ARTICLE

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

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Predictive genomic profiling used to produce personalized nutrition and other lifestyle health recommendations is currently offered directly to consumers. By examining previous meta-analyses and HuGE reviews, we assessed the scientific evidence supporting the purported gene-disease associations for genes included in genomic profiles offered online. We identified seven companies that offer predictive genomic profiling. We searched PubMed for meta-analyses and HuGE reviews of studies of gene-disease associations published from 2000 through June 2007 in which the genotypes of people with a disease were compared with those of a healthy or general-population control group. The seven companies tested at least 69 different polymorphisms in 56 genes. Of the 56 genes tested, 24 (43%) were not reviewed in meta-analyses. For the remaining 32 genes, we found 260 meta-analyses that examined 160 unique polymorphism-disease associations, of which only 60 (38%) were found to be statistically significant. Even the 60 significant associations, which involved 29 different polymorphisms and 28 different diseases, were generally modest, with synthetic odds ratios ranging from 0.54 to 0.88 for protective variants and from 1.04 to 3.2 for risk variants. Furthermore, genes in cardiogenomic profiles were more frequently associated with noncardiovascular diseases than with cardiovascular diseases, and though two of the five genes of the osteogenomic profiles did show significant associations with disease, the associations were not with bone diseases. There is insufficient scientific evidence to conclude that genomic profiles are useful in measuring genetic risk for common diseases or in developing personalized diet and lifestyle recommendations for disease prevention.

Introduction

Advances in genomics are expected to increase our understanding of the etiology and pathogenesis of common diseases such as type 2 diabetes, cardiovascular disease, and cancer. They are also expected to offer new opportunities for the prevention, early detection, and treatment of these diseases, in part by allowing health care providers to use individualized preventive and therapeutic strategies based on patients' genomic profiles.[1] So far, the complex interactions between genetic and environmental causes of most common diseases are poorly understood and the potential usefulness of genome-based interventions is unclear. Nevertheless, several companies already offer personalized lifestyle health recommendations and nutritional supplements based on clients' genomic profiles, and many others are developing similar strategies (see Web Resources).[2]

Because most common diseases are caused by complex interactions among multiple genetic and nongenetic factors, each of which confer only minor increases in risk, the predictive value of genomic profiling may be insufficient as a useful basis for personalized nutritional and lifestyle recommendations. When differences in disease risk between high-risk and low-risk groups are small, we would expect both groups to benefit fairly equally from general interventions unless the interventions are proven more effective for individuals with certain genotypes; however, evidence of such gene-environment interactions is still lacking. For these reasons, it has been argued that the use of genomic profiles to devise personalized lifestyle recommendations is premature and misleading.[2–6]

A pervasive problem of research on genetic associations is that positive results are often difficult to replicate.[7,8] Results of individual gene-disease association studies have a high probability of being false-positive, and therefore adequate replications of the same gene-disease association in independent-study populations are essential.[7,9] Systematic reviews and meta-analyses of epidemiologic studies on genotype-disease associations are valuable approaches for assessing the credibility of associations reported in single studies.[6,7,10] In this study, we assess the scientific evidence for the usefulness of commercially available genomic profiles by reviewing meta-analyses of gene-disease associations for the genetic variants included in the profiles.

Material and Methods

Searching

Starting from the Genewatch 2006 report on individually tailored nutrition recommendations based on genomic profiling,[2] we searched the Internet and identified seven companies that offer predictive genetic testing using multiple markers (Genelex, Genovations, Genosolutions, Integrative Genomics, Salugen, Sciona and Suracell). We obtained information about the genes and

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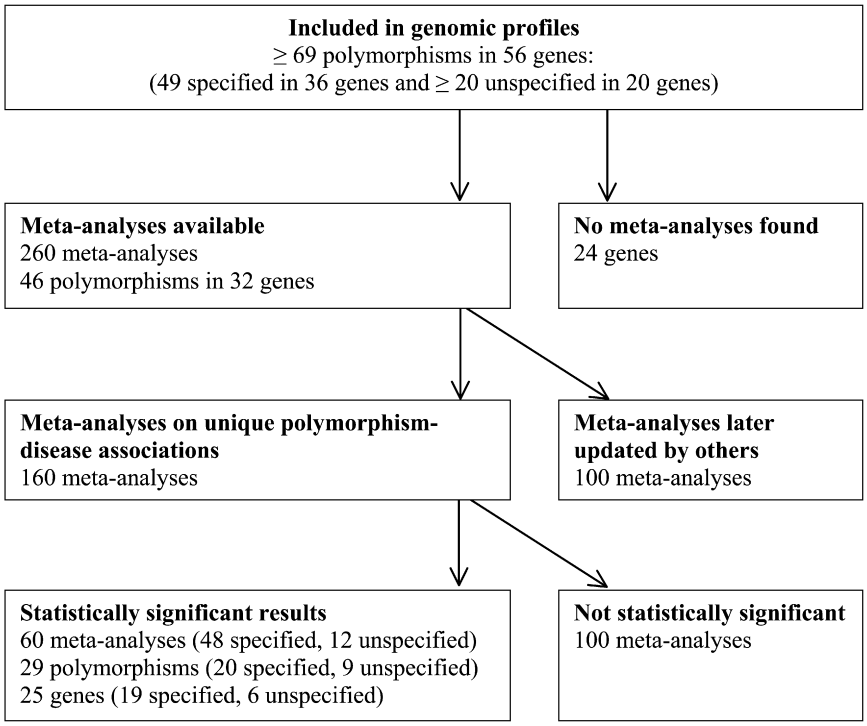

Figure 1. Flow Chart of Selection of Meta-Analyses

polymorphisms included in these profiles from the companies' Web sites (see Web resources), from online sample reports, and from a published article.[11] The genes and polymorphisms included in the profiles are listed in Table S1 (available online). Three companies did not specify the polymorphisms that they tested. We assumed that these companies tested the same polymorphisms in genes also tested by other companies; however, when their profiles included a gene not tested by any other company, we reviewed available literature on any polymorphism of the gene. We searched PubMed for meta-analyses and Human Genome Epidemiology (HuGE) reviews published from 2000 through June 2007 regarding susceptibility to any disease associated with these polymorphisms.

Selection of Meta-Analyses

In conducting the PubMed literature search, we used both the abbreviation and the full name of each of the 56 genes tested by the seven companies, in combination with the query term "meta-analysis and (gene or polymorphism)," without specifying any polymorphisms or diseases. Next, we hand-searched all retrieved references for the exact polymorphism(s) studied, the study population, and the disease examined. We considered alternative annotations of polymorphisms and verified them in the Online Mendelian Inheritance in Man (OMIM) database. We included only meta-analyses published in English that compared the frequency of a polymorphism among people with the disease in question with the frequency among healthy or general-population controls. We did not exclude studies because of statistically significant heterogeneity in the effect sizes of the individual studies. For meta-analyses in which there was significant heterogeneity, we report the meta-analysis with one or two outlying studies removed or a subgroup analysis of three or more studies involving populations of Western European descent (the most commonly studied subgroup), if these had less or no significant heterogeneity, depending on the availability of information. If more than one meta-analysis examined the same polymorphism-disease association, we used the most comprehensive one.

Data Extraction

We retrieved data on the gene, the polymorphism, and the disease examined in each study, as well as the number of case and of control subjects involved; the odds ratio and 95% confidence interval (CI) for the polymorphism-disease association; and the heterogeneity in effect sizes of the individual studies. Many of the meta-analyses we examined presented multiple odds ratios for the same polymorphism-disease association by considering different genetic models (e.g., dominant effect of risk alleles, recessive effect, or per allele effect). We used the per-allele odds ratio if all models yielded the same conclusion about the presence of association. If the per-allele odds ratio was not statistically significant, we selected the model (dominant or recessive effect of risk allele) with the highest odds ratio, assuming that the companies were referring to that specific association. If random and fixed effects models were presented, we obtained the odds ratios from the random-effects models.

Results

The seven companies tested at least 69 different polymorphisms in 56 genes (Table S1). Only one gene (*MTHFR* [MIM 07093]) was tested by all seven companies, seven genes (*CETP* [MIM 118470], *COL1A1* [MIM 120150], *GSTM1* [MIM 138350], *GSTP1* [MIM 134660], *IL-6* [MIM 147620], *TNF-α* [MIM 191160], and *VDR* [MIM 601769]) were tested by five or six companies, and 19 genes (34%) were tested by only one company.

We identified 260 meta-analyses that met our criteria; they addressed 46 of the 69 polymorphisms and 32 (57%) of the 56 genes tested by the seven companies (Figure 1 and Table S1), as well as 160 unique associations between a genetic polymorphism and a disease. Sixteen meta-analyses (10%) addressed the two polymorphisms in the *MTHFR* gene (C677T and A1298C), 13 addressed polymorphisms in *TNF-α*, 12 addressed polymorphisms in *GSTM1*, 11 addressed polymorphisms in *GSTP1* and *GSTT1*, and ten addressed polymorphisms in *VDR*.

Of the 160 unique polymorphism-disease associations that had been examined by meta-analysis, 60 were statistically significant (Figure 1 and Table S2), including significant associations for 29 of 69 polymorphisms in 25 (45%) of the 56 genes. However, statistically significant associations were generally modest, with significant odds

ratios (ORs) ranging from 0.54 to 0.88 for protective alleles or genotypes and from 1.04 to 1.50 for risk alleles or genotypes, except for the risk for systemic lupus erythematosus associated with *TNF-α* (OR 2.1, 95% CI 1.6-2.7) and the risk for Alzheimer's disease associated with *APOE-4* (OR 3.2, 95% CI 2.7-3.8; [MIM 107740]). Polymorphisms were associated with significantly increased or decreased risk for 28 different diseases. The *MTHFR* C677T polymorphism was significantly associated with risk for seven different diseases, *GSTT1* [MIM 600436] with risk for six, *TNF-α* with risk for five, and *GSTM1* and *MTHFR* A1298C with risk for four. Twelve meta-analyses showed significant associations between polymorphisms and risk for cardiovascular disease (including myocardial infarction, coronary stenosis, coronary artery disease, and coronary heart disease), five between polymorphisms and stroke, and four between polymorphisms and Alzheimer's disease or acute leukemia.

On average, meta-analyses showed a significant association with disease risk for 58% of the genes included in each profile (range 38%–83%) (Table 1). These significant associations, however, were often with risk for disease outcomes other than those associated with the "profile" (Table 1). For example, statistically significant associations with disease risk were found for only two of the five genes included in osteogenomic profiles, and these associations were with risk for Alzheimer's disease, asthma, non-Hodgkin's lymphoma, obesity, and systemic lupus erythematosus, rather than with risk for bone disorders.

Discussion

Although companies offering genomic profiles did not specify how they selected polymorphisms for inclusion in the profiles, they probably did so on the basis of statistically significant results from association studies. Because positive results from single gene-disease association studies are often not replicated in subsequent studies,[12] one study showing a statistically significant association is considered insufficient evidence of genetic association.[10] Our review of meta-analyses found significant associations with disease risk for fewer than half of the 56 genes that are tested in commercially available genomic profiles. Various polymorphisms of these genes were associated with risk for 28 different disorders. Many of these disorders were unrelated to the ostensible target condition, and the associations were generally modest.

Before interpreting our results, we need to clarify four issues regarding the review strategy we used. First, our paper addressed predictive genomic profiles that are sold online and that aim to personalize nutrition and other lifestyle health recommendations. The review did not assess the scientific basis of gene-expression profiles and pharmacogenomic applications. Although there may be applications that have stronger scientific support than others, there are clearly promising developments in this area.[13,14] Second, the information on genes and polymorphisms in this study was obtained from company websites and online sample reports. As of November 2007, all seven companies were still selling the profiles, but two no longer specified on their Web sites which genes they were actually testing. Although these companies may now use other polymorphisms to profile the disease risk of their clients, the scientific evidence for the disease risk associated with these other polymorphisms is likely to be similar to that for the polymorphisms we reviewed. Third, we limited our search for meta-analyses to those on the association between polymorphisms and disease susceptibility, and we excluded those on associations with intermediate, quantitative phenotypes or risk factors such as blood pressure or bone mass density because the need for preventive intervention varies with the level of these traits. We did include meta-analyses of associations between polymorphisms and risk for conditions defined by clinically relevant thresholds, such as hypertension or osteoporotic fractures. Because the genetic profiles of the companies are offered to the general public, we restricted our search to meta-analyses of studies that included healthy or general-population controls. Because the predictive value of genetic testing depends on disease risk, genotype frequencies, and odds ratios for the association between disease risk and polymorphisms in a particular genetic profile, all of which may differ between populations, the profiles should be evaluated in the target population.[15] This explains why genetic testing for *APOE*, *Factor II* [MIM 176930], and *Factor V* [MIM 227400] can have lower predictive value in a general population context but be very informative to persons with a family history. Fourth, we did not exclude meta-analyses on the basis of quality criteria, even though there were obvious differences in quality among meta-analyses. The authors of larger meta-analyses often selected studies according to a set of strict criteria, whereas the authors of smaller ones often combined all available studies. In addition, more than a quarter of the meta-analyses in Table S2 reported statistically significant heterogeneity in effect sizes among studies. Several of the meta-analyses that found a significant association involving heterogeneous study populations did not find a significant association when the analyses were restricted to a subgroup of more homogenous studies.[16,17] Application of strict quality criteria would have reduced the number of meta-analyses in the present review substantially.

These methodological choices partly explain why we found no meta-analyses for 24 of the 56 genes. There were meta-analyses available for many of these genes, but these meta-analyses could not evidence the utility of genomic profiling in the general population. For example, we found several meta-analyses of pharmacogenomic studies (e.g., for *CYP2C9* [MIM 601130] and *CYP2C19* [MIM 124020][18,19]), several meta-analyses on diseases that do not affect the average individual in the general population (such as *IL-10* [MIM 124092] and recurrent pregnancy loss[20]), and meta-analyses on health traits (e.g., smoking

Table 1. Overview of Meta-Analyses of Gene-Disease Association Studies by Genomic Profile

Company	Genomic Profile	Polymorphisms[a]	Genes		Meta-Analyses		Diseases Associated with Polymorphisms in the Meta-Analyses
			Total	Significant Association with Disease	Total[b]	Significant Association with Disease	
1	Heart health	15	13	5	43	21	Acute leukemia, Alzheimer's disease, asthma, colorectal cancer, coronary artery disease, coronary heart disease, depression, gastric cancer, IgA nephropathy, non-Hodgkin's lymphoma, obesity, psoriasis, schizophrenia, systemic lupus erythematosus (SLE), stroke, venous thrombosis
	Bone health	7	4	2	28	6	Alzheimer's disease, asthma, non-Hodgkin's lymphoma, obesity, psoriasis, SLE
	Insulin resistance	6	5	4	32	10	Acute leukemia, Alzheimer's disease, asthma, bladder cancer, breast cancer, colorectal cancer, head and neck cancer, non-Hodgkin's lymphoma, obesity, psoriasis, Parkinson's disease, SLE
	Inflammation health	7	6	5	48	17	Acute leukemia, bladder cancer, head and neck cancer, breast cancer, colorectal cancer, Parkinson's disease, Alzheimer's disease, asthma, non-Hodgkin's lymphoma, obesity, psoriasis, SLE
	Antioxidant/ detoxification	8	6	4	31	12	Acute leukemia, bladder cancer, breast cancer, colorectal cancer, coronary heart disease, head and neck cancer, Parkinson's disease
2[c]	OsteoGenomic	5	5	2	22	6	Alzheimer's disease, asthma, non-Hodgkin's lymphoma, obesity, psoriasis, SLE
	ImmunoGenomic	≥ 4	4	2	17	6	Asthma, non-Hodgkin's lymphoma, obesity, psoriasis, schizophrenia, SLE
	CardioGenomic	13	10	6	30	18	Acute leukemia, age-related macular degeneration, Alzheimer's disease, colorectal cancer, coronary heart disease, coronary stenosis, hypertension, myocardial infarction, schizophrenia, stroke
	DetoxiGenomic	≥ 19	16	6	62	15	Acute leukemia, bladder cancer, breast cancer, colorectal cancer, endometriosis, esophageal cancer, head and neck cancer, obsessive compulsive disorder, Parkinson's disease
3	Cardiogenomic	≥ 13	12	7	39	26	Acute leukemia, Alzheimer's disease, age-related macular degeneration, colorectal cancer, coronary artery disease, coronary heart disease, coronary stenosis, depression, gastric cancer, hypertension, myocardial infarction, schizophrenia, stroke, venous thrombosis
	Estrogenomic	≥ 14	13	9	73	32	Acute leukemia, Alzheimer's disease, asthma, age-related macular degeneration, colorectal cancer, coronary artery disease, coronary heart disease, coronary stenosis, depression, endometriosis, esophageal cancer, gastric cancer, myocardial infarction, non-Hodgkin's lymphoma, obesity, obsessive compulsive disorder, psoriasis, schizophrenia, SLE, stroke, venous thrombosis
	Immunogenomic	≥ 5	5	2	19	6	Asthma, non-Hodgkin's lymphoma, obesity, psoriasis, SLE, schizophrenia
	Neurogenomic	≥ 6	5	4	46	17	Acute leukemia, Alzheimer's disease, bladder cancer, colorectal cancer, coronary artery disease, depression, gastric cancer, head and neck cancer, obsessive compulsive disorder, schizophrenia, stroke, venous thrombosis

Table 1. ***Continued***

Company	Genomic Profile	Polymorphisms[a]	Genes		Meta-Analyses		Diseases Associated with Polymorphisms in the Meta-Analyses
			Total	Significant Association with Disease	Total[b]	Significant Association with Disease	
	Osteogenomic	≥5	5	2	22	6	Alzheimer disease, asthma, non-Hodgkin's lymphoma, obesity, psoriasis, SLE
	Inflammation	≥6	5	4	37	18	Acute leukemia, Alzheimer's disease, asthma, colorectal cancer, coronary artery disease, depression, gastric cancer, hypertension, non-Hodgkin's lymphoma, obesity, psoriasis, schizophrenia, SLE, stroke, venous thrombosis
4	Enhanced Basic Screening Panel	≥12	12	5	52	21	Acute leukemia, Alzheimer's disease, asthma, colorectal cancer, coronary artery disease, depression, gastric cancer, hypertension, myocardial infarction, non-Hodgkin's lymphoma, obesity, Parkinson's disease, schizophrenia, SLE, stroke, venous thrombosis
5	GenoScore	≥5	5	4	15	10	Acute leukemia, alcoholism, anorexia nervosa, Alzheimer's disease, colorectal cancer, schizophrenia, type 2 diabetes
6	Nutritional Genetic Profile	24	19	9	87	33	Acute leukemia, Alzheimer's disease, asthma, bladder cancer, breast cancer, colorectal cancer, coronary artery disease, coronary heart disease, depression, gastric cancer, head and neck cancer, IgA nephropathy, non-Hodgkin's lymphoma, obesity, Parkinson's disease, schizophrenia, SLE, stroke, type 2 diabetes, venous thrombosis
7[d]	Personal DNA Analysis Starter Kit	19	19	9	91	33	Acute leukemia, Alzheimer's disease, asthma, bladder cancer, breast cancer, colorectal cancer, coronary heart disease, gastric cancer, head and neck cancer, IgA nephropathy, Parkinson's disease, coronary artery disease, depression, schizophrenia, stroke, venous thrombosis, type 2 diabetes, non-Hodgkin's lymphoma, obesity, SLE

[a] When companies did not specify exact polymorphisms, the number indicates the number of specified polymorphisms plus the number of genes for which polymorphisms were not specified, indicating that they test at least one polymorphism in these genes.
[b] Refers to total number of unique meta-analyses (see Figure 1).
[c] This company now also offers neurogenomic and estrogenomic profiles, but no specific information was available for these profiles.
[d] This company did not specify polymorphisms, but it only tests genes that are also considered by other companies. Hence, we assumed that this company also tests the same polymorphisms as do the other companies.

behavior and *CYP2A6* [122720][21]). Furthermore, for many genes we found meta-analyses on other polymorphisms (e.g., *IL-10* G[−1082]A[22] and *LPL* Asn291Ser[23]) or on related genes (e.g., Leptin Receptor gene (*LEPR*; [MIM 601007]), but not for *Leptin* [MIM 164160]).[24]

This review shows that the excess disease risk associated with many genetic variants included in genomic profiles has not been investigated in meta-analyses or has been found to be minimal or not significant. These results raise concern about the validity of combining tests for many different genetic variants into profiles, especially when the companies offering them do not describe how they create a composite profile from the results of tests for single genetic markers. One company reports that they use complex mathematical algorithms to produce personalized diet and lifestyle recommendations. Another recommends basic nutritional or lifestyle-change support for homozygous negatives, added support for heterozygous positives, and maximum support for homozygous positives, which suggests that they are using single genetic markers as the basis for their recommendations. This reliance on single genetic markers is particularly worrisome given the limited predictive value of results from testing single susceptibility genes with small effects.[25–27] To be meaningful, a genetic risk profile should combine information about the disease risk associated with multiple genes, and creating such a profile would require extensive knowledge of gene-gene interactions, which are even less well understood than the disease risk associated with individual polymorphisms.

How the companies we examined use their clients' genetic profiles to tailor individualized nutrition-supplement and lifestyle recommendations is another intriguing puzzle. Evidence on gene-diet interactions is still preliminary because trials designed to test these interactions have thus far yielded mainly inconclusive results.[28] Furthermore, several genes, such as *ACE* [MIM 106180], *APOE*, and *MTHFR*, increase people's risk for some diseases and decrease their risk for others (Table S2). For example, *MTHFR* 677TT was associated with an increased risk for depression, stroke, coronary artery disease, gastric cancer, schizophrenia, and venous thrombosis, but it was associated with a decreased risk for colorectal cancer. Hence, the putative health effects of preventive interventions tailored to a person's *MTHFR* genotype may not be entirely beneficial. Finally, when profiles are composed of low-risk susceptibility genes, people with purportedly "high-risk" profiles may be at only slightly higher risk of disease than are people with "low-risk" profiles. One possible danger of marketing lifestyle recommendations to people with "high-risk" profiles is that those with "low-risk" profiles could be led to mistakenly believe that they have little need to make healthy lifestyle changes. The predictive value of genomic profiling may simply be insufficient for targeting interventions when low-risk groups will receive no intervention at all.[29] It also needs to be investigated whether genomic profiling can usefully identify the better from the worse responders in the choice between two treatments.

Although genomic profiling may have potential to enhance the effectiveness and efficiency of preventive interventions, to date the scientific evidence for most associations between genetic variants and disease risk is insufficient to support useful applications. Despite advances in nutrigenomics and pharmacogenomics research,[30] it could take years, if not decades, before lifestyle and medical interventions can be responsibly and effectively tailored to individual genomic profiles.

Supplemental Data

Two tables can be found with this paper online at http://www.ajhg.org/.

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Web Resources

The URLs for data presented herein are as follows:

23andme, www.23andme.com
Genelex, www.genelex.com
Genovations, www.genovations.com
Genosolutions, www.genosolutions.com
HuGENet, www.hugenavigator.net
Integrative genomics, www.integrativegenomics.com
Interleukin genetics, www.ilgenetics.com
Navigenics, www.navigenics.com
Nutrilite, www.nutrilite.com
Salugen, www.salugen.com
Sciona, www.sciona.com
Suracell, www.suracell.com
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/
PubMed, http://www.ncbi.nlm.nih.gov/pubmed

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