Genes & Nutrition Vol. 1, No. 1, pp. 5-12, 2006
ISSN 1555-8932 print,

HARNESSING NUTRIGENOMICS: DEVELOPMENT OF WEB-BASED COMMUNICATION, DATABASES, RESOURCES, AND TOOLS

Jim Kaput[1, 2,3], Siân Astley[1, 4], Marten Renkema[5], Jose Ordovas[6], and Ben van Ommen[1]

[1] NuGO, European Nutrigenomics Organization (www.nugo.org), [2] Laboratory of Nutrigenomic Medicine, University of Illinois Chicago, Chicago, IL 60612, [3] NCMHD Center of Excellence in Nutritional Genomics, University of California Davis, Davis, CA 95616, [4]Institute of Food Research, Norwich, UK, [5] Topshare International BV, Wageningen, The Netherlands, and [6] Jean Mayer USDA HNRCA at Tufts University, Boston, MA 02111 - 1524

[Received January 23, 2006; Accepted February 10, 2006]

ABSTRACT: ***Nutrient – gene interactions are responsible for maintaining health and preventing or delaying disease. Unbalanced diets for a given genotype lead to chronic diseases such as obesity, diabetes, cardiovascular, and are likely to contribute to increased severity and/or early-onset of many age-related diseases. Many nutrition and many genetic studies still fail to properly include both variables in the design, execution, and analyses of human, laboratory animal, or cell culture experiments. The complexity of nutrient – gene interactions has led to the realization that strategic international alliances are needed to improve the completeness of nutrigenomic studies – a task beyond the capabilities of a single laboratory team. Eighty-eight researchers from 22 countries recently outlined the issues and challenges for harnessing the nutritional genomics for public and personal health. The next step in the process of forming productive international alliances is the development of a virtual center for organizing collaborations and communications that foster resources sharing, best practices improvements, and creation of databases. We describe here plans and initial efforts of creating the Nutrigenomics Information Portal, a web-based resource for the international nutrigenomics society. This portal aims at becoming the prime source of information and interaction for nutrigenomics scientists through a collaborative effort.***

KEY WORDS: Best practices, Information portal, International alliances, Nutrigenomics

Corresponding Author: Dr. Jim Kaput, Laboratory of Nutrigenomic Medicine, Department of Surgery, University of Illinois Chicago, 840 South Wood Street. MC 958, Chicago, IL 60612; FAX: 708.458.8586; Email: jkaput@uic.edu

INTRODUCTION

The considerable worldwide investment in health research since the 1960s has resulted in remarkable advances in understanding disease processes, the molecular and genetic workings of biological systems, and increase in health and longevity in many countries. For example, the United States appropriations for biomedical research funding to the National Institute of Health (NIH) were $334.9 billion for the 55 year period ending in 2005(http://officeofbudget.od.nih.gov/ui/AppropriationsHistoryByIC.htm). Such comprehensive figures for Europe or other international regions are difficult to find. The original European Union 15 countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, UK) provided a funding of € 536.3 million (approximately $0.9 billion US) from 1993 – 2003. During the same period, NIH appropriations were $137.8 billion. Progress in improved health outcomes and increased longevity came from associating the responses of populations to nutrients (epidemiology), from inbred laboratory animal strains, and from in vitro systems. While gains in health measures have been impressive, it is still not possible to describe in full the interconnected metabolic and molecular pathways that lead to disease, or identify genetic susceptibility, let alone the combined use of the above for a mechanism based and "individualized" disease prevention and health optimization, which is, of course, the prime target for healthy nutrition.

Only recently has it become obvious that the standard research approaches, while producing data and in some cases useful and applicable knowledge, are at best, incomplete. One estimate is that most published research findings are statistically false (Ioannidis, 2005) listing limitations that others have observed:

sample sizes that lack appropriate statistical power, control groups that are not appropriately matched to cases, population stratification that occurs because of genetic admixtures among study participants, and over-interpretation of data (among others, see: [Cardon and Bell, 2001; Lander and Kruglyak, 1995; Risch, 1997; Tabor et al., 2002]). HuGENet™ (http://www.cdc.gov/genomics/hugenet/default.htm), a global collaboration of individuals and organizations committed to the analyses of human genome variation on population health and determination of how human genetic information can be used to improve health and prevent disease, was formed in 1998 in response to these concerns and to provide accurate information to scientists and the public (Khoury, 2004). P^{3}G, the Public Population Project in Genomics (http://www.p3gconsortium.org/), is another international network promoting transparency and collaboration for human epidemiology studies. More recently, members of the epidemiology community (Ioannidis et al., 2006) have announced a "network of investigator networks" for improving human genetic research for sharing best practices, tools, and methods for analyses of associations between genetic variation and common diseases (http://www.cdc.gov/genomics/hugenet/default.htm).

We and others (Kaput, 2004; Kaput et al., 2005; Ordovas and Corella, 2004) added that (i) chronic disease may result from multiple molecular pathways that may obscure gene – disease or gene – nutrient – phenotype association analyses, (ii) the physiological response to the presence of a disease may alter expression of genetic information, (iii) genotype X environment interactions are rarely taken into account in nutritional or genetic epidemiological experiments, and these interactions are known to affect the expression of genetic information in response to different environments, (iv) ancestral background should be included because of epistasis (interaction of genes that are not alleles, especially the suppression of the effect of one gene by another), and (iv) laboratory animals and cultured cells may not account for genetic or nutritional variations found in humans.

The human genome (Lander et al., 2001; Venter et al., 2001) and HapMap (Consortium, 2004; Consortium, 2003; The International HapMap, 2005) projects have developed tools and produced genetic data that will be used to pursue the goals of personalized medicine and nutrition, but environmental variables (e.g. diet) must be included in experimental designs for epidemiology, laboratory animal, cell culture, and drug studies for this toolset to be of value. Recognizing and acknowledging the limitations of current research designs and strategies, 88 scientists from 22 countries called for strategic international alliances to harness nutrigenomic research for personal and public health (Kaput et al., 2005). The goals outlined were to (i) create a federation for sharing data from cell culture experiments, laboratory animal studies, and in particular human nutritional intervention and cohort (prospective and retrospective) studies, (ii) develop more highly powered human studies, (iii) improve analyses and consistency of phenotypes, (iv) develop better measurements of food intake, (v) introduce controls for population stratification, (vi) analyze a wider array of genetic makeup by recruiting individuals from different ethnic groups, (vii) include other environmental variables that alter expression of genetic information, and (viii) promote interactions between academia and industry to convert knowledge for the public good.

Turning these lofty goals into reality is challenging even in the Internet age: we learn of studies and resources primarily through peer-reviewed publication, the end of the experiment and analyses processes rather than the beginning. To begin the process of converting these goals to practice, we are developing a nutrigenomics information portal that will serve the needs of academic scientists, consumers, health and allied professionals, and food, biotechnology, and pharmaceutical companies. We present these plans and progress to encourage others to contribute to their refinement and implementation.

THE WEB SERVICE PROVIDER: NuGO

Nutrigenomics research is now being conducted in individual laboratories, multidisciplinary centers, departments, institutes, and companies. The majority if not all of these initiatives have specific goals or missions. Examples include: the biological basis of health disparities at the Center of Excellence in Nutritional Genomics (CENG) at the University of California Davis; cause and control of inflammatory bowel diseases at the New Zealand Centre of Excellence in Nutrigenomics (NZ-CEN); study of cardiovascular disease at Nutrition and Genomics Laboratory at Tufts University; and the Center for Gene Nutrient Interactions at the University of Alabama at Birmingham, which focuses on polyphenols and other plant bioactives in cancer (space limits this list). The National Cancer Institute's Dietary Prevention program was instrumental in NCI funding four nutrigenomics centers involved in cancer research. However, many government programs must target funding to their disease area and hence a general nutrigenomics database is outside their mandate. Other agencies such as the US Department of Agriculture (USDA) or the National Science Foundation (NSF) have targeted national mandates and similar arguments could be made for other nations' funding agencies.

The only nutrigenomics organization whose mission is multinational and not explicitly linked to a specific research program is The European Nutrigenomics Organization (NuGO). NuGO is funded by the European Union and consists of 23 partner institutions in 10 European Countries. The mission of NuGO is to develop, integrate, and facilitate genomic technologies, infrastructure and research for nutritional science, to train a new generation of nutrigenomics.

Figure 1. Nutrigenomics Information Portal.
The site map of showing four major nodes (Nutrigenomics Society Portal, Personalized Nutrition, Allied & Professional Health, and Food, Pharmaceutical & Biotechnology. The content of the Personalized Nutrition node is expanded to show the proposed content topics.

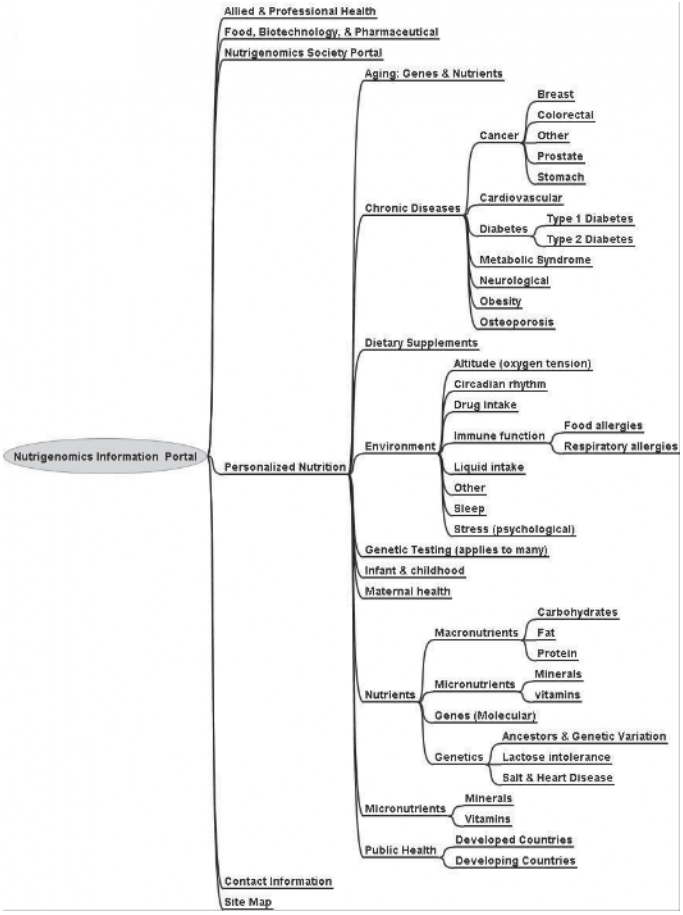
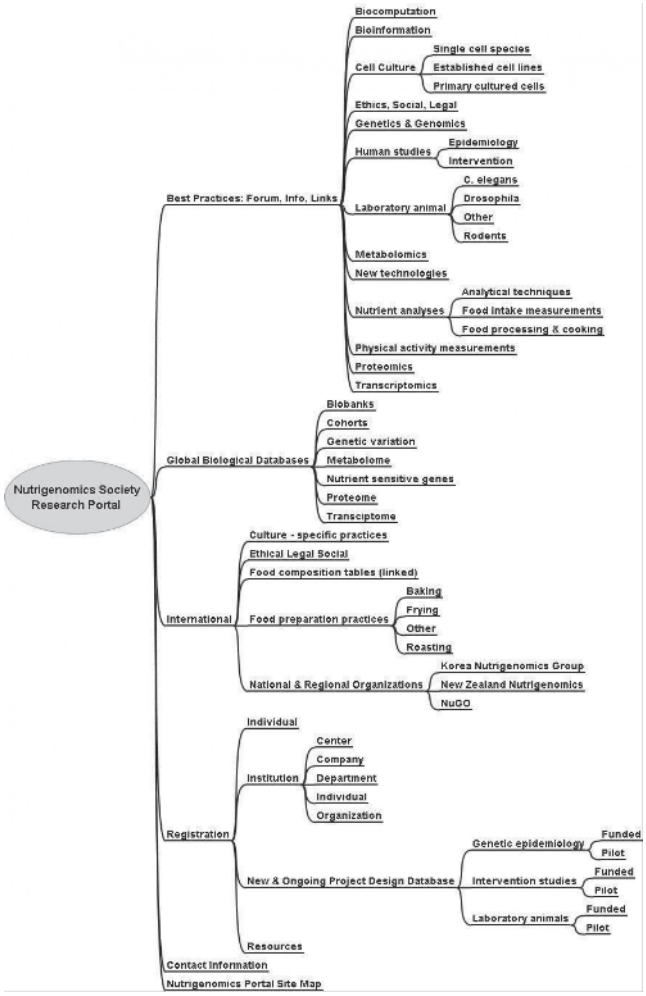


Figure 2. Nutrigenomic Society Research Portal.
The site map of the Nutrigenomic Research Information Portal, the top node of Figure 1. The content of the node is expanded to show the proposed content topics.



scientists, in order to improve the impact of nutrition in health promotion and disease prevention. NuGO has created a website environment that fosters communication among institutes, laboratories, and individuals. Many of the goals and plans for nurturing strategic collaborations within NuGO are similar to those of the International nutrigenomic community (see (Kaput et al., 2005). NuGO has offered and already provides the resources and infrastructure to host the international nutrigenomics website, which will eliminate the need to find and justify funding from other countries and programs for the initial years of development of this knowledge structure. However, it is in the best interest of all that cost sharing is instituted in the future.

THE SITE MAP DRAFT

As a part of the evaluation of requirements for a nutrigenomics information portal, we first focused on stakeholders who in one way or another have an interest in nutrigenomics. The four primary and broadly defined stakeholders are research and policy scientists, allied and professional health workers, the food, pharmaceutical, and biotechnology companies, and the consumer. Media interests are accommodated within all of these areas. Each of the four groups has slightly different interests and needs, all of which can be accommodated on one integrated website (Figure 1).

Research Scientists

A key stakeholder of the nutrigenomics information portal is the researcher. Our goal is to create an environment that will foster interactions, collaborations, and sharing of knowledge: research funding is scare and duplication of efforts is less than ideal. We describe key aspects of this virtual nutrigenomics society.

The need for registration

Nutrition, and in some cases nutrigenomics, differs from many scientific disciplines because perceived "authority" often comes from publishing books for the general public, regardless of credentials or quality assurances for the information content. While

there is a need for well-researched and written general audience texts, the discussions and collaborations we wish to foster require scientific expertise normally associated with advance degrees or publications in peer-reviewed journals. Access to the Nutrigenomics Research Portal section of the website will require registration. The established process (usually) requires one working day for the activation of privileges. In addition to individuals, we are asking that Centers, departments, companies, and other organizations register their expertise, resources, and interests, which will allow others to locate those interested in or working on specific nutrigenomic initiatives.

Several websites exist that describe networks or individual epidemiological projects (e.g., P^3G). However, information about each project design requires (usually) extraction of the number of study participants, phenotypes, measured genotypes, or other study specific data elements by copy and paste into other software (such as worksheets). While larger projects develop websites, information about individual study specifics requires time-consuming searches and copying, and publishing this information is a low priority. In contrast, the projects database envisioned for the Nutrigenomics Research Portal will be stored in a relational database allowing for data to be exported to other programs. For example, a researcher may want to know details of all planned or ongoing studies for Type 2 diabetes to identify one or more collaborators for increasing the power of experiments *before* publication. The international project registry database will not contain data from such studies but rather information about the studies' designs, sharing best practices whilst protecting research data before publication. Data from scientific studies will be deposited and managed in a separate set of databases also accessible from this site (Figure 2, Global Biological Databases).

International Nutrient and Cultural Information

Nutrigenomic research requires knowledge of the nutrient composition of foods within a culture. Such databases have been developed for several countries but the macro- and micro-nutrient content of local foods remains a significant challenge for the diverse cultures and diets throughout the world. The Food and Agriculture Organization (FAO) of the United Nations (http://www.fao.org/infoods/publications_en.stm) and various national governments have compiled food composition tables for many countries worldwide, but data must often be extracted from unlinked flat files or from publications and then it is incomplete particularly for bioactive compounds. A relational database of food composition is being developed by the European Food Information Resource Network (EuroFIR - http://www.eurofir.net/) through international collaborations in partnership with national government agencies.

Nutrigenomicists are also beginning to account for cultural differences in food manufacturing, preparation, and eating which includes religious customs. Capturing this information in epidemiological studies will be another challenge for researchers. The type and detail that need or should be obtained for epidemiological studies will require discussions and consensus among nutrigenomics researchers.

A full description of nutrient – gene interactions requires inclusion of as many ancestral groups and cultures as possible. One could make a strong argument that nutrigenomics research should first focus on populations in most need of food since delivering the appropriate nutrients at key developmental windows would do the most good in terms of personal and public health. The current research funding infrastructure makes that impractical at best since tax payers view research as an investment in their own cultures and national population. However, disadvantaged individuals and populations can be included in new and ongoing studies through appropriate collaborations with scientists and institutions in developing countries as can those most vulnerable sub-populations in developed countries. Since genetic testing costs are continually falling, economies of scale may allow the inclusion of DNA from many different populations at only incrementally higher costs. Transfer of technologies and information in any economies is desirable, but are outside the scope of these discussions.

Attention to the ethics of including individuals in developing countries is well recognized by the international nutrigenomic community. The Nuffield Council on Bioethics (http://www.nuffieldbioethics.org/) have thoroughly reviewed this topic in 1999 (Bioethics, 2002) with follow-up discussions published in 2005 (Bioethics, 2005). Their recommendations and policies will contribute to the design of human research studies throughout the world.

Best Practices

One of the most important aspects of the Nutrigenomics Society will be the development of best practices for improving the quality of experimental design, analyses, and results. NuGO already has begun this process with ongoing meetings and discussions among European scientists at different institutions. This effort has generated three best practices papers in transcriptomics (Garosi et al., 2005), metabolomics (Gibney et al., 2005), and proteomics (Fuchs et al., 2005). These papers and recommendations focus on the technologies of each discipline rather than experimental designs for human, laboratory animal, cell culture experiments, or for pre- and post-experiment biocomputation methods. Because technologies and experience change, these best practices will require ongoing discussions, which will, in the near future, include non-European scientists. NuGO does not currently have teams dedicated solely to the development of food frequency questionnaires and physical activity measurement tools, and these may be initiated in collaborations among international and NuGO scientists in the near future. Online forums will be created to foster interactions across national and physical divides.

Discussion and exchange platform

The Nutrigenomics Information Portal allows for (and currently hosts) a large variety of nutrigenomics related discussions and forums, structured into a number of research, technology, training and "outreach" areas.

Global Biological Databases

The ultimate goal of the website, registration of individuals and projects, resource development, and best practice is to create

data that can be shared across studies. The limitations imposed on nutrigenomic studies, specifically genetic variation, population architecture, individual and cultural food preferences, among others require large study populations and consistent phenotypes, common data elements, and database interoperability. None of these can be achieved without forethought and planning.

The databases described in Figure 2, cohorts, transcriptomics, genetic variation, nutrient sensitive genes, metabolome, proteome, and biobanks will be developed in collaboration with ongoing efforts within NuGO and appropriate members of the international nutrigenomics community. These "omic" specific databases will be cross-linked to data from food frequency questionnaires or data generated by yet-to-be developed means for measuring food intakes accurately, a necessity for complete analyses of the datasets.

"High end" nutrigenomics applications

As nutrigenomics will need collaborations, standardization in data structures is essential. A number of tools are currently being developed and implemented related to a variety of applications. As an example, NuGO has adopted the Base2 LIMS system (http://base.thep.lu.se/index.phtml) for coverage of data and study capture, and develops a nutrition and nutrigenomics specific ontology to link to Base in capturing the complete study. This will also serve for uploading datasets to public depositories like ArrayExpress (http://www.ebi.ac.uk/arrayexpress/). This activity aligns with the "Reporting Structure for Biological Investigations" (RSBI", http://www.mged.org/Workgroups/rsbi/rsbi.html) activity, which provides an overall structure for "omics" study capturing". Other high-end applications are related to data sharing and federation, allowing for cohort merging.

Personalized Nutrition

The consumer, designated here as Personalized Nutrition, is used as an example for describing the content of the site. We envision and plan to have 3 – 5 experts contribute short (500 word) descriptions, in relation to nutrigenomics concepts and, where possible, data and results, on the topics listed to the left of this figure. These postings will likely be conservative descriptions of what is known and what has to be discovered on a specific concept with the goal of presenting or directing users to an authoritative source for information on a given topic. Certain topics in this section are modeled on the CENG website at UC Davis (http://nutrigenomics.ucdavis.edu > information > Concepts in Nutrigenomics). For consistency and accuracy, section editors will be recruited from the international community of researchers. These individuals will have responsibilities similar to those of any peer-reviewed journal. Converting the science for the lay public will likely require media and science writer expertise that will be recruited from academic centers or commercial enterprises specializing in these tasks. Overall editorial control will reside with a committee chosen by NuGO and the international scientists involved. The concept for this section will not be to dumb down the science, but rather to provide understandable balanced information. Each of these pages may be linked to organizations and agencies that provide other information relevant to the topic. For example, the cancer pages may be inked to the NCI web pages for patients, cardiovascular to NIH, the American Heart Association, the European Heart Network (http://www.ehnheart.org), similar educational groups or specific research projects worldwide.

Allied and Professional Health

This stakeholder group consists of primary and specialty physicians, dietitians, genetic counselors, nurses, pharmacists, and others who interpret health information for the public and individual patients. These individuals are likely to request and require additional information about the details of studies, results, and opinions of experts about each of the topics shown in Figure 1 as it applies to their specialty. This information may be in the form of longer and more detailed description of individual or meta-analyses studies with links to primary documents and publications or clinical scenarios. Genetic counselors and dietitians versed in nutritional genomics concepts and technologies are likely authors for these topics in this section although some nutrigenomics scientists will also be involved.

Food, Pharmaceutical, and Biotechnology

Improving personal and public health through nutrigenomics will not be possible unless knowledge is converted to products or technologies that are accessible to individuals in all countries. The Food, Pharmaceutical, and Biotechnology section of the nutrigenomics information portal will be written for professionals interested in translating basic research to marketable products. Market opportunities exist in virtually all of the topics listed in Figure 1. The nature of competitive business practices and intellectual property considerations may require that this section be overviews of potential market possibilities as well as more basic information. Authors may be recruited from business schools or consortia of companies in the area. This section may serve as an information area for researchers and technology transfer agents at institutions to identify potential corporate partners giving an incentive for these commercial entities to participate.

A significant limitation for the involvement of commercial enterprises in developing nutrigenomics' products is that the majority of bioactives from food are generally regarded as safe (GRAS, a United States term) and as such, is not invented. That is, a company cannot patent an existing chemical and recover

SUMMARY

The proposed structure and topics of the nutrigenomics information portal and specifically the Nutrigenomic research web pages should be considered a work in progress. Our goal in publishing our activities and plans is precisely to solicit input in order to hone the utility of the website and planned databases. The figures from this paper as well as suggested topics for inclusion on the Allied & Professional Health and Food, Pharmaceutical, & Biotechnology areas have been posted on the NuGO International website (http://www.nugo.org/international) and on the Nutrigenomics Society pages within the NuGO website.

To participate, register at www.NuGO.org and request linkage to the international section. We view the development of these resources as an ongoing effort but also one that will be functional by the end of 2006.

ACKNOWLEDGEMENTS

The preparation of this manuscript was supported by the National Center for Minority Health and Health Disparities Center of Excellence in Nutritional Genomics, Grant MD 00222; from the National Institutes of Health/NHLBI grant HL54776, contracts 53-K06-5-10 and 58-1950-9-001 from the US Department of Agriculture Research Service,; and from the European Union, EU FP6 NoE Grant, Contract No. CT2004-505944.

REFERENCES

Cardon, L. R. and Bell, J. I. (2001) Association study designs for complex diseases. *Nature Reviews Genetics* **2**, 91-99.

Fuchs, D., Winkelmann, I., Johnson, I. T., Mariman, E., Wenzel, U. and Daniel, H. (2005) Proteomics in nutrition research: Principles, technologies and applications. *British Journal of Nutrition* **94**, 302-314.

Garosi, P., De Filippo, C., van Erk, M., Rocca-Serra, P., Sansone, S. A. and Elliott, R. (2005) Defining best practice for microarray analyses in nutrigenomic studies. *British Journal of Nutrition* **93**, 425-432.

Gibney, M. J., Walsh, M., Brennan, L., Roche, H. M., German, B. and van Ommen, B. (2005) Metabolomics in human nutrition: Opportunities and challenges. *American Journal of Clinical Nutrition* **82**, 497-503.

International HapMap Consortium. (2003) The international hapmap project. *Nature* **426**, 789-796.

International HapMap Consortium. (2004) Integrating ethics and science in the international hapmap project. *Nature Reviews Genetics* **5**, 467-475.

International HapMap Consortium. (2005) A haplotype map of the human genome. *Nature* **437**, 1299-1320.

Ioannidis, J. P. (2005) Why most published research findings are false. *Public Library of Science Med*icine **2**, e124.

Ioannidis, J. P. A., Gwinn, M., Little, J., Higgins, J. P. T., Bernstein, J. L., Boffetta, P., Bondy, M., Bray, M. S., Brenchley, P. E., Buffler, P. A., Casas, J. P., Chokkalingam, A., Danesh, J., Smith, G. D., Dolan, S., Duncan, R., Gruis, N. A., Hartge, P., Hashibe, M., Hunter, D. J., Jarvelin, M.-R., Malmer, B., Maraganore, D. M., Newton-Bishop, J. A., O'Brien, T. R., Petersen, G., Riboli, E., Salanti, G., Seminara, D., Smeeth, L., Taioli, E., Timpson, N., Uitterlinden, A. G., Vineis, P., Wareham, N., Winn, D. M., Zimmern, R., Khoury, M. J. and The Human Genome Epidemiology Network and the Network of Investigator, N. (2006) A road map for efficient and reliable human genome epidemiology. *Nature Genetics* **38**, 3-5.

Kaput, J. (2004) Diet-disease gene interactions. *Nutrition* **20**, 26-31.

Kaput, J., Ordovas, J. M., Ferguson, L., van Ommen, B., Rodriguez, R. L., Allen, L., Ames, B. N., Dawson, K., German, B., Krauss, R., Malyj, W., Archer, M. C., Barnes, S., Bartholomew, A., Birk, R., van Bladeren, P., Bradford, K. J., Brown, K. H., Caetano, R., Castle, D., Chadwick, R., Clarke, S., Clement, K., Cooney, C. A., Corella, D., Manica da Cruz, I. B., Daniel, H., Duster, T., Ebbesson, S. O., Elliott, R., Fairweather-Tait, S., Felton, J., Fenech, M., Finley, J. W., Fogg-Johnson, N., Gill-Garrison, R., Gibney, M. J., Gillies, P. J., Gustafsson, J. A., Hartman Iv, J. L., He, L., Hwang, J. K., Jais, J. P., Jang, Y., Joost, H., Junien, C., Kanter, M., Kibbe, W. A., Koletzko, B., Korf, B. R., Kornman, K., Krempin, D. W., Langin, D., Lauren, D. R., Ho Lee, J., Leveille, G. A., Lin, S. J., Mathers, J., Mayne, M., McNabb, W., Milner, J. A., Morgan, P., Muller, M., Nikolsky, Y., van der Ouderaa, F., Park, T., Pensel, N., Perez-Jimenez, F., Poutanen, K., Roberts, M., Saris, W. H., Schuster, G., Shelling, A. N., Simopoulos, A. P., Southon, S., Tai, E. S., Towne, B., Trayhurn, P., Uauy, R., Visek, W. J., Warden, C., Weiss, R., Wiencke, J., Winkler, J., Wolff, G. L., Zhao-Wilson, X. and Zucker, J. D. (2005) The case for strategic international alliances to harness nutritional genomics for public and personal health. *British Journal of Nutrition* **94**, 623-632.

Khoury, M. J. (2004) The case for a global human genome epidemiology initiative. *Nature Genetics* **36**, 1027-1028.

Lander, E. and Kruglyak, L. (1995) Genetic dissection of complex traits: Guidelines for interpreting and reporting linkage results [see comments]. *Nature Genetics* **11**, 241-247.

Lander, E. S., Linton, L. M., Birren, B., Nusbaum, C., Zody, M. C., Baldwin, J., Devon, K., Dewar, K., Doyle, M., FitzHugh, W., Funke, R., Gage, D., Harris, K., Heaford, A., Howland, J., Kann, L., Lehoczky, J., LeVine, R., McEwan, P., McKernan, K., Meldrim, J., Mesirov, J. P., Miranda, C., Morris, W., Naylor, J., Raymond, C., Rosetti, M., Santos, R., Sheridan, A., Sougnez, C., Stange-Thomann, N., Stojanovic, N., Subramanian, A., Wyman, D., Rogers, J., Sulston, J., Ainscough, R., Beck, S., Bentley, D., Burton, J., Clee, C., Carter, N., Coulson, A., Deadman, R., Deloukas, P., Dunham, A., Dunham, I., Durbin, R., French, L., Grafham, D., Gregory, S., Hubbard, T., Humphray, S., Hunt, A., Jones, M., Lloyd, C., McMurray, A., Matthews, L., Mercer, S., Milne, S., Mullikin, J. C., Mungall, A., Plumb, R., Ross, M., Shownkeen, R., Sims, S., Waterston, R. H., Wilson, R. K., Hillier, L. W., McPherson, J. D., Marra, M. A., Mardis, E. R., Fulton, L. A., Chinwalla, A. T., Pepin, K. H., Gish, W. R., Chissoe, S. L., Wendl, M. C., Delehaunty, K. D., Miner, T. L., Delehaunty, A., Kramer, J. B., Cook, L. L., Fulton, R. S., Johnson, D. L., Minx, P. J.,

Clifton, S. W., Hawkins, T., Branscomb, E., Predki, P., Richardson, P., Wenning, S., Slezak, T., Doggett, N., Cheng, J. F., Olsen, A., Lucas, S., Elkin, C., Uberbacher, E., Frazier, M., Gibbs, R. A., Muzny, D. M., Scherer, S. E., Bouck, J. B., Sodergren, E. J., Worley, K. C., Rives, C. M., Gorrell, J. H., Metzker, M. L., Naylor, S. L., Kucherlapati, R. S., Nelson, D. L., Weinstock, G. M., Sakaki, Y., Fujiyama, A., Hattori, M., Yada, T., Toyoda, A., Itoh, T., Kawagoe, C., Watanabe, H., Totoki, Y., Taylor, T., Weissenbach, J., Heilig, R., Saurin, W., Artiguenave, F., Brottier, P., Bruls, T., Pelletier, E., Robert, C., Wincker, P., Smith, D. R., Doucette-Stamm, L., Rubenfield, M., Weinstock, K., Lee, H. M., Dubois, J., Rosenthal, A., Platzer, M., Nyakatura, G., Taudien, S., Rump, A., Yang, H., Yu, J., Wang, J., Huang, G., Gu, J., Hood, L., Rowen, L., Madan, A., Qin, S., Davis, R. W., Federspiel, N. A., Abola, A. P., Proctor, M. J., Myers, R. M., Schmutz, J., Dickson, M., Grimwood, J., Cox, D. R., Olson, M. V., Kaul, R., Shimizu, N., Kawasaki, K., Minoshima, S., Evans, G. A., Athanasiou, M., Schultz, R., Roe, B. A., Chen, F., Pan, H., Ramser, J., Lehrach, H., Reinhardt, R., McCombie, W. R., de la Bastide, M., Dedhia, N., Blocker, H., Hornischer, K., Nordsiek, G., Agarwala, R., Aravind, L., Bailey, J. A., Bateman, A., Batzoglou, S., Birney, E., Bork, P., Brown, D. G., Burge, C. B., Cerutti, L., Chen, H. C., Church, D., Clamp, M., Copley, R. R., Doerks, T., Eddy, S. R., Eichler, E. E., Furey, T. S., Galagan, J., Gilbert, J. G., Harmon, C., Hayashizaki, Y., Haussler, D., Hermjakob, H., Hokamp, K., Jang, W., Johnson, L. S., Jones, T. A., Kasif, S., Kaspryzk, A., Kennedy, S., Kent, W. J., Kitts, P., Koonin, E. V., Korf, I., Kulp, D., Lancet, D., Lowe, T. M., McLysaght, A., Mikkelsen, T., Moran, J. V., Mulder, N., Pollara, V. J., Ponting, C. P., Schuler, G., Schultz, J., Slater, G., Smit, A. F., Stupka, E., Szustakowski, J., Thierry-Mieg, D., Thierry-Mieg, J., Wagner, L., Wallis, J., Wheeler, R., Williams, A., Wolf, Y. I., Wolfe, K. H., Yang, S. P., Yeh, R. F., Collins, F., Guyer, M. S., Peterson, J., Felsenfeld, A., Wetterstrand, K. A., Patrinos, A., Morgan, M. J., Szustakowki, J., de Jong, P., Catanese, J. J., Osoegawa, K., Shizuya, H., Choi, S. and Chen, Y. J. (2001) Initial sequencing and analysis of the human genome. *Nature* **409**, 860-921.

Nuffield Council on Bioethics. (2002) The ethics of research related to healthcare in developing countries. 190.

Nuffield Council on Bioethics. (2005) The ethics of research related to healthcare in developing countries: A follow-up discussion paper.

Ordovas, J. M. and Corella, D. (2004) Nutritional genomics. *Annual Review of Genomics & Human Genetics* **5**, 71 - 118.

Risch, N. (1997) Evolving methods in genetic epidemiology. Ii. Genetic linkage from an epidemiologic perspective. *Epidemiology Review* **19**, 24-32.

Tabor, H. K., Risch, N. J. and Myers, R. M. (2002) Opinion: Candidate-gene approaches for studying complex genetic traits: Practical considerations. *Nature Reviews Genetics* **3**, 391-397.

Venter, J. C., Adams, M. D., Myers, E. W., Li, P. W., Mural, R. J., Sutton, G. G., Smith, H. O., Yandell, M., Evans, C. A., Holt, R. A., Gocayne, J. D., Amanatides, P., Ballew, R. M., Huson, D. H., Wortman, J. R., Zhang, Q., Kodira, C. D., Zheng, X. H., Chen, L., Skupski, M., Subramanian, G., Thomas, P. D., Zhang, J., Gabor Miklos, G. L., Nelson, C., Broder, S., Clark, A. G., Nadeau, J., McKusick, V. A., Zinder, N., Levine, A. J., Roberts, R. J., Simon, M., Slayman, C., Hunkapiller, M., Bolanos, R., Delcher, A., Dew, I., Fasulo, D., Flanigan, M., Florea, L., Halpern, A., Hannenhalli, S., Kravitz, S., Levy, S., Mobarry, C., Reinert, K., Remington, K., Abu-Threideh, J., Beasley, E., Biddick, K., Bonazzi, V., Brandon, R., Cargill, M., Chandramouliswaran, I., Charlab, R., Chaturvedi, K., Deng, Z., Di Francesco, V., Dunn, P., Eilbeck, K., Evangelista, C., Gabrielian, A. E., Gan, W., Ge, W., Gong, F., Gu, Z., Guan, P., Heiman, T. J., Higgins, M. E., Ji, R. R., Ke, Z., Ketchum, K. A., Lai, Z., Lei, Y., Li, Z., Li, J., Liang, Y., Lin, X., Lu, F., Merkulov, G. V., Milshina, N., Moore, H. M., Naik, A. K., Narayan, V. A., Neelam, B., Nusskern, D., Rusch, D. B., Salzberg, S., Shao, W., Shue, B., Sun, J., Wang, Z., Wang, A., Wang, X., Wang, J., Wei, M., Wides, R., Xiao, C., Yan, C., Yao, A., Ye, J., Zhan, M., Zhang, W., Zhang, H., Zhao, Q., Zheng, L., Zhong, F., Zhong, W., Zhu, S., Zhao, S., Gilbert, D., Baumhueter, S., Spier, G., Carter, C., Cravchik, A., Woodage, T., Ali, F., An, H., Awe, A., Baldwin, D., Baden, H., Barnstead, M., Barrow, I., Beeson, K., Busam, D., Carver, A., Center, A., Cheng, M. L., Curry, L., Danaher, S., Davenport, L., Desilets, R., Dietz, S., Dodson, K., Doup, L., Ferriera, S., Garg, N., Gluecksmann, A., Hart, B., Haynes, J., Haynes, C., Heiner, C., Hladun, S., Hostin, D., Houck, J., Howland, T., Ibegwam, C., Johnson, J., Kalush, F., Kline, L., Koduru, S., Love, A., Mann, F., May, D., McCawley, S., McIntosh, T., McMullen, I., Moy, M., Moy, L., Murphy, B., Nelson, K., Pfannkoch, C., Pratts, E., Puri, V., Qureshi, H., Reardon, M., Rodriguez, R., Rogers, Y. H., Romblad, D., Ruhfel, B., Scott, R., Sitter, C., Smallwood, M., Stewart, E., Strong, R., Suh, E., Thomas, R., Tint, N. N., Tse, S., Vech, C., Wang, G., Wetter, J., Williams, S., Williams, M., Windsor, S., Winn-Deen, E., Wolfe, K., Zaveri, J., Zaveri, K., Abril, J. F., Guigo, R., Campbell, M. J., Sjolander, K. V., Karlak, B., Kejariwal, A., Mi, H., Lazareva, B., Hatton, T., Narechania, A., Diemer, K., Muruganujan, A., Guo, N., Sato, S., Bafna, V., Istrail, S., Lippert, R., Schwartz, R., Walenz, B., Yooseph, S., Allen, D., Basu, A., Baxendale, J., Blick, L., Caminha, M., Carnes-Stine, J., Caulk, P., Chiang, Y. H., Coyne, M., Dahlke, C., Mays, A., Dombroski, M., Donnelly, M., Ely, D., Esparham, S., Fosler, C., Gire, H., Glanowski, S., Glasser, K., Glodek, A., Gorokhov, M., Graham, K., Gropman, B., Harris, M., Heil, J., Henderson, S., Hoover, J., Jennings, D., Jordan, C., Jordan, J., Kasha, J., Kagan, L., Kraft, C., Levitsky, A., Lewis, M., Liu, X., Lopez, J., Ma, D., Majoros, W., McDaniel, J., Murphy, S., Newman, M., Nguyen, T., Nguyen, N., Nodell, M., Pan, S., Peck, J., Peterson, M., Rowe, W., Sanders, R., Scott, J., Simpson, M., Smith, T., Sprague, A., Stockwell, T., Turner, R., Venter, E., Wang, M., Wen, M., Wu, D., Wu, M., Xia, A., Zandieh, A. and Zhu, X. (2001) The sequence of the human genome. *Science* **291**, 1304-1351.