

Genomic Nutritional Profiling: Innovation and Regulation in Nutrigenomics

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I. INTRODUCTION

Hippocrates advised to let food be your medicine, but he could not have anticipated the quagmire of ethical and legal issues that would arise with the advent of nutritional genomics. Nutrigenomics is a fast-evolving field that straddles the food-medicine distinction in order to understand the genetic underpinnings of the effects of nutrient metabolism on health. The core idea behind this emerging field is that nutrients in our food interact with our genes in ways that are typically benign, but can also be deleterious in other circumstances.¹ These harmful interactions are implicated in the development of major chronic diseases. Given that individuals have slightly different genetic constitutions and different diets, and given that the interaction generates a spectrum of outcomes, the science of nutrigenomics faces an enormous analytical task to identify and categorize nutrient-gene interactions and elucidate the interactions' contribution to disease. Nevertheless, the intent is to provide, as soon as possible, scientifically grounded predictions about the consequences of nutrigenomics to the public.

Like other nascent fields arising from the Human Genome Project, such as pharmacogenomics,² nutrigenomics must meet

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1. Ruan Elliott & Teng Jin Ong, *Science, Medicine, and the Future: Nutritional Genomics*, 324 BRIT. MED. J., 1438, 1448–39 (2002).

2. Pharmacogenomics is the study of the heterogeneous response to drugs attributable to the effects of individual genetic differences that cause variation in drug metabolism. See, e.g., William E. Evans & Julie A. Johnson,

a double burden of proof before it will become widely accepted. On the one hand, the field is encumbered with many questions about the strength of the science at this early stage in its development. A wide range of opinion exists about the predictive, let alone the descriptive, capacity of genomics science to support the claims of nutrigenomics.³ It is fair to say that, while there is general consensus in the field that nutrients and genes interact and may be causally implicated in the development of disease,⁴ present uncertainties in the science lead many researchers to guard what they say about the relationship between nutrigenomics and chronic disease. On the other hand, assuming the scientific burden of proof is met, there remains the constellation of issues associated with public access to nutrigenomic products and services. These include problems about regulating tests and claims made about information disclosed by tests, decisions about public versus private provision of nutrigenomics, and whether nutrigenomics is offered direct-to-consumer or via health care practitioners.⁵

Perhaps in an ideal world all relevant scientific questions would be identified and answered before new products and services reach the public. The logic of this approach is what motivates the costly and lengthy clinical trials that are required for the development and marketing of new pharmaceuticals, for example. Yet despite this system, even in the case of clinical trials for pharmaceuticals not all relevant issues are identified

Pharmacogenomics: The Inherited Basis for Interindividual Differences in Drug Response, 2 ANN. REV. GENOMICS & HUM. GENETICS 9, 9–10 (2001).

3. For claims about the focus and scope of nutrigenomics, see, for example, Jim Kaput & Raymond L. Rodriguez, *Nutritional Genomics: The Next Frontier in the Postgenomic Era*, 16 PHYSIOLOGICAL GENOMICS 166 (2004). For doubts about genomics supporting downstream applications, see, for example, Richard S. Cooper & Bruce M. Psaty, *Genomics and Medicine: Distraction, Incremental Progress, or the Dawn of a New Age?*, 138. ANNALS INTERNAL MED. 576 (2003). For more specific concerns regarding the development of tools of nutrigenomic science and applications, see, for example, Lenore Arab, *Individualized Nutritional Recommendations: Do we have the Measurements Needed to Assess Risk and Make Dietary Recommendations?*, 63 PROC. NUTRITION SOC'Y 167, 169–71 (2004).

4. Michael Müller & Sander Kersten, *Nutrigenomics: Goals and Strategies*, 4 NATURE REVIEWS GENETICS 315, 315–19 (2003).

5. David Castle et al., *Nutrients and Norms: Ethical Issues in Nutritional Genomics*, in NUTRITIONAL GENOMICS: DISCOVERING THE PATH TO PERSONALIZED NUTRITION, 419, 422–33 (Jim Kaput & Raymond L. Rodriguez ed., 2006).

and dealt with, as the recent worldwide market withdrawal of Merck's osteoarthritic drug Vioxx demonstrates.⁶ The situation with nutrigenomics is even more complicated because commercial products and services have been made available to the public for several years, but unlike pharmaceuticals, nutrigenomic products and services do not find their way to market with a system to evaluate their utility. This is *not* to recommend that nutrigenomics ought to follow a clinical trial protocol; it is to point out that what would count as an appropriate regulatory regime for nutrigenomics continues to be an open question. In fact, it is an evolving question, one whose parameters are not fixed and cannot be, for at least three reasons. First, the science is rapidly changing, which means that regulators must evaluate a field whose scope, exemplars and evidentiary base are constantly changing. Second, because nutrigenomics is already available to the public, regulators must contend with the fact that the private sector is adapting quickly to competition and to market signals. Third, in light of the evolution of the science and commercial developments, regulators must cope with the problem of fitting existing regulations and regulatory practices to nutrigenomics even though these regulations existed prior to the advent of this field.

This paper argues that nutrigenomics regulation cannot be achieved by simply identifying potential hazards and then regulating proportionately to those harms. Instead, nutrigenomics presents an on-going regulatory challenge because the field as a whole is genuinely innovative, meaning that existing regulations and regulatory approaches lack built-in capacity for the new field. While this may seem like an obvious claim in light of the controversy surrounding nutrigenomics regulation, the reasons for it, and implications to be drawn, are somewhat more subtle. To begin with, clarity about the status of the science must be reached before claims about regulatory deficiencies can be addressed. Regulatory gaps can take the form of instances where identified hazards call for new regulations, but the more important point is that the evaluation of nutrigenomics discloses a persistent problem in regulatory systems where food and nutrition are regulated separately from medicine and drugs.⁷ Nutrigenomics is an

6. Richard Horton, *Vioxx, the Implosion of Merck, and Aftershocks at the FDA*, 364 LANCET 1995, 1995 (2004).

7. In the United States, the Food and Drug Administration (FDA) regulates foods and drugs under the same act, Federal Food, Drug, and

innovative field in which much of the novelty lies in a deliberate convergence between the traditionally separated fields of food and medical regulation. The important implication arising from the development of this thesis is that regulators will not find a simple, elegant solution to the regulation of nutrigenomics so long as they attempt to retrofit existing food and drug regulations to a fast moving, innovative field. An important indicator is the use of non-statutory tools for regulations, such as guidance documents, which are on the rise in the attempt to keep pace with nutrigenomics.

II. HUMAN GENETICS AND NUTRIGENOMICS

If the Human Genome Project is considered in light of the time it took for the human genome to evolve, it is a very recent event. Yet for those who have invested their careers in the Project since its inception in 1990 and before, it seems quite long. Many are impatient to see the fruits of the multi-billion investment of public and private funds, and lament that the “sequencing of the human genome, once thought to be the key to unlocking the discovery of common genetic contributors to cancer, heart disease, diabetes and other complex disease, has turned out to be only a first step along a much longer path.”⁸ Perhaps one day, human genetics will become a routine part of the medical practice, an aspiration that was certainly part of the motivation for early release of the draft sequences once they were completed in 2001.⁹ Part of the problem in translating the Project into application is that the early estimates of the number of human genes—sometimes ranging as high as

Cosmetic Act, 21 U.S.C. §§ 301–399 (2000), but the regulation of foods and drugs are carried out under different sections of the Act and under separate authority of the Administration. See OFFICE OF MGMT. PROGRAMS, FDA ORGANIZATION CHART (2007), available at <http://www.fda.gov/oc/orgcharts/FDA.pdf>. The situation is similar in Canada, where Health Canada is the regulatory authority, but treats food and drugs separately under the Food and Drugs Act, R.S.C., ch. F-27 (1985). See Health Canada: Branches and Agencies, http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/index_e.html (last visited Feb. 28, 2008).

8. M.W. Foster et al., *The Routinisation of Genomics and Genetics: Implications for Ethical Practices*, 32 J. MED. ETHICS 635, 635 (2006).

9. See J. Craig Venter et al., *The Sequence of the Human Genome*, 291 SCIENCE 1304, 1305 (2001); Int'l Human Genome Sequencing Consortium, *Initial Sequencing and Analysis of the Human Genome*, 409 NATURE 860, 862–63 (2001).

120,000—fell dramatically to about 30,000.¹⁰ This has meant that the idea of a central dogma in which one gene would produce one structural or functional protein gave way to a one-to-many problem in which the multiple roles of genes must now be elucidated. Compounding the problem is that of the three billion base pairs in each human genome, there is an inborn error rate of approximately one in every one thousand base pairs being a substitute for the correct version. This error rate gives rise to at least three million, possibly as many as 10 million, single nucleotide polymorphisms (SNPs). SNPs are structural variations in a genome which give rise to functional variations in gene products or in the regulation of genes.¹¹ With fewer genes, but more common built-in errors, the science of functional genomics is much more complicated.

To further complicate matters, in the course of the Human Genome Project it has become apparent that genes neither give rise to their products nor regulate their activity isolated from their environment. Environmental exposure to drugs,¹² toxins¹³ and nutrients have quickly become of great interest to those wishing to understand functional genetics in light of systems biology.¹⁴ Gene-environment interaction “refers to the differential phenotypic effects of diverse environments on individuals with the same genotype or to the discrepant effects of the same environment on individuals with different genotypes.”¹⁵ Twin studies are often used to illustrate this point since genetically identical twins interact with dissimilar environments with different outcomes, in fact, a journal

10. Venter et al., *supra* note 9; Int'l Human Genome Sequencing Consortium, *supra* note 9.

11. The International HapMap Project, which evolved out of the SNP Consortium, is dedicated to cataloguing SNPs and to devising improved methods for detecting human genetic variation. See INT'L HAPMAP PROJECT, ABOUT THE HAPMAP, <http://snp.cshl.org/thehapmap.html.en> (last visited Feb. 28, 2008).

12. See, e.g., Werner Kalow, *Historical Aspects of Pharmacogenetics*, in PHARMACOGENOMICS 1, 4 (Werner Kalow et al. eds., 2nd ed. 2005).

13. See, e.g., Charles W. Schmidt, *Toxicogenomics: An Emerging Discipline*, 110 ENVTL. HEALTH PERSP. 750, 750–52 (2002).

14. See, e.g., Leroy Hood, *Systems Biology: Integrating Technology, Biology, and Computation*, 124 MECHANISMS AGEING & DEV. 9, 13 (2003); Ben van Ommen, *Nutrigenomics: Exploiting Systems Biology in the Nutrition and Health Arenas*, 20 NUTRITION 4, 4–7 (2004).

15. Dolores Corella et al., *APOA5 Gene Variation modulates the Effects of Dietary Fat Intake on Body Mass Index and Obesity Risk in the Framingham Heart Study*, 85 J. MOLECULAR MED. 119, 120 (2007).

dedicated to twin research and human genetics exists.¹⁶ Twins represent a kind of controlled natural experiment, but they are the exception. The reality is much more like the difference between Winston Churchill, who famously enjoyed his drink and cigars and lived to the age of 90, and James Fixx, author of the *Complete Book of Running*,¹⁷ who nevertheless met an early death at the age of 52.

Nutrigenomics investigates the interaction between nutrients and genes. Genes affect how nutrients are metabolized, and reciprocally, nutrients affect how genes are expressed and regulated.¹⁸ The goals of nutrigenomics are thus two-fold.¹⁹ On the one hand, the goal is to understand the functional interaction between bioactive food components with the genome at the molecular, cellular and systemic level.²⁰ The goal is to understand the role of nutrients in gene expression, generally speaking, and more importantly how diet can be used to prevent or treat disease. On the other hand, if one takes into account the phenomenon of human genetic variation, the second goal of nutrigenomics is to understand the effect of genetic variation on the interaction between diet and disease.²¹ In this respect, the focus is on an individual's specific response to food due to genetic variants or polymorphisms in order to develop dietary recommendations regarding the risks and benefits of specific diets or dietary components to individuals as well as populations.²²

16. A recent example concerning food choice is Birgit Teucher et al., *Dietary Patterns and Heritability of Food Choice in a UK Female Twin Cohort*, 10 TWIN RES. & HUM. GENETICS 734 (2007). While it is tempting to think that twin studies point definitively to the contribution of environmental factors to development, it is often difficult to clearly identify causal factors from confounding events. On this issue see, for example, Eric Turkheimer et al., *Analysis and Interpretation of Twin Studies Including Measures of the Shared Environment*, 76 CHILD DEV. 1217 (2005).

17. JAMES FIXX, *THE COMPLETE BOOK OF RUNNING* (1977).

18. See, e.g., Evans & Johnson, *supra* note 2, at 11–14.

19. See, e.g., Dolores Corella & Jose M. Ordovas, *Single Nucleotide Polymorphisms that Influence Lipid Metabolism: Interaction with Dietary Factors*, 25 ANN. REV. NUTRITION 341, 353 (2005).

20. See Artemis P. Simopoulos, *Genetic Variation and Dietary Response: Nutrigenetics/Nutrigenomics*, 11 ASIA PAC. J. CLINICAL NUTRITION S117, S117 (2002).

21. *Id.*

22. DAVID CASTLE ET AL., *SCIENCE, SOCIETY AND THE SUPERMARKET: THE OPPORTUNITIES AND CHALLENGES OF NUTRIGENOMICS* 10–12, 22–33 (2007).

An example of nutrigenomics involves the relationship between caffeine intake from beverages like coffee, tea and soft drinks and a gene for an enzyme, cytochrome P450 1A2.²³ There are known variants of the gene, CYP1A2, which come in two forms: the CYP1A2*1A variant which is associated with rapid caffeine metabolism, and the CYP1A2*1F variant, which is associated with slow caffeine metabolism.²⁴ In the study conducted by Cornelis and her colleagues, 2014 people had their CYP1A2 genes sequenced, of which slightly more than half (1114) had the variant associated with slower caffeine metabolism.²⁵ While controlling for caffeine consumption, a slightly higher incidence of non-fatal myocardial infarctions was reported for the group of coffee drinkers who were slow metabolizers as compared to those who were fast metabolizers of caffeine.²⁶ The conclusion is that there is an association between having the CYP1A2*1F variant, caffeine consumption, and non-fatal myocardial infarction, whereas having the CYP1A2*1A might confer a relative protective effect because caffeine is metabolized up to four times as quickly.²⁷

Another example of nutrigenomics concerns lipid metabolism. Using participants from the Framingham Offspring Study, Corella and Ordovas studied the relationships between variants of the APOA5 gene, lipid metabolism, and body-mass index (BMI).²⁸ The APOA5 gene has several known SNPs, of which the 1131T>C is in linkage disequilibrium, which is to say the alleles occur in non-random patterns, and the 56C>G is not.²⁹ In their study, presence or absence of the 56C>G SNP had no discernable impact on the relationship between BMI and the total caloric intake attributable to lipid.³⁰ That is, irrespective of genotype, the phenotype associated with higher percentage of caloric intake attributable to lipids was always the same—higher BMI. The same was not true with 1131T>C variants.³¹ The majority has the TT variant, and shows a standard dose

23. Marilyn C. Cornelis et al., *Coffee, CYP1A2 Genotype, and Risk of Myocardial Infarction*, 295 JAMA 1135, 1135 (2006).

24. *Id.*

25. *Id.* at 1136.

26. *Id.* at 1136–38.

27. *Id.* at 1138–40.

28. Corella & Ordovas, *supra* note 19, at 348–55.

29. PHILIP W. HEDRICK, GENETICS OF POPULATIONS 525–40 (3rd ed. 2005).

30. Corella & Ordovas, *supra* note 19, at 350–52.

31. *Id.* at 378–79.

response to increasing the proportion of calories attributable to lipids.³² As the participants increase lipid intake as a percentage of calories consumed, their BMI goes up.³³ Yet for the 13% of the study group that has the CT variant, the opposite effect is observed.³⁴ For men and women in this group, the T>C variant has a protective effect against increased BMI, particularly when the composition of lipids is weighted toward mono unsaturated fatty acids (MUFAs).³⁵

These examples are typical of the kind of nutrient-gene association studies that comprise most studies in nutrigenomics. In these studies, a gene with known variants is identified because it has known or suspected significance in a metabolic pathway, and because the variants occur in non-trivial numbers in the population. The method is designed to establish a statistically significant correlation between the variant, one or more nutrients, and a measurable outcome, such as increased risk of non-fatal myocardial infarction or increased body-mass index.

Another approach to nutrigenomics is to examine trends in phenotypes that happen in ostensibly distinct populations of people, and to try to clarify the underlying gene-nutrient cause.³⁶ For example, most non-Europeans have some level of lactose intolerance because they have two polymorphisms that lack the enzyme, lactase, necessary to break down this milk sugar.³⁷ Similarly, Asian populations generally have low levels of alcohol dehydrogenase, the enzyme necessary to break down alcohol.³⁸ African American populations have higher than average levels of hypertension, attributable to the different activity angiotensinogen, an α -2 globulin protein released

32. *Id.*

33. *Id.*

34. *Id.*

35. *Id.* at 358–62.

36. See generally Richard S. Spielman et al., *Common Genetic Variants Account for Differences in Gene Expression Among Ethnic Groups*, 39 NATURE GENETICS 226 (2007).

37. Todd Bersaglieri et al., *Genetic Signatures of Strong Recent Positive Selection at the Lactase Gene*, 74 AM. J. HUM. GENETICS 1111, 1111–12 (2004); see also Sarah A. Tishkoff et al., *Convergent Adaptation of Human Lactase Persistence in Africa and Europe*, 39 NATURE GENETICS 31, 32–34 (2007).

38. H.W. Goedde et al., *Distribution of ADH₂ and ALDH₂ Genotypes in Different Populations*, 88 HUM. GENETICS 344, 345–46 (1992).

largely by the liver.³⁹ Some, but not all people are able to taste bitterness, and to varying degrees as a result of activity of the taste receptor gene TASR.⁴⁰

The hope of being able to develop public health measures for genetically identified groups is a powerful motivation for studying the genetics of populations. The scientific difficulty lies in being able to use genetics to draw definitive lines between “races” or “ethnicities.” Geneticists have long known that within populations there can be a great deal of intra-group variation, in fact, statistically speaking there can be greater intra-group variation compared to inter-group variation.⁴¹ Ioannidis et al. conducted a study in which they examined forty-three disease-gene associations in 697 study populations in search of “racial” differences that would underlie complex diseases.⁴² They found that genetic variants do exist within populations, but they were unable to conclude that these made significant contributions to disease progression attributable to “races” or “ethnicities.”⁴³ Yet at the same time there are well-known situations that suggest that searching for these differences in populations is not a pointless undertaking. Pima Indians in the United States have nearly twenty times higher incidence of type II diabetes compared with the rest of the U.S. population.⁴⁴ This high incidence is partially attributable to their diet, for their counterparts in Mexico who consume a more traditional diet, as well as evidence drawn from the historical record, suggests that Pima Indians have no higher background rates of type II diabetes when they consume their traditional diet.⁴⁵ Yet changes to dietary patterns do not explain why their incidence

39. Richard S. Cooper et al., *Heritability of Angiotensin-Converting Enzyme and Angiotensinogen: A Comparison of US Blacks and Nigerians*, 35 HYPERTENSION 1141, 1144–45 (2000).

40. Dennis Drayna, *Human Taste Genetics*, 6 ANN. REV. GENOMICS & HUM. GENETICS 217, 218–20 (2005).

41. See generally, Richard C. Lewontin, *The Appointment of Human Diversity*, 6 EVOLUTIONARY BIOLOGY 381 (1972); Noah A. Rosenberg et al., *Genetic Structure of Human Populations*, 298 SCIENCE 2381 (2002).

42. John P.A. Ioannidis et al., *‘Racial’ Difference in Genetic Effects for Complex Diseases*, 36 NATURE GENETICS 1312 (2004).

43. *Id.* at 1315–16.

44. William C. Knowler et al., *Diabetes Incidence and Prevalence in Pima Indians: A 19-Fold Greater Incidence than in Rochester, Minnesota*, 108 AM. J. EPIDEMIOLOGY 497, 498–99 (1978).

45. V.L. Boyce & B.A. Swinburn, *The Traditional Pima Indian Diet. Composition and Adaptation for Use in a Dietary Intervention Study*, 16 DIABETES CARE 369, 369–70 (1993).

of diabetes is drastically higher than the rest of the U.S. population. A genetic basis shared by the Pima for this uniquely detrimental dietary response is a reasonable hypothesis.

III. SOURCES OF CONTROVERSY: PUBLIC ACCESS TO NUTRITIONAL GENOMICS

Nutrigenomics research is being undertaken to accomplish the twin goals of generating a genomic science of nutrient-gene interaction as well as a science of personal genetics and diet. Obviously, these must work in concert to have a complete science working from general principles translated to practical applications.⁴⁶ Although there is no disputing that environmental influences on genomes are causes of differential gene expression and regulation, and equally there is no doubt that nutrients can have these effects on genes, there is disagreement about the conclusions one can draw from nutrient-gene associations, particularly with respect to implications for disease etiology and progression. The concerns that have been voiced tend to fall along three lines: the view that the basic science has not matured to the point where it can be translated into applications;⁴⁷ the view that the public provision of nutrigenomics is premature;⁴⁸ and the view that nutrigenomics targeted at populations is premature and problematic because not enough is known about disease susceptibility genes.⁴⁹ Each of these will be considered in turn.

Optimism for the theory behind nutrigenomics can be distinguished from positive views about the extent to which the science can be applied, particularly in the form of commercialized products and services. In this respect, nutrigenomics gets swept up in a general claim about the prematurity of translating any genomic science into publicly available applications. In their widely read and influential paper, Susanne Haga, Muin Khoury and Wylie Burke argued that using genomics to develop individual risk profiles is “not

46. CASTLE ET AL., *supra* note 22, at 8–12, 33–42; Simopoulos, *supra* note 20.

47. Arab, *supra* note 3, at 169–70.

48. Susanne B. Haga et al., *Genomic Profiling to Promote a Healthy Lifestyle: Not Ready for Prime Time*, 34 NATURE GENETICS 347, 348–49 (2003).

49. Kathleen Ries Merikangas & Neil Risch, *Genomic Priorities and Public Health*, 302 SCIENCE 599, 599–600 (2003).

ready for primetime.”⁵⁰ They contend that even if one could come up with reliable genetic profiles for individuals, translating them into clinically valid and clinically useful applications is in the future.⁵¹ What they have in mind is “personalized nutrition,” in which individual are tested for a panel of genes and given dietary advice depending on which SNPs are identified.⁵² They focus on methylenetetrahydrofolate reductase (MTHFR), which is an often cited example of nutrigenomics.⁵³ A well-characterized polymorphism, 677C>T leads to lower activity of the enzyme, which lowers the conversion of homocysteine to methionine.⁵⁴ Increased blood levels of homocysteine is considered a cardiovascular disease risk factor. While the nutrient-gene interaction is well characterized,⁵⁵ there is dispute in the literature about whether dietary supplementation with folate really does lower the risk of cardiovascular disease.⁵⁶ Part of the problem is that the frequency for the 677C>T polymorphism is estimated at 10–15%, making it difficult to follow its effects outside of studies with large samples.⁵⁷ Furthermore, cohort and intervention studies need to be conducted to show, in controlled conditions, the effect of folate supplementation.

As Ordovas and Corella have pointed out in their 2004 review of nutrigenomics, MTHFR exemplifies many of the gaps in knowledge in nutrigenomics: lack of knowledge of all system components; the need to improve experimental design, dietary assessments and statistics; and the tools to study and visualize complex interaction with the support of massive computing power.⁵⁸ One day nutrigenomics might be able to support the

50. Haga et al., *supra* note 48, at 347.

51. *Id.* at 348–49.

52. *Id.*

53. Peter J. Gillies, *Nutrigenomics: The Rubicon of Molecular Nutrition*, 103 J. AM. DIETETIC ASS'N (SUPPLEMENT 2) S50, S52 (2003).

54. Raymond Meleady et al., *Thermolabile Methylenetetrahydrofolate Reductase, Homocysteine, and Cardiovascular Disease Risk: The European Concerted Action Project*, 77 AM. J. CLINICAL NUTRITION 63, 63 (2003).

55. Pauline A.L. Ashfield-Watt et al., *Methylenetetrahydrofolate Reductase 677C→T Genotype Modulates Homocysteine Responses to a Folate-Rich Diet or a Low-Dose Folic Acid Supplement: A Randomized Controlled Trial*, 76 AM. J. CLINICAL NUTRITION 180, 181 (2002).

56. Lydia A. Bazzano et al., *Effect of Folic Acid Supplementation on Risk of Cardiovascular Diseases*, 296 JAMA 2720, 2721, 2723–25 (2006).

57. The Homocysteine Studies Collaboration, *Homocysteine and Risk of Ischemic Heart Disease and Stroke*, 288 JAMA 2015, 2021 (2002).

58. Jose M. Ordovas & Dolores Corella, *Nutritional Genomics*, 5 ANN. REV.

nutritional preemption of disease, but it will have to overcome complex obstacles of integrating basic science with practical applications and service delivery.⁵⁹

The lightning rod of nutrigenomics has been directly providing nutrigenomic tests to consumers (i.e. consumers are able to buy over-the-counter, at-home genetic tests). The issue began shortly after the 2001 formation of Sciona, a private company in the United Kingdom, which began offering nutrigenomic tests directly to consumers through retail outlets. Sciona was soon embroiled in a controversy started by the non-governmental organization and genetics watchdog GeneWatch and the U.K. Consumers Association, operating under the trade name “Which?”⁶⁰ These organizations were concerned with the potential to mislead consumers and mistreat genetic data. Soon, the Guardian, a U.K. daily newspaper took up the issue, and the Human Genetics Commission, a governmental advisory body, began its review of direct-to-consumer genetic tests.⁶¹ Part of the problem stemmed from the novelty of nutrigenomics itself, which raised legitimate questions, discussed above, about the quality of the science that was being translated into applications, but there are more fundamental concerns about the quality of the tests themselves⁶² and the enforceability of the few regulations that applied.⁶³

More recently, the Government Accountability Office (GAO) in the United States “ghost shopped” several nutrigenomics firms using fourteen fictitious personae in order to evaluate the

GENOMICS & HUM. GENETICS 71, 102–03, 106–07 (2004).

59. See Peter J. Gillies & Elaine S. Krul, *Using Genetic Variation to Optimize Nutritional Preemption*, 137 J. NUTRITION 270S, 271S–73S (2007).

60. James Meek, *Public ‘Misled by Gene Test Hype:’ Scientists Cast Doubt on ‘Irresponsible’ Claims for Checks Offered by Body Shop*, GUARDIAN (U.K.), Mar. 12, 2002, at 9; Press Release, GeneWatch UK, *Leaked Document Exposes Government Failure to Regulate Human Genetic Tests* (June 4, 2002), available at [http://www.genewatch.org/article.shtml?als\[cid\]=492860&als\[itemid\]=504430](http://www.genewatch.org/article.shtml?als[cid]=492860&als[itemid]=504430); see generally *Which? Home Page*, <http://www.which.co.uk> (last visited Feb. 21, 2008).

61. HUMAN GENETICS COMM’N, *GENES DIRECT: ENSURING THE EFFECTIVE OVERSIGHT OF GENETIC TESTS SUPPLIED DIRECTLY TO THE PUBLIC* (2003), available at http://www.hgc.gov.uk/UploadDocs/DocPub/Document/genesdirect_full.pdf.

62. Marcus Stevenson, *Good Gene Hunting: Commercializing Safety and Efficacy of Home Genetic Test Kits*, 3 J. BIOLAW & BUS. 29, 30–38 (1999).

63. James Meek, *Genetic Testing Rules ‘Unenforceable:’ Watchdog Calls for Suspension of Unusable Code of Practice*, GUARDIAN (U.K.), June 4, 2002, at 7.

genetic tests, the assessments of the nutrigenomics profile, and the linkages between nutrigenomics testing services and the sale of dietary supplements.⁶⁴ The GAO secretly paid for services of nutrigenomics companies, sending fictitious personal and lifestyle information to several companies.⁶⁵ The GAO reported inconsistencies in the results, questioned the methods of the firms, and challenged the veracity and utility of the claims provided by the companies.⁶⁶ Although there are several methodological flaws in the report, the conclusion that at-home genetic tests offered to consumers are snake-oil was uncritically repeated.⁶⁷ The flaws in the methodology and conclusions of the GAO report are serious and potentially damaging to private interests in nutrigenomics, as well as public confidence in the Food and Drug Administration (FDA). There is, however, an equal claim that the direct-to-consumer market is not immune from criticism. As we shall see below, the net effect, intended or not, is that the FDA must now take steps to address the real and perceived regulatory lacunae falling within its mandate. As with the Human Genetics Commission in the United Kingdom, this is not merely a matter of inter-mural jostling between parts of government, aided and abetted by non-governmental organizations.

There are concerns about direct-to-consumer genetic tests garnering media attention where they may shape the public's perception of nutrigenomics.⁶⁸ Unfortunately, very little information of consumer awareness, attitudes and intent to purchase nutrigenomics products and services is available. The Institute for the Future in California has conducted research for its members on the potential for nutrigenomics market development,⁶⁹ but social science research from an academic

64. U. S. GOV'T ACCOUNTABILITY OFFICE, REPORT NO. GAO-06-977T, NUTRIGENETIC TESTING: TESTS PURCHASED FROM FOUR WEB SITES MISLEAD CONSUMERS (2006).

65. *Id.*

66. *Id.*

67. Gene Russo, *Home Health Tests are 'Genetic Horoscopes,'* 442 NATURE 497, 497 (2006); Andrew Pollack, *The Wide, Wild World of Genetic Testing*, N.Y. TIMES, Sept. 12, 2006, at G4; Unmesh Kher, *Can a DNA Test Tell You How to Live Your Life?*, TIME, Aug. 1, 2006, <http://www.time.com/time/nation/article/0,8599,1221727,00.html>.

68. INT'L FOOD INFO. COUNCIL, 2005 CONSUMER ATTITUDES TOWARD FUNCTIONAL FOODS/FOODS FOR HEALTH 12-13 (2006).

69. MARY CAIN & GREG SCHMID, INST. FOR THE FUTURE, FROM NUTRIGENOMIC SCIENCE TO PERSONALIZED NUTRITION: THE MARKET IN 2010, at 45-60 (2003).

setting lags behind.

In light of the concerns regarding the readiness of the science for translation into practice and direct-to-consumer provision of nutrigenomic tests, population-level applications which would target genetic sub-populations using race as a proxy for genetic variation might seem more appealing than targeting individual genetic differences. Two different approaches to population-level nutrigenomics exist. One is the development of a research platform that seeks to understand the causes of health disparities between groups, for instance The National Center on Minority Health and Health Disparities Center for Excellence for Nutritional Genomics at the University of California, Davis which has as its mission “to reduce and ultimately eliminate racial and ethnic health disparities resulting from environment x gene interactions, particularly those involving dietary, economic and cultural factors.”⁷⁰ The private sector has a similar interest in populations. For example, the company Interleukin Genetics has interest in targeted marketing for osteoporosis tests because they believe that the COL1A1 SNP test can differentiate osteoporosis risk in Caucasians and Asians.⁷¹ Yet it is precisely this research and these applications of genetics that attract criticism from those who are concerned about the integration of unwarranted racial profiling in research and market development.⁷² Part of the concern is the error-prone misuse of race as a proxy for genetic variation, the other part is the perpetuation of racial stereotypes that neither fit social nor biological realities. The fear is that genetics could repeat the ills of the past by becoming a new eugenics,⁷³ or eugenomics,⁷⁴ in

70. National Center for Minority Health and Health Disparities (NCMHD) Center of Excellence for Nutritional Genomics Home Page, <http://nutrigenomics.ucdavis.edu/nutrigenomics/> (last visited Feb. 21, 2008).

71. Press Release, Interleukin Genetics, Interleukin Genetics Initiates Study of IL-1 Gene Variation and Osteoporosis in Korean Women (Sept. 7, 2006), available at <http://ilgenetics.com/content/about-interleukin/newsDetail.jsp/q/news-id/93>.

72. Sandra Soo-Jin Lee, *Racializing Drug Design: Implications of Pharmacogenomics for Health Disparities*, 95 AM. J. PUB. HEALTH 2133, 2137–37 (2005).

73. Garland E. Allen, *Is a New Eugenics Afoot?*, 294 SCIENCE 59, 59–60 (2001).

74. Julie M. Aultman, *Eugenomics: Eugenics and the Ethics in the 21st Century*, 2 GENOMICS, SOC’Y & POL’Y 28, 44–46 (2006).

which science and technology are channeled in the direction of replacement or augmentation of traits, rather than disease prevention and therapy. One study, however, finds no direct evidence of states directly coercing their population to undergo genetic testing—which if true speaks directly against the concerns just described in which eugenics features as a state-supported campaign against unwanted genetic variation. As the authors of the study say, people do not appear to be “regulated, sanctioned and manipulated by others who press them to comply with public health objectives.”⁷⁵ But it may be that what people “conceive as rational, morally binding and desirable, reproduces collective imperatives and social control.”⁷⁶ That is, individual adoption of eugenics or eugenomics is a more seditious reality because groups can be manipulated to create, or replicate, messages not necessarily of their own making.

IV. NUTRIGENOMICS INNOVATION: AN EXAMPLE OF CONVERGENT TECHNOLOGIES

Nutrigenomics is a highly innovative field in which new science and technology is being generated, creating opportunity to develop innovative regulatory responses. Nutrigenomics explores novel environmental genomics linkages between nutrients and genes. These associations create the potential for individual, group and public health interventions. At the same time, nutrigenomics raises many intriguing issues about establishing regulatory environments which address the legal and ethical dimensions of the field.⁷⁷ Among these: the need to address the collection and storage of biological samples and genetic data, privacy issues, distributive justice issues about access, and models of service delivery.⁷⁸ Practical issues also extend to considerations about the necessary training and development of competency in health care professions who must respond to public demand for services and advice.⁷⁹

75. Wolfgang van den Daele, *The Spectre of Coercion: Is Public Health Genetics the Route to Policies of Enforced Disease Prevention?*, 9 COMMUNITY GENETICS 40, 41 (2006).

76. *Id.*

77. Nola M. Ries & Timothy Caulfield, *First Pharmacogenomics, Next Nutrigenomics: Genohype or Genohealthy?*, 46 JURIMETRICS J. 281, 285–300, 302–04 (2006).

78. Castle et al., *supra* note 5.

79. David Castle & Nola M. Ries, *Ethical, Legal and Social Issues in Nutrigenomics: The Challenges of Regulating Service Delivery and Building*

Discussions of ethical and legal issues raised by nutrigenomics focus on regulatory systems' capacity to adapt existing regulations to unanticipated applications arising from nutrigenomics because some perceive the field as entirely unregulated.⁸⁰ In general, this is a sensible approach to practical problems in identifying and filling in regulatory gaps arising from new science and technology. Further attention devoted to the system of innovation that gives rise to nutrigenomics facilitates and enhances success in tackling the practical regulatory issues. Nutrigenomics is the product of several decades of advances in molecular nutrition science,⁸¹ leveraged by comparatively more recent human genomics and genetics.⁸² Whereas nutrition science has tended to reside more on the side of human physiology and biochemistry than within the context of medicine, the distinctly biomedical framework of the Human Genome Project has permanently changed the course of nutrition science in the direction of biomedicine. The role of genomics as an environmental determinant of health has further broadened nutrition science to include the social and environmental sciences in a more expansive and evolving conception of the field.⁸³

Whereas some fields of science and technology tend to stay within rather narrowly prescribed boundaries, changes in nutrition science, particularly because of the advent of nutrigenomics, cross over those boundaries. It is useful to distinguish between conventional and convergent science and technology.⁸⁴ Conventional science and technology tends to be bounded by the subject matter or methods employed in the science—embryology is a common example drawn from the history of science. Convergence in science and technology happens when fields that might otherwise be regarded as conventional are overlapped to leverage new opportunities to ask different kinds of questions and to use blends of scientific methodologies. Among the more obvious recent examples are

Health Professional Capacity, 622 MUTATION RES. 138, 141–42 (2007).

80. *Id.*

81. Ordovas & Corella, *supra* note 58, at 71–73.

82. Müller & Kersten, *supra* note 4, at 315–16.

83. See Geoffrey Cannon & Claus Leitzmann, *The New Nutrition Science Project*, 8 PUB. HEALTH NUTRITION 673, 679–82, 687–91 (2005).

84. DAVID CASTLE ET AL., CONVERGENCE IN BIOTECHNOLOGY INNOVATION: CASE STUDIES AND IMPLICATIONS FOR REGULATION 24–28 (2006).

nanoscience and nanotechnology, particularly as these areas drive convergence between information technology, biotechnology and cognitive science.⁸⁵ As with nanoscience and nanotechnology, there is interest in the development of new technologies destined to be marketable products and services, as well as the development of enabling scientific platforms based on technological advances that will further enable research and development.⁸⁶ Predictably, there is uptake on the issue about whether the commercial science and technology are moving too quickly in advance of regulatory science and public acceptance.⁸⁷

Innovation in convergent science and technology has an impact on regulation because it exposes the limitations of existing regulations to cope with new products and services. A case in point is the regulation of direct-to-consumer genetic tests. In other situations, convergent science and technology join disparate fields of science and technology, but the regulations for the conventional fields may not also converge, creating gaps in regulation. Concerns about the regulation of plant-made products, for instance, often focus on regulatory gaps.⁸⁸ In a third case, convergent science and technology raises the potential for new hazards requiring identification, characterization, and the development of regulations proportionate to the risk posed by the new science and technology. Nanoscience and nanotechnology find themselves in this exact situation; the challenge is for regulatory science to develop scientific tools that will enable regulators to precisely define and respond to regulatory issues.⁸⁹

85. See, e.g., CONVERGING TECHNOLOGIES FOR IMPROVING HUMAN PERFORMANCE: NANOTECHNOLOGY, BIOTECHNOLOGY, INFORMATION TECHNOLOGY AND COGNITIVE SCIENCE (Mihail C. Roco & William Sims Bainbridge eds., 2003).

86. See, e.g., GILL RINGLAND ET AL., NEW TECHNOLOGY WAVE: TRANSFORMATIONAL EFFECT OF NBIC TECHNOLOGIES ON THE ECONOMY 5–6, 8–12, 17–19, 24 (2004), available at http://ec.europa.eu/research/conferences/2004/ntw/pdf/sig3_en.pdf.

87. See, e.g., M.C. Roco, *Broader Societal Issues of Nanotechnology*, 5 J. NANOPARTICLE RES. 181, 184–86 (2003); WORLD COMMISSION ON THE ETHICS OF SCIENTIFIC KNOWLEDGE AND TECHNOLOGY (COMEST), NANOTECHNOLOGIES AND ETHICS: POLICIES AND ACTIONS 8–10 (2007).

88. Julian K-C. Ma et al., *Molecular Farming for New Drugs and Vaccines: Current Perspectives on the Production of Pharmaceuticals in Transgenic Plants*, 6 EUR. MOLECULAR BIOLOGY ORG. REP. 593, 595–97 (2005).

89. See Michael D. Mehta, *From Biotechnology to Nanotechnology: What Can We Learn from Earlier Technologies?*, 24 BULL. SCI., TECH. & SOC'Y 34, 35–37 (2004).

The convergence of genomics and genetics with nutrition science raises generic issues for regulators, but of course the urgency and severity of the problem varies considerably among jurisdictions. In general, it is safe to say that as more is known about the bioactivity of food components, with or without the augmentation of genetic profiling, the regulation of functional foods, nutraceuticals and supplements will encroach upon drug regulations.⁹⁰ Regulatory gaps can appear if foods with high bioactivity, or derivatives thereof, are not regulated and thus fall through domains of regulatory scrutiny. Nutrigenomic tests present other challenges for regulators who must decide if products and services offered are along the spectrum of life-style tests, disease susceptibility tests, or constitute tests that deserve more advanced regulatory control as they would if regulated as a medical device. Regulators might also consider whether the clinical validity and utility of nutrigenomic tests requires regulatory oversight. Access to the tests and the information they generate is also a major regulatory issue if it is believed that nutrigenomic tests ought to conform to a high level of patient consent, rather than *caveat emptor* for clients, and whether strict controls on testing children ought to be enforced. In general, nutrigenomics creates uncertainty for regulators because it is somewhat discretionary to decide if a nutrigenomic product or service needs regulation because it concerns patient, not client data; or whether the information provided to the client or patient is medical advice, not wellness advice, that falls within the scope of practice of a regulated health care professional.⁹¹

V. INNOVATION, UNCERTAINTY, REGULATION AND NUTRIGENOMICS

Convergence in biotechnology innovation facilitates the leveraging of new biotechnology innovation, often at a surprisingly accelerated pace. Corresponding regulatory adaptation to new products and services is often warranted, but

90. See, e.g., David J.A. Jenkins et al., *A Dietary Portfolio Approach to Cholesterol Reduction: Combined Effects of Plant Sterols, Vegetable Proteins, and Viscous Fibers in Hypercholesterolemia*, 51 *METABOLISM* 1596, 1600–02 (2002).

91. These issues are considered fully in CASTLE ET AL., *supra* note 22, at 111–32.

obstacles lie in the path of regulatory initiatives. This is particularly the case when regulatory agencies are strongly “siloed,” which is to say they have a narrow mandate that is maintained with well-integrated vertically controlled policies and procedures, but lack horizontal collaborative capacity, policies or procedures that would enable inter-mural regulatory cooperation to a greater extent. In previous work on convergent biotechnology regulation, five obstacles besetting regulatory agencies have been identified.⁹² These are: the complexity of a problem that may escape the scope of the regulatory agency’s mandate and capacity; a regulatory culture in which a given agency is uncooperative with other agencies; a reactive, rather than proactive mode of the agency; an obsession with “sound science” to the point where it alone is believed to solve all aspects of regulatory problems; and finally, the desire to focus on domestic regulation only when international harmonization of standards might be equally important.⁹³

Overcoming these obstacles requires, at minimum, regulatory analysis to identify limits of existing regulation and to close gaps with new regulations. It might also be necessary to be quite innovative in the development of regulatory frameworks to address the challenges of new classes of product and services if the novelty, range and hazardousness of identified risks are outside the known and familiar scope of regulation. In short, science and technology innovation can drive regulatory innovation. Evidence of change, or the need for change, can be found in situations where there is demand for four types of regulatory innovation: new regulatory concepts and definitions; new regulatory processes; new regulatory structures; and new regulatory paradigms. A fifth and final source of innovation arises when the first four developments are synthesized into evolving, over-arching conceptions of governance and regulation.⁹⁴

Demands for regulatory change can easily outstrip the capacity of regulatory agencies to identify and respond to new issues. Sometimes it is the case that basic issues are not yet resolved and so a new regulatory regime cannot be imposed until the fact situation is resolved. Take, for example, the role of the health practitioner, an issue which is relevant in

92. CASTLE ET AL., *supra* note 84 at 65–67.

93. *Id.*

94. *Id.* at 71.

nutrigenomics. One option for addressing concerns about the advice given to clients and patients is to make sure that regulated health care professionals are involved in, or are the sole provider, of the advice. While appealing on the surface, health care practitioners do not have reassuring levels of appropriate training to address issues in nutrigenomics. Reviews of North American medical school curriculae indicate that genetics and genomics training are low priority for health care practitioners.⁹⁵ In their daily practice, the training gap is reinforced because practitioners are more like than not to say that while genetics and genomics are important scientifically, they do not have immediate relevance and impact to clinical practice.⁹⁶ In the absence of detailed knowledge, confidence in applications of genetics and genomics, and an obvious clinical need, health care practitioners do not view the future of genetics and genomics in clinical practice as positive, current knowledge.⁹⁷ No health care practitioner field has “claimed” nutrigenomics as its territory, and so fundamental issues requiring public education are likely to remain touched by health care practitioners for the foreseeable future.⁹⁸ In a situation such as this, a regulator cannot expect regulated professions to take up the regulatory slack, or to be effective resources to guide regulators in identifying issues. The opposite is true: regulators likely have more insight than professional groups when it comes to nutrigenomics because they are closer to the problems presented by rapid innovation, whereas professional groups are penultimate end users of commercialized technologies.

Nutrigenomics can be regulated in the United States principally through the control of genetic tests.⁹⁹ The two

95. See Alan E. Guttmacher, Mary E. Porteous & Joseph D. McInerney, *Educating Health-Care Professionals About Genetics and Genomics*, 8 NATURE REVIEWS: GENETICS 151, 154–55 (2007); Ann Silversides, *The Wide Gap Between Genetic Research and Clinical Needs*, 176 CAN. MED. ASS'N J. 315, 316 (2007).

96. See Guttmacher, Porteous & McInerney, *supra* note 95, at 153–55.

97. David Castle, *Clinical Challenges Posed by New Biotechnology*, 79 POST-GRADUATE MED. J. 65, 66 (2003).

98. See Stephanie Kurzenhäuser & Ralph Hertwig, *How to Foster Citizens' Statistical Reasoning: Implications for Genetic Counseling*, 9 COMMUNITY GENETICS 197, 198–99 (2006).

99. For a full discussion of relevant U.S. regulations, and comparison with other jurisdictions, see Nola M. Ries, *Regulating Nutrigenetic Tests: An*

applicable statutes are the Clinical Laboratory Improvement Amendments (CLIA)¹⁰⁰ and the Food, Drug, and Cosmetic Act (FDCA).¹⁰¹ CLIA certification of laboratories conducting genetic tests, which are regarded as “high complexity tests,” ensures that genetic tests meet standards for quality control and testing proficiency.¹⁰² The FDA also has authority to regulate genetic tests under the FDCA, particularly the sale of genetic tests kits, which are regulated as *in vitro* diagnostic devices (IVDs).¹⁰³ The FDA decides which of three classes of medical device an IVD falls into, depending on the risk that it poses. In addition to CLIA and the FDCA, the Federal Trade Commission (FTC) protects consumers from deceptive commercial practices and false advertising.¹⁰⁴ In this respect, the FTC ensures that tests that have been approved by the FDA are marketed with truthful advertising.

The GAO report and the Senate Special Committee on Aging hearing held in Washington D.C. on July 27, 2006¹⁰⁵ was intended to put pressure on the FDA to use existing regulations, and to develop new regulations, in order to protect consumers. The central claim of the GAO report is that there is no nutrigenomic-specific regulation that would protect consumers from maleficent private sector interests.¹⁰⁶ Given the newness of the field, it should come as no surprise that tailor-made regulations have not been developed for this budding field. More importantly, direct-to-consumer nutrigenomic tests presently comprise a very small market, and so it is unlikely that nutrigenomic-specific regulations will be developed until the market grows significantly. The regulatory issue, then, is whether existing regulations meet the regulatory challenges posed by nutrigenomics.¹⁰⁷

Despite the gap in health care practitioner knowledge about

International Comparative Analysis, 16 HEALTH L. REV. (forthcoming 2008).

100. Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a (2000).

101. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–399 (2000).

102. 42 U.S.C. § 263a(b) (2000).

103. 21 U.S.C. § 321(h) (2000).

104. 15 U.S.C. §§ 45, 52 (2000).

105. U. S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 64; *At Home DNA Tests: Marketing Scam or Medical Breakthrough?*: Hearing Before the S. Spec. Comm. on Aging, 109th Cong. (2006).

106. U. S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 64, at 22.

107. Whether the regulations are being enforced is a separate issue beyond the scope of this paper. For consideration of this issue, see Ries, *supra* note 99.

genetics and genomics discussed earlier, the FTC has noted that consumers might be taking tests for which they may wish to seek independent advice. To this end, the FTC has encouraged the public to speak with their physicians about at-home genetic tests.¹⁰⁸ The FTC's advice to the public regarding at-home genetic tests has a dual function. On the one hand, by issuing the advice to consumers, the FTC has taken action which is consistent with the FTC's approach to the marketing of genetic tests. Second, the FTC does not over-reach its regulatory authority, since it generally receives guidance from the FDA about what would constitute appropriate claims for genetic test kit.¹⁰⁹

With respect to the adequacy of existing regulations, to say that there are no efforts to address the regulatory gaps associated with nutrigenomics misses some of the more interesting actions by the FDA. There are, for example, regulatory amendments that would extend powers to the FDA's oversight of clinical laboratories.¹¹⁰ In addition, the FDA has issued two important guidance documents—public documents stating the FDA's position on the correct interpretation of legislated regulation.

In the first guidance document, the FDA attempts to bring regulatory clarity to the question of what counts as an analyte specific reagent (ASR) for commercial distribution and how it will be regulated.¹¹¹ This is an important guidance document,

108. FEDERAL TRADE COMMISSION, TALK TO YOUR DOCTOR OR HEALTHCARE PRACTITIONER ABOUT HOME GENETIC TESTS (2006), *available at* <http://www.ftc.gov/opa/2006/07/fyi0650.shtm>; FEDERAL TRADE COMMISSION, AT-HOME GENETIC TESTS: HEALTHY DOSE OF SKEPTICISM MAY BE THE BEST PRESCRIPTION (2006), *available at* <http://www.ftc.gov/bcp/edu/pubs/consumer/health/hea02.shtm>.

109. Working Agreement Between the Federal Trade Commission and the Food and Drug Administration, 3 Trade Reg. Rep. (CCH) ¶ 9850.01 (1954) (as originally enacted). In 1971, the Agreement was amended to provide the FDA with explicit and primary authority over prescription drug advertising. Memorandum of Understanding, 36 Fed. Reg. 18,539, 4 Trade Reg. Rep. (CCH) ¶ 9851 (Sept. 16, 1971).

110. FDA Guidance Document: "Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices," 73 Fed. Reg. 5,574 (Jan. 30, 2008).

111. Guidance for Industry and FDA Staff Regarding Commercially Distributed Analyte Specific Reagents 72 Fed. Reg. 52,568 (Sept. 14, 2007). Analyte Specific Reagents (ASRs) are defined as "antibodies, both polyclonal

because ASRs are necessary components of any genetic test kit, or any so-called “home brew” test which is offered as a laboratory service rather than a test kit. Under the broad definition provided by the FDA for ASRs in this guidance document, many of the reagents used in DNA typing will be controlled by FDA regulations, meaning that nutrigenomic tests offered either as a genetic test kit or a home-brew test would generally be subject to regulations subsequent to this draft guidance. The major implication for nutrigenomics is that the use of some reagents can have significant implications for the medical device classification of a test.

In the draft guidance, the FDA also made a direct connection between tests likely to use ASRs and some kind of analytical step, potentially an algorithm that performs a calculation based on the results of an ASR-based test.¹¹² The conjunction of these two steps, in an *in vitro* diagnostic, multivariate index assay (IVDMIA) would be regulated together because the two parts are “inextricably linked in obtaining the patient-specific result.”¹¹³ This means that the diagnostic assay and the algorithm must be considered together, which de facto extends the FDA’s regulatory reach to the algorithm, which was not previously regulated. The guidance document has implications for how nutrigenomic tests will be classified and

and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reactions with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens.” *Id.* (citing 21 CFR 864.4020(a) (2006)).

112. *Id.*

113. OFFICE OF IN VITRO DIAGNOSTIC DEVICE EVALUATION & SAFETY, U.S. DEP’T OF HEALTH AND HUMAN SERVICES, GUIDANCE DOCUMENT 1610, DRAFT GUIDANCE FOR INDUSTRY, CLINICAL LABORATORIES AND FDA STAFF: IN VITRO DIAGNOSTIC MULTIVARIATE INDEX ASSAYS 3 (2006), available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/06d-0347-gdl0001.pdf>. The document reads:

[e]ven if a laboratory or other IVDMIA manufacturer physically or procedurally separates the analyte measurement portion of the test system (i.e., the first step described above) from the calculation portion of the test system (i.e., the second step described above), the two parts are inextricably linked in obtaining the patient-specific result that is reported in the third step. A physician could not use the variables derived in step one for the intended use of the test absent the algorithm that integrates them to calculate the patient-specific result. Likewise, the physician could not use the algorithm without the assay portion of the test system (step one) as specified by the manufacturer. Use of the complete test system—assay and algorithm—is required to obtain a meaningful test result. *Id.*

regulated as medical devices if they are in fact based on an algorithm-supported calculation which is interpreted as part of an IVDMIA.

VI. CONCLUSION

The controversy surrounding the regulation of nutrigenomics is partly attributable to the newness of the field. The promise of nutrigenomics will be fulfilled only if the science and technology is demonstrably useful and translated into products and services of use to patients and consumers. The availability of direct-to-consumer nutrigenomic tests has been a lightning rod for scrutiny of these offerings and for the science as a whole. Amidst legitimate questions about the strength of the science and utility of its applications, there has been increasing scrutiny of the regulatory capacity needed to ensure public safety. Because nutrigenomics is a convergent science and technology, it is to be expected that limits of regulations and gaps between regulations will be exposed, particularly with public offerings of nutrigenomics. Yet this chain of events, far from supporting calls for nutrigenomic-specific regulations, points to a more general conclusion about innovation, convergent technologies and regulation.

There cannot be a law for everything one might wish to regulate, but there are viable, non-statutory means for regulating a field like nutrigenomics. Given that the field is rapidly changing and regulatory issues are still being evaluated, guidance documents give regulators non-statutory tools by which they can regulate the field. The ASR guidance document and the IVDMIA draft guidance document address one of the central issues in nutrigenomics—the regulation of genetic tests in the commercial environment. Of course, there remain the issues about health claims and associated supplement regulation, and these issues will surely be taken up in the future. In the meantime, it is worth reflecting on the fact that regulatory innovation requires time, thoughtful consideration of the issues and options, as well as intensive and extensive resources.¹¹⁴

114. *See generally* NEW MODES OF GOVERNANCE IN THE GLOBAL SYSTEM (Mathias Koenig-Archibugi & Michael Zürn eds., 2006); REGULATORY INNOVATION: A COMPARATIVE ANALYSIS (Julia Black, Martin Lodge & Mark Thatcher eds., 2005).