First, variables of interest were selected after review of: (1) websites identified in the pilot study, (2) data collection forms used in one published[19] and one unpublished study (Lubin I, unpublished data) of genetic services promoted on-line, (3) the FTC consumer fact sheet regarding at-home genetic testing, and (4) other internet content analysis studies. Selected variables included: (1) organization characteristics (i.e., name, organization type, geographic location, laboratory accreditation, ownership, privacy policies, staff mix, other services provided, affiliation with other NG service providers, at-home testing, on-line sale), (2) NG service characteristics (i.e., commercial name, trademark and registration symbols, purpose of test, health conditions evaluated, genes evaluated, evidence regarding test validity, medical evaluation or consultation services, cost, FDA review), and (3) other website characteristics (i.e., on-line shopping carts, links to other organizations selling NG services, date stamps, logos or seals of approval or certification).

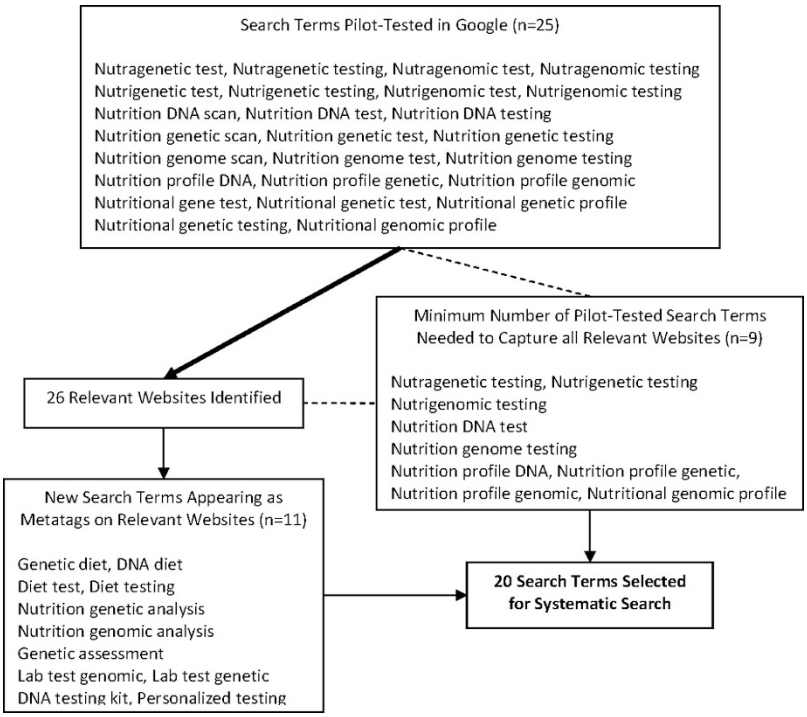

Fig. 1. Pilot study to select search terms to identify websites promoting or selling nutrigenomic services.

Second, a codebook establishing definitions and coding rules for all variables of interest was used to train one research assistant (RA). Electronic data collection forms (i.e., code sheets) were pilot tested and refined by the author (RS) and research assistant using five websites varying in host organization type, services promoted, and website complexity. Remaining websites were coded independently by RS (all websites) and the RA (60% of websites). Established variable definitions were refined periodically (every 6–10 websites) in face-to-face meetings between RS and the RA to incorporate newly identified characteristics. Open-coding was used to collect health conditions focused on and genes profiled. Health conditions were defined liberally to include illness, disease, risk factors for disease, and physical traits or abilities associated with age or health status. All saved pages of each website were reviewed, including pages targeted to physicians. After completion of all coding, any differences were discussed until a final agreement was reached.

Data were collected and analyzed in Microsoft Access 2007. To capture variation in the promotion and sale of NG services, the unit of analysis was a NG test mentioned on a particular website. Therefore, if seven different websites mentioned the same NG test, then seven observations were added to the dataset. Similarly, if one website mentioned five different NG tests, then five observations were added to the dataset. Each NG test was linked to the website on which it was mentioned. Each website was linked to its host organization.

Health conditions mentioned in NG test descriptions were searched in the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Version for 2007* (ICD-10)[25] to determine whether or not the condition, as named on each website, fit into standard diagnostic (Dx) nomenclature. Gene names or symbols mentioned in test descriptions were searched in the National Center for Biotechnology Information (NCBI) Entrez Gene database to determine whether or not genes, as named on each website, fit into standard gene nomenclature.[26]

RESULTS

The systematic search for websites promoting and selling NG services resulted in 2135 URLs eligible for review (see Fig. 2), including up to 30 URLs per search in main results (one term resulted in <30 URLs) and a variable number of sponsored links or advertisements per search (range from 1 to 26). The majority of URLs (70%, 1492/2135) did not sell or promote a health-related product or service. Health-related products or services were sold or promoted on 643 URLs, and 85% (551/643) of these URLs mentioned a genetic-related product or service. Half (276/551) of the URLs promoting a genetic-related product or service did not mention NG services. These URLs promoted social-related genetic (SG) testing (e.g., genealogy, ancestry, prenatal sex determination, semen detection and infidelity testing, DNA storage); HG testing that did not highlight associations among diet, genes, and disease (e.g., pharmacogenetic testing for cytochrome P450 2D6, genetic screening for sickle-cell disease, *BRCA1/2* testing for breast cancer); or other genetic services (e.g., animal sex or pedigree testing, genetic technologies, DNA analysis, etc).

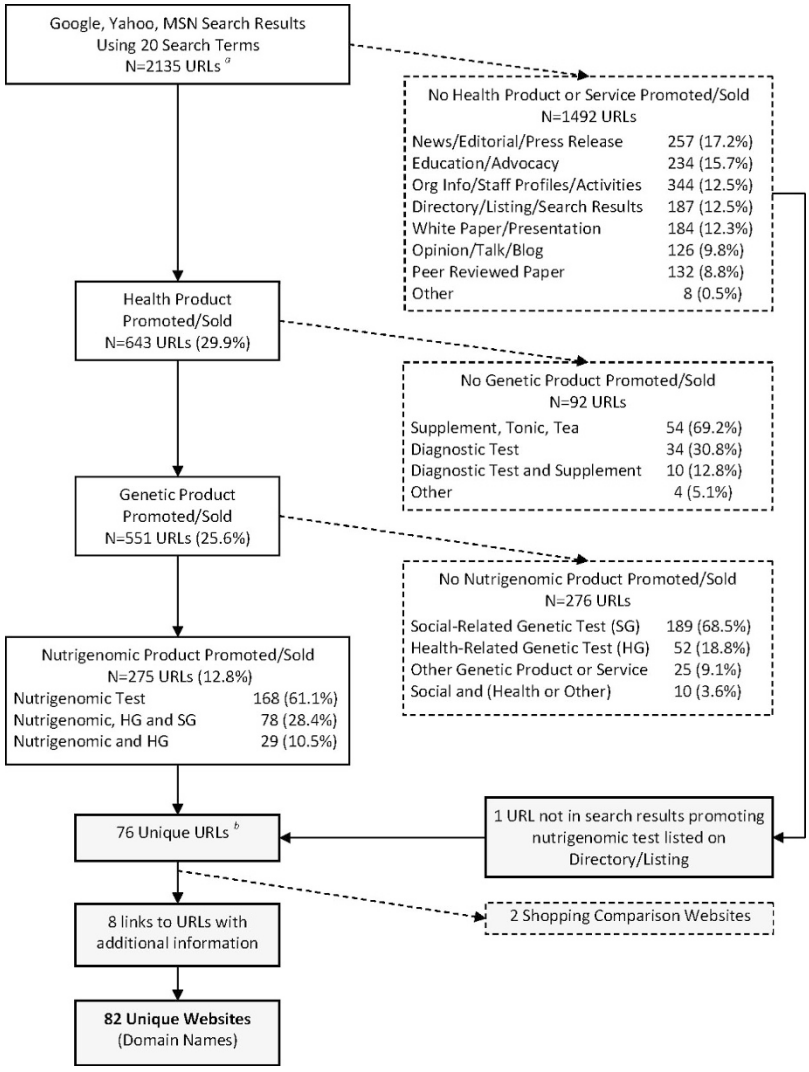

Fig. 2. Systematic search results for websites promoting and selling nutrigenomic services and website selection, October 2006. [a]Excludes 16 uniform record locators (URLs) whose primary webpage content could not be determined. Includes URLs appearing in main search results and listed as sponsored advertisements. [b]Values presented in shaded boxes do not include duplicate URLs. All other values include duplicate URLs.

NG services were mentioned on 275 URLs, 39% of which also promoted SG or HG testing. After eliminating duplicates, 76 URLs remained. Of these URLs, two presented search results from comparison shopping websites (i.e., NexTag, Inc., PriceGrabber.com, Inc.) providing minimal information about NG services (i.e., product name, truncated description, cost) and direct links to another URL appearing in search results. These two URLs were excluded. The 74 remaining websites included eight links to separate domains providing additional information about the host organization or its services. With the inclusion of these links, the final sample included 82 unique domains or websites.

Organizations promoting NG services

The 82 identified websites were hosted by 64 organizations (see Supplemental Table 1 for complete listing and select characteristics), one of which was not-for-profit. At-home testing was offered by 24 organizations (defined here when a consumer could purchase or order a NG test at home and receive test results directly with no explicit requirement for consultation with a health practitioner or genetic counselor, on- or off-staff, pre- or post-testing). Five other organizations provided a direct link to one of these 24 organizations on its website.

Ten organizations did not have a location within the US and did not mention any residency requirements for testing. Residency requirements or state-specific conditions for NG testing (e.g., test requisition by licensed physician, general reference to state-specific restrictions) were mentioned by eight US-based organizations. Where mentioned, locations in which residents could not test or had to satisfy special requirements included New York (6/8), New Jersey (1/8), Rhode Island (1/8), Massachusetts (1/8), Canada (1/8), and the United Kingdom (2/8).

To suggest its safety, trustworthiness, or popularity, 14 organizations placed one or more stamps on their website, including professional society seals (3/14), TRUSTe (4/14) and

HONcode (1/14) logos,[27,28] awards for quality of content (2/14), and logos for technical as features such as privacy protection (4/14) and registration of domain name (1/14). Affiliation, distribution, and private labeling opportunities targeted to health professionals and independent entrepreneurs seeking to start an internet business were mentioned on 15 websites.

Half of the organizations identified in the search (32/64) provided healthcare or wellness (HW) services (e.g., physical exams, Dx tests for nongenetic biomarkers, digital infrared thermal imaging, acupuncture, spiritual retreats, medical spa services), of which 41% (13/32) listed a naturopathic doctor as staff, 34% (11/32) listed a medical doctor (MD), 25% (8/32) listed a nutritionist or dietician, and 16% (5/32) listed a chiropractor. Seven HW service providers did not mention the source of testing on their website, two being medical centers with in-house laboratories. Twenty-seven percent (17/64) of identified organizations were companies (to include biotech companies, laboratories, and testing facilities), most of which offered at-home testing (9/17, 53%). Across all organizations, one HW service provider and two companies listed a genetic counselor as staff, and one company listed "genetic trained advisors" as staff.

NG services were sold directly to consumers through on-line "shopping carts" on 17 websites hosted by seven companies, four HW service providers, five organizations classified as eVendors (i.e., not a biotech company or laboratory, no in-house NG services, no HW services, offer on-line sale), and one other promoter. Direct links to one or more of these 19 websites appeared on websites hosted by seven other organizations. The five organizations that allowed consumers to access their test results on-line also sold NG tests through on-line shopping carts.

Types of NG services promoted

NG tests

Websites included 167 mentions of NG tests using a specific commercial name or generic reference (e.g., genomic testing). The majority of organizations (67%, 43/64) named up to three different NG tests (range, 1–8). In most cases, each test evaluated a different health condition or offered a different level of service (e.g., NG test results, NG test results with a weight loss plan, NG test results with clinical consultation). Several phenomena made it difficult to count the unique number of NG tests mentioned across websites as follows.

1. Organization without an in-house laboratory using different commercial names for what appeared to be the same test.
2. Multiple organizations without an in-house laboratory using very similar by not identical names for tests (e.g., DetoxGenomic Profile, DetoxiGenomic® Profile, DetoxicGenomic Profile).
3. Multiple companies offering a test with identical test descriptions or identical sample reports but different commercial names.
4. Organization without an in-house laboratory not mentioning the source of their test.
5. Company mentioning an organization without an in-house laboratory as a partner and the named partner not mentioning the company as the source of testing.
6. Organization without an in-house laboratory mentioning one company very prominently (e.g., website banner, direct link to shopping cart) and a second company less prominently (e.g., passing reference in response to frequently asked questions, mention in sample test report linked to website) as the source of testing.

Given this lack of transparency, two factors were used to identify the most frequently mentioned tests: (1) mention of company name or commercial test name, and (2) verbatim text or identical imagery in all or part of the test description.

Three organizations were linked to 56% (93/167) of all test mentions: GenovaDiagnostics®, Genelex Corp., and Sciona, Inc., all of which were identified in the search. By far, the most frequently and transparently mentioned NG tests (by 15 organizations) were Genovations™ Predictive Genomic Testing offered by GenovaDiagnostics®, formerly Great Smokies Diagnostic Laboratories. Offered tests included a CardioGenomicPlus® Profile, OsteoGenomic® Profile, DetoxiGenomic® Profile, ImmunoGenomic™ Profile, NeuroGenomic™ Profile, and EstroGenomic™ Profile.[29] The genes evaluated by Genovations™ were not mentioned by name and advertised as "carefully selected based on their relatively high prevalence in the general population, their clinical relevance to each health condition, and most importantly, their innate ability to be influenced by preventive interventions."[30]

All organizations mentioning Genovations™ on their website were HW service providers, with the exception of one consumer organization. GenovaDiagnostics® does not offer DTC sale of its NG services and interested consumers were encouraged to contact a physician for more information on the Genovations™ website. GenovaDiagnostics® reference to "physicians" may be broader than MDs as HW service providers who did not list a MD as staff also offered these tests.

The second most frequently mentioned NG test (by 10 organizations) was the Genetic Nutrition Analysis Panel offered by Genelex Corp. The panel is advertised to "optimize the health of your skin and bones; heart and mind by optimizing your personal diet and supplement intake . . . [The panel focuses on] seven areas in which the link between gene variations and lifestyle has been scientifically established, . . . including heart health, bone health, B Vitamin use, detoxification, antioxidants, inflammation, and insulin sensitivity."[31] The Genelex website "About Us" page stated that Sciona, Inc. supplied the analytical technology for its NG test.[32] This information was not mentioned on web pages providing detailed information about the test.

Six organizations mentioned Cellf™ Genetic Assessments offered by Sciona. The Cellf™ Genetic Assessment was promoted as one comprehensive assessment and/or five different

assessments for antioxidant and detoxification, bone health, heart health, inflammation, and insulin resistance. The comprehensive NG test was advertised by Sciona as "an at-home DNA collection kit for genetically-personalized nutrition and health assessment tool that will create a personalized diet and lifestyle report based on a scientific analysis of an individual's unique genetic profile, [so that] individuals can make their most important health decisions based not on fads, but on a personalized scientific roadmap."[33] Sciona (but not the Cellf™ Genetic Assessment) was mentioned in test descriptions appearing on two of the four websites affiliated with marketAmerica, Inc. and its partner, nutraMetrix™. No references to Sciona were found on the marketAmerica or nutraMetrix websites.

Health conditions and genes evaluated

The primary health condition evaluated by each NG test mentioned, as identified in the test name, appears in Table 1. Most test mentions (19%, 31/167) were for comprehensive assessments addressing several health conditions. Among tests focusing on one area of health, heart health was most common (16%, 27/167), followed by bone (11%, 19/167), immune system (11%, 18/167), detoxification (9%, 15/167), and general health and nutrition (8%, 13/167). Most NG test descriptions (80%, 133/167) mentioned more than one health condition, with an average of six conditions per description (range, 1–47).

Table 1
Primary area of health evaluated by nutrigenomic tests promoted or sold on-line, October 2006

Area of health identified in name of test	Tests[a], N (%)
Heart	27 (16.2)
Bone	19 (11.4)
Immune system	18 (10.8)
Detoxification	15 (9.0)
Nutrition (general reference to health/nutrition)	13 (7.8)
Antioxidant and detoxification	6 (3.6)
Oxidative stress	5 (3.0)
Nervous system	4 (2.4)
Inflammation	3 (1.8)
Athletics	2 (1.2)
Autism	2 (1.2)
Insulin sensitivity	2 (1.2)
Macular degeneration	2 (1.2)
Pregnancy	2 (1.2)
Aging	1 (0.6)
Cancer	1 (0.6)
Methylation cycle	1 (0.6)
Obesity	1 (0.6)
Comprehensive (multiple specific conditions)	31 (18.6)
Women's health comprehensive	6 (3.6)
Men's health comprehensive	4 (2.4)
Not clear (general reference to a genomic test)	2 (1.2)
Total	167 (100.0)

[a]Total test count includes all mentions of tests across websites, including multiple mentions of the same test on different websites.

Over 250 health conditions were mentioned across test descriptions, including multiple terms to reference the same or related conditions (e.g., heart health, heart attack, myocardial infarction, heart disease, cardiovascular disease [CVD], heart muscle cell growth). Almost all mentioned conditions could be assigned to an ICD-10 chapter. Ten conditions could not be assigned because the condition, as stated in the test description, was vague (e.g., "aging"), was mentioned in multiple ICD-10 chapters (e.g., "allergies"), or was not mentioned in any ICD-10 chapter (e.g., "DNA repair"). Five of the eight areas of health most often evaluated by NG tests (i.e., immune system, detoxification, antioxidant handling, inflammation, oxidative stress) could not be assigned using this standardized classification system.

Only 30 test descriptions (by 17 organizations) mentioned the genes evaluated by the test. A total of 85 gene names or symbols appeared in test descriptions, including six commercial gene symbols (e.g., *BH-2* or bone health gene, *OS-1* gene or oxidative stress-1 gene); and 15 gene symbols that were alias, but not official, gene symbols (e.g., *PAI-1* for *SERPINE1*, *MEPX* or *mETHX* for *EPHX1*). After replacing commercial or alias gene symbols with official gene symbols, 73 genes remained. A total of 256 associations were claimed between groups of related conditions (68 groups) and identified genes (see Supplemental Table 2 for list of conditions and associated genes).

Recommendations based on NG tests

Most organizations (73%, 47/64) mentioned that consumers could use test results to inform their own diet and lifestyle decision-making or provided consumers with specific recommendations. Illustrative of consumer empowerment in the use of test results, Quixtar, Inc. offered on-line DTC sale of the GENSONA™ Heart Health Genetic Test by Interleukin Genetics, Inc., which was advertised to identify "your genetic predisposition to certain types of heart disease. The results can help you determine what adjustments you may want to make in your nutrition, exercise, lifestyle, and healthcare practices."[34]

As a second example, Suracell, Inc. advertised a "DNA Profile test that identifies your hereditary genetic needs, a DNA Assessment urine test that measures levels of oxidative stress, and a recommended DNA repair and nourishment protocol" inclusive of supplements that are "designed to interact with five cellular processes that are key to wellness and aging: methylation, inflammation, glycation, oxidation, and DNA repair."[35] Of note, Suracell offered both NG and nongenetic Dx testing, and both tests were used to inform health and lifestyle recommendations for consumers. In total, 53% (34/64) of organizations promoted Dx tests, most of which were HW ser-

vice providers (76%, 26/34). These Dx tests evaluated areas of health similar to NG tests, some of which included serum homocysteine for heart health, toxin levels in hair for detoxification, free radicals in urine for antioxidant handling, type 1 collagen levels in urine for bone health, and serum food allergies for immune health. Five organizations promoted comprehensive health profiles that bundled Dx and NG tests or mentioned that results from Dx tests increased in utility when combined with NG test results. Six organizations bundled NG and pharmacogenetic tests.

Recommendations for dietary intake or supplementation were provided by 34 organizations, of which 41% (14/34) sold NG supplements or "nutraceuticals" and 18% (6/34) promoted NG supplements provided by another organization. One of these 34 organizations based its "nutritional supplement" recommendations on its Dx test and not its NG test. Eight other organizations sold or promoted supplements that were not marketed as NG supplements.

The standard FDA disclaimer (or similar variation) regarding supplements appeared on eight websites: "Statements regarding dietary supplements have not been evaluated by the US FDA and are not intended to diagnose, treat, cure, mitigate, or prevent any disease or health condition." Other supplement-related disclaimers appeared on four websites regarding the need to review package inserts, to consult a physician familiar with the brand of supplements, or to consult a physician before starting any supplement program. Six websites mentioned that statements regarding the NG test had not been evaluated or approved by the FDA.

Cost and coverage

Cost information was provided by 45% (29/64) of organizations. The average cost per NG service was $442.59, ranging from $89.99 for a single condition NG test sold on-line to $2,200.00 for a comprehensive NG test (i.e., osteoporosis, CVD risks, stroke, cancer, thrombosis, drug and nutrition metabolism) including "consultation and debriefing" with an unspecified person. On average, NG services offered by HW service providers were most expense ($529.81 per service), followed by companies ($409.81 per service).

Six organizations stated explicitly on their website that NG services were not covered by most health insurance plans, including four HW service providers, one organization promoting a service provider, and one company. Tests provided by these six organizations were slightly higher in cost than average (ranging from $449.00 to $700.00 where provided) and focused on a single condition. Eleven organizations provided billing information to consumers that could be used to request reimbursement from an insurance company, including 10 HW service providers and one company. Tests provided by these 11 organizations were lower in cost than average (ranging from $99.00 to $345.00), and all but one focused on a single condition.

FTC caveats for at-home genetic testing

As demonstrated in Table 2, a large majority of organizations promoting NG services did not provide information on their website(s) that would address caveats mentioned in the FTC fact sheet regarding at-home genetic testing; however, a greater proportion of organizations offering or promoting at-home NG testing did provide this information when compared with organizations not offering or promoting at-home NG testing.

Scientific validity of tests

Across organizations, information addressing scientific validity included references to published research with or without a specific citation (30%, 19/64), and the genes evaluated by the test (27%, 17/64). Only three organizations mentioned the specific gene variants evaluated by the test. In addition, seven organizations mentioned the analytical (i.e., how often the test accurately identifies the evaluated gene) or clinical validity (i.e., how often the test predicts the health condition associated with the evaluated gene) of their NG tests with varying degrees of detail.

CyGene Laboratories, Inc. mentioned that its tests were more than 99% accurate in genotype determination and made more general reference to clinical validity in stating "this [level of accuracy] does not mean that someone who is found to be at increased risk for a health concern will be affected."[36] Suracell also quantified the accuracy of its test as, "99.5% accurate. That means there are essentially no false positives for DNA deterioration or damage."[37]

Interleukin Genetics made general reference to research when describing the validity of their tests, noting that "individuals who are positive for one of these three IL1 genetic patterns have a lifelong tendency to over-express markers of inflammation. Individuals who test positive have been shown in multiple clinical studies to be at increased risk for early CVD. Individuals who test negative for the IL1 heart test have no known increased risk due to variations in their IL1 genes. These individuals may of course have increased risk for CVD due to other risk factors."[38]

Less specific information regarding validity was mentioned by five organizations referencing the quality of the test or laboratory analyzing the test. For example, Sanoviv Medical Institute described its NG test as, "highly accurate genetic diagnostic testing [that] can clearly pinpoint health risks which previously would have been lurking out-of-sight."[39] In answering a "frequently asked question" about the reliability of test results, The LabSafe Company mentioned that, "You can always be confident when testing with LabSafe, we use the leading national laboratories, which are fully accredited, licensed medical reference labs. LabSafe provides you access to the very same labs used by your physician."[40]

Laboratory qualifications

Thirteen organizations mentioned one or more specific approvals or certifications obtained by the laboratory analyzing the test, including Clinical Laboratory Improvement Act (CLIA) (8/13), American Association of Blood Banks (3/13), College of American Pathologists (1/13), Academy of Clinical, Environmental, Research and Information Services (1/13), and other international certifications (2/10 US organizations,

Table 2
Organizations presenting information on website addressing caveats raised in US federal trade commission (FTC) fact sheet regarding at-home genetic testing, October 2006

		Organizations providing information		
Caveats raised by FTC	Information presented on websites	All organizations ($N = 64$), % (N)	At-home testing offered or promoted[a] ($n = 29$)[b], % (n)	At-home testing not offered or promoted ($n = 35$), % (n)
Scientific validity	Referenced peer-reviewed research[c]	30 (19)	41 (12)	20 (7)
	Genes evaluated by test	27 (17)	31 (9)	23 (8)
	Impact of evaluated genes	25 (16)	28 (8)	23 (8)
	Referenced in-house research[c]	19 (12)	24 (7)	14 (5)
	Limitations of test or science	13 (8)	10 (3)	14 (5)
	Analytical or clinical validity[c]	11 (7)	17 (5)	6 (2)
Laboratory qualifications	Specific laboratory approval or certification	20 (13)	28 (8)	14 (5)
	Residency requirement for testing	13 (8)	28 (8)	0 (0)
	General reference to laboratory quality[d]	13 (8)	14 (4)	11 (4)
Test interpretation	Interpret test results in larger context[e]	25 (16)	17 (5)	31 (11)
	Test for risk not certainty	22 (14)	31 (9)	14 (5)
	Relevance of test results to family members	8 (5)	3 (1)	11 (4)
Medical evaluation and counseling in testing process	"See Your Physician . . ." disclaimer	38 (24)	52 (15)	26 (9)
	Suggested physician involvement	25 (16)	38 (11)	14 (5)
	Required physician involvement	11 (7)	0 (0)	20 (7)
	Suggested nutritionist involvement	14 (9)	17 (5)	11 (4)
	Suggested other provider involvement	14 (9)	7 (2)	20 (7)
	Suggested genetic counselor involvement	6 (4)	10 (3)	3 (1)
	Required genetic counseling	3 (2)	0 (0)	6 (2)
Privacy	General privacy policy	69 (44)	72 (21)	66 (23)
	Mentions test result handling	44 (28)	52 (15)	37 (13)
	Mentions specimen handling	33 (21)	48 (14)	20 (7)

[a]At-home testing defined here when a consumer can purchase or order the test at-home and receive test results directly with no explicit requirement for consultation with a health practitioner or genetic counselor, on- or off-staff, pre- or post-testing.
[b]Includes one healthcare/wellness service provider and four organizations classified as "Other Promoters" providing direct links to one of the 24 organizations offering at-home NG testing.
[c]Research and information regarding analytical/clinical validity in support of NG services and health claims.
[d]Does not mention a specific laboratory certification or approval but makes more general reference to the quality of the laboratory (e.g., "state of the art," "industry leader," and "reliable and responsible").
[e]Mentions the need to consider the impact of nongenetic factors (e.g., environment, stress, and "harmful agents") on disease risk when interpreting test results.

2/3 off-shore organizations). The LabSafe Company was the only organization to mention FDA approval of their laboratory, as follows: "LabSafe has contracts with major CLIA-certified clinical laboratories. All of our laboratories are certified at both the federal and state level, are approved by the FDA, and perform the same standard tests that are offered through a hospital or doctor's office."[41] Only six of the 44 organizations that did not have in-house laboratories provided any information (specific certification or general reference) about the quality of the laboratory analyzing the test.

Test interpretation, medical evaluation, and counseling

In regard to the interpretation of test results and medical examination, 36% (23/64) of all organizations mentioned on their websites the involvement (suggested or required) of a physician as part of the testing process. Nutritionist or dietician involvement in testing was mentioned by nine organizations. Through "fine print" disclaimers on websites, 38% (24/64) of organizations advised consumers to contact their physician or healthcare practitioner regarding concerns about existing health conditions (15/24), treatment (9/24), test results (6/24), and/or medical issues in general (4/24).

Two organizations drew comparisons to HG testing when discussing genetic counseling on their website. GeneCare Molecular Genetics noted that although their familial cancer and pharmacogenetic tests required extensive genetic counseling, their NG test "requires the involvement of a dietician who has been trained to interpret the test results and provide expert

advice on dietary intervention aimed at cancer risk reduction. Since cancer involves a complex interaction between genetic susceptibility, nutritional requirements, and other influences such as smoking and obesity, it is becoming increasingly important to understand how the diet can be manipulated to reduce cancer risk."[42] Similarly, CyGene's website described the goal of genetic counseling and noted that it may not be required for their current line of services because consumers "may find all the information [they] need regarding [their] increased risk for thrombosis [as an example] from the resources provided on [their] report or from [their] physician." The website also mentioned that the internet is "an excellent source of health-related information for the areas covered by CyGene's genetic profiles," and pointed consumers interested in genetic counseling to the National Society of Genetic Counselors website where "finding a genetic counselor is easy."[43]

The need to consider nongenetic factors in the interpretation of test results (i.e., the larger context) was mentioned by 16 organizations, five of which offered or promoted at-home testing. Organizations that offered or promoted at-home testing (31%, 9/29) were more likely than other organizations (14%, 5/35) to mention that NG tests are for risk and not certainty of disease. As stated by Gene-Testing.com, "In most cases these diseases are not linked to one specific gene; rather, your risk of developing them is part of a complicated equation that involves numerous genes and lifestyle factors."[44]

Only 8% (5/64) of organizations discussed family history (beyond brief mention of inherited risk) and the relevance of test results to family members. The use of NG test results to augment information about family history was mentioned by two organizations. The Sanoviv Medical Institute website included a testimonial from a MD noting that, "Most people go through life knowing they have a family history of a degenerative disease like heart disease, cancer or diabetes, but they don't know what it means for them or how it can impact their health down the road. It's exciting to discover what's going on in the body genetically. So if you know if you have a certain genetic risk, there are changes you can make now, and it's worth making them."[45] In addition, GenovaDiagnostics noted, "When conditions 'run in families' they often have a genetic component. Testing can show what specific genetic factors could pose a potential problem for you. Once you have this information, you can develop a focused plan to 'break the pattern' and better prevent your family risks from turning into realities."[46]

Sharing test results with family members was mentioned by three organizations, two of which highlighted ethical issues surrounding disclosure. For example, GeneCare Molecular Genetics noted, "The main dilemma arises from a conflict between the right of the individual to personal privacy on the one hand and the interest of family members to be made fully aware of available information which would play a part in making important life decisions on the other."[47] The Cedars-Sinai GenRISK® Adult Genetics Program noted the potential for sharing or discovering unwanted information as follows: "Family relationships may be affected by this information . . . In the process of sharing your genetic risk information, family members may learn things about you that you do not want known. In addition, you may learn things about relatives that you did not want to know. For example, it may be revealed that a family member is adopted."[48]

Privacy

Among the 44 organizations providing privacy statements on their website (e.g., use of "cookies" to track website browsing, encryption technology, handling of personal contact, and other information), 68% (30/44) mentioned the handling of specimens and/or test results, including 13 companies, 10 HW providers, five eVendors, and two other organizations.

The handling of both specimens and test results was addressed by 19 organizations, of which 14 mentioned destroying (12/14) or unidentifying specimens (2/14), and keeping test results confidential (8/14) or unidentified (6/14). The other five organizations did not destroy specimens but kept them confidential, and kept test results confidential (3/5) or unidentified (2/5). Among the 11 organizations addressing the handling of either specimens or test results, nine organizations addressed only test results (8/9 kept results confidential, 1/9 kept results unidentified), and two organizations addressed only specimens (1/2 destroyed specimens, 1/2 kept specimens confidential).

Overall, 29 organizations mentioned storing test results (28/29) or specimens (12/29), of which less than half (38%, 11/29) mentioned how test results or specimens would be used. These 11 organizations mentioned using stored test results for future research (8/11), and follow-up, future reference, quality improvement, or accreditation-related activities (6/11).

Longevity

In March 2008, 77% (49/64) of identified organizations continued to promote NG services on-line. Eight of these organizations made substantial changes to the graphic design and layout of their website, including the addition of a Spanish language version by one company. A modified domain name or a new organization name was found for three organizations. New NG services were promoted by two companies, the first offering new NG tests for healthy aging, comprehensive cardiovascular, bone health, general nutrition, CoQ10 efficiency, and metabolic syndrome; and the second offering a new DNA fitness program based on NG test results. In addition, one HW provider added an on-line shopping cart for DTC sale and one company received CLIA certification for its laboratory.

Eight organizations no longer mentioned NG services on their websites, the majority of which were HW providers (4/8) and companies (2/8) offering NG tests for single conditions. Six of these eight organizations were affiliated with another company identified in the search (i.e., Cygene, Genelex, GenovaDiagnostics, Sciona). Websites could not be found for seven organizations including one HW provider, three eVendors, and three companies. Four of these seven organizations were affiliated with another company identified in the search (i.e., DaVinci Laboratories of Vermont, Genelex, Market America: Unfranchise® Business, Sciona).

DISCUSSION

The present study demonstrates that a wide variety of organizations were involved in the on-line promotion and sale of NG tests in the months following the GAO investigation. These organizations ranged from a book author providing a direct link to a company offering at-home NG testing, to a large medical center with an in-house clinical laboratory also offering a variety of HG tests. Similar to previous analyses of commercial website content, this study found less than adequate information about important caveats associated with genetic testing; however, organizations promoting at-home testing were more likely to address these caveats.

The majority of websites promoting NG services were hosted by HW service providers. In a recent study of public awareness and use of NG tests, Goddard et al.[49] found that consumers reporting health professionals as a source of information were more likely to have purchased NG services than consumers receiving information from any other source. Although evidence suggests that current findings in NG research do not support the use of genetic information to improve individual health, service provider websites described NG tests as a useful tool for understanding and improving the health of their patients and in some cases integrated NG tests into a panel of other Dx tests. The use of NG tests in combination with Dx tests may indicate an understanding that genetic information alone does not provide a complete picture of health. Alternatively, service providers may combine NG and Dx tests under the belief that NG test results have some distinct and measurable utility above Dx tests, to compensate for the lack of established clinical validity for NG tests, or to capitalize on novelty of NG tests.

The American Society of Human Genetics highlighted the importance of provider education regarding the analytical and clinical validity of genetic tests in its statement regarding the DTC marketing of genetic tests.[50] Several findings from the present study suggest that such education efforts should cast a wide net. First, a variety of health professionals were found to promote NG services. Naturopathic doctors were most often listed as staff in identified organizations, followed by nutritionists or dieticians and MDs in almost equal numbers, and chiropractors. Second, nutraMetrix™ made an open call on its website for "health professionals in all fields" to become "certified Nutraceutical Consultants" trained in the use of NG services. Two organizations identified in this search appeared to take advantage of this opportunity. Finally, descriptions of affiliation and distribution opportunities indicate a concerted effort to not only encourage the use NG services, but also to increase the on-line presence of NG services through the creation of web-based businesses, customized web-portals, and direct links to the on-line shopping carts by independent entrepreneurs.

The need to establish regulations or guidance for the marketing of genetic services was demonstrated by the varied levels of information provided on different websites promoting the same NG test. Under conditions of on-line DTC sale or at-home genetic testing, commercial websites are akin to product labels. Legal scholars have argued that commercial websites for prescription drugs should be regulated by the FDA as "product labeling" (held to strict content standards) because web-based information is often similar to the package insert information consumers receive with a purchased product and can be far greater than what is provided in a traditional print or televised advertisement.[51] A parallel argument can be made regarding commercial websites for NG or other genetic services. Greater levels of consumer autonomy in the purchase of genetic services increases the need for commercial websites to present high quality information, particularly information regarding product risks and limitations.

Clearly, information provided on commercial websites will not be the only information consumers receive when they purchase NG services on-line. Companies offering DTC sale of NG services often mail consumers a specimen collection kit including a package insert with instructions for use and other information. Studies have yet to examine this source of information and compare it to website content. In addition, consumers may obtain other important information by contacting company representatives (if they know the right questions to ask). Nonetheless, consumers interested in at-home genetic testing are likely to use website information to make an initial decision. The provision of contact, payment, or other personal information raises concerns about consumers receiving advertisements for related services such as NG supplements, skin creams, or weight-loss products; or genome-wide profiling services offered by relatively new companies like 23andMe and deCODE genetics.[52,53]

Six organizations stated explicitly on their website that NG services were not covered by most health insurance plans. Based on recommendations from the Secretary's Advisory Committee on Genetics, Health, and Society, NG services will not be covered until there is enough evidence to establish analytical and clinical validity, and clinical utility.[54] The inability to classify health conditions assessed by the majority of NG tests using standard codes for disease states (i.e., ICD-10) will further complicate billing and reimbursement efforts. Therefore, consumers interested in NG services, believing that they provide some clinical utility or other perceived benefit, will pay out-of-pocket.

Regardless of purchase, the internet has been noted as a medium that provides a "rich" product experience,[55] and may have a greater impact on attitudes than other media.[56] The internet also is an important and at times preferred source of information about genetics, despite its limitations.[57] Internet users are likely to come across websites promoting NG services when searching for genetic services in particular, or when searching for other health information, such as diet, nutrition, supplements, or fitness—topics included among the most popular health topics searched for on-line.[58]

On-line promotional materials for genetic services have the potential to educate consumers and health providers about advances in the field of genetics, and the benefits and limitations of genetic testing. On the other hand, promotional ma-

terials also have the potential to foster deterministic views about genes (i.e., "I am my genes") and unwarranted fear or anxiety about future health. Despite the potential for consumers to misunderstand the impact of genes on different types of health conditions, few websites mentioned the involvement of a genetic counselor or other genetic expert as part of the testing process. Furthermore, two websites suggested that genetic counseling was not as important for NG testing relative to HG testing.

Although the FDA does not have direct authority over advertising for NG or other laboratory services, it has requested meetings with several companies identified here regarding the lack of premarket review (to assess validity, quality, and clinical interpretation) for their laboratory services.[13] Both the FDA and the FTC have reported limited oversight and resources to monitor the promotion and sale of genetic services,[59,60] increasing the importance of consumer reporting. However, researchers have found that internet users rarely: (1) look at organization information (i.e., "About Us") provided on websites, (2) remember where they found information on-line, or (3) remember who was responsible for the website from where they found information.[61] In the absence of knowledge about NG or genetic testing, internet users may use less substantive factors to determine website credibility (and thereby organization and test credibility), including third party endorsements, quality seals, appealing pictures of staff, and professional appearance of the website.[56,61] These patterns suggest that consumers may not be a reliable source for reporting misleading or fraudulent marketing.

Despite release of the GAO report and unfavorable media coverage,[62,63] few organizations identified in October 2006 were found to stop promoting NG services in March 2008. In fact, companies identified in this search reported expanding their NG services, establishing new agreements for their distribution, and targeting new consumer markets on-line.[64–66] The continued premature marketing and sale of NG services is problematic. First, although NG is a promising field of research working diligently toward realizing its goal of personalized nutrition, there is currently little evidence to support the use of NG services. In a rigorous review of meta-analyses, Janssens et al.[67] found insufficient evidence to support the gene-disease associations in NG tests offered by seven companies. Four of these companies were identified in this study (Genelex, GenovaDiagnostics' Genovations, Sciona, Suracell) and linked to 57% (95/167) of all NG test mentions across identified websites.

Second, commercial websites failed to provide adequate and transparent information for informed decision-making and rarely highlighted the importance of consumer consultation with a genetics professional. NG test descriptions overestimated the validity and utility of test results and often ignored limitations in NG research or services. Consumer and health professional efforts to gather specific information about the validity and utility of NG tests may be complicated by the use of unofficial gene symbols and commercial gene names on some websites. Furthermore, incomplete and conflicting information about the companies analyzing NG tests complicates the selection of a "qualified" laboratory.

In the absence of federal regulation regarding the content of advertisements and other promotional materials, organizations that continue to promote NG services on-line should address important caveats in genetic testing highlighted by the FTC and the DTC marketing-related issues outlined in position statements by professional societies.[50,68,69] In addition, organizations should follow long standing principles for the ethical provision of health information on-line.[70–72]

Limitations

Study results are based solely on publicly-accessible (i.e., login or registration not required) website content and may not reflect all organization or test characteristics. Companies were not contacted to confirm the accuracy of website content. Second, the automated archival feature in Internet Researcher© did not capture every item on all pages of each website (e.g., video, automated features, Adobe Acrobat files, links to on-line shopping cart, links to other web pages). There were <20 cases where visible links to content not retrieved appeared to contain NG test-specific information. In these cases, the Internet Archive Wayback Machine (http://www.archive.org/web/web.php) was used to find web page content archived at the same time as this study. In most cases, additional content was not identified.

Finally, in their internet search, Janssens et al.[67] identified seven companies offering predictive genomic profiles, three of which were not identified in this study—GenoSolutions, IntegrativeGenomics, Salugen.[67] According to the Wayback Machine, websites for two of these three companies were active during the month this search was conducted (October 2006). The internet search methodology used by Janssens et al.[67] was not described; however, authors mentioned starting with a Genewatch (2006) report on "individually tailored nutrition recommendations based on genomic profiling."[73] This report mentions 12 companies involved in NG services, four identified in the Janssens et al.[67] study and six identified in this study. The reason why three companies identified by Janssens et al.[67] did not appear in search results for this study are unclear, but plausible explanations include: (1) the absence of search terms used in this study as metatags on company websites, (2) the appearance of URLs beyond the first three pages of search results (not reviewed in this study), or (3) temporary inactivity or malfunction of the website at time of this search.

Strengths

Websites identified in this study are most likely to include those the average US consumer would have identified in a search for NG services in October 2006. The review of websites 3 months after release of the GAO report and the FTC consumer fact sheet provided time for organizations promoting NG services on-line to review and improve website content. The content analysis included websites with on-line DTC sale, DTC marketing, health professional marketing, and more general promotion by a variety of organizations. The broad inclusion criteria allowed for a

more rich understanding of on-line promotional materials for NG services. Finally, findings from the present study add to those of four previous studies increasing the potential for longitudinal analyses of anticipated growth and change in the promotion of NG and other genetic services.

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