PHARMACOGENOMIC DRUG DISCOVERY: REAL ACTORS AND REAL ISSUES FOR NATIVE PEOPLES[1]

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In the early 1990s, human rights activists drew international public attention to the Human Genome Diversity Project (HGDP), which they dubbed "the vampire project" and condemned as a threat to the world's indigenous and tribal peoples.[2] That was before the sequencing of the human genome and its revolutionary impact on drug discovery. As Big Pharma[3] shift to functional genomic platforms for their drug discovery research, will "gene mining" isolated ethnic groups replace biodiversity prospecting in underdeveloped countries as a global bioethical and legal challenge?

This paper presents original data on: (1) the extent to which researchers have been collecting human tissues for genetic diversity studies; (2) the aims and uses of research in this field; (3) the extent to which genetic diversity research has contributed to patent drug development; and (4) the extent to which publications, freely accessible tissue collections and databases, and new laboratory techniques may reduce the incentives for future human genetic diversity collecting. A review of studies and patent applications demonstrate that most intellectual and financial effort continues to be focused on *historic genomics*, rather

[1] Prepared for and supported by the International Institute for Indigenous Resource Management.

[2] E.g., L. Andrews and D. Nelkin, BODY BAZAAR; THE MARKET FOR HUMAN TISSUE IN THE BIOTECHNOLOGY AGE (Crown Publishers, New York, 2001); L. Lone Dog, Whose Genes Are They? The Human Genome Diversity Project, JOURNAL OF HEALTH & SOCIAL POLICY 10: 51-66 (1999); M. Dodson and R. Williamson, Indigenous Peoples and the Morality of the Human Genome Diversity Project, JOURNAL OF MEDICAL ETHICS 25: 204-208 (1999); H. T. Greely, Legal, Ethical, and Social Issues in Human Genome Research, ANNUAL REVIEW OF ANTHROPOLOGY 27: 473-502 (1998); H. Cunningham, Colonial Encounters in Postcolonial Contexts: Patenting Indigenous DNA and the Human genome Diversity Project, CRITIQUE OF ANTHROPOLOGY 18: 205-233 (1998). For a lucid overview of aims of human genetic diversity research generally see M. H. Crawford, Anthropological Genetics in the 21st Century: Introduction, HUMAN BIOLOGY 72: 3-13 (2000).

[3] Big Pharma is industry jargon for two dozen large, well-established, vertically integrated, publicly traded multinational corporations that are capable of taking pharmaceuticals from "lab bench to bottle." Emerging Pharma refers to numerous research and technical services firms that concentrate on making and marketing on-patent innovations, and rely heavily on venture capital financing. R. L. Barsh, Who Steals Indigenous Knowledge? PROCEEDINGS 9th ANNUAL MEETING AMERICAN SOCIETY OF INTERNATIONAL LAW 153-161 (2001).

than on *epidemiological* genomics, which has more direct implications for drug discovery and public health.[4] If there has been an injustice to indigenous peoples, I suggest that it is not from any commercialization of their genetic particularities, but from a failure to focus genetic diversity research on the health and survival of indigenous peoples themselves.

How useful is diversity?

Research on historically isolated "founder populations" has been justified either on the grounds that such groups represent windows into humanity's prehistory, or that they may be reservoirs of rare human genetic variations of medical interest.[5] While this paper was being prepared, for example, NIH launched a major collaborative study with Italy of an isolated Sardinian village to learn more about human aging and longevity,[6] and Israeli researchers confirmed the gene responsible for the widespread cardiac disease PVT by studying its expression in seven severely affected Bedouin lineages.[7] In small, relatively isolated communities it is also possible to obtain more complete lineage records and to sample multiple generations of the same lineage.[8]

The key to applying genetic diversity to drug discovery is gene expression. Genes encode the chemical structures of proteins that serve as structural elements, transporters,

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[4] A. Arnaiz-Villena, Historic Genomics: An Emergent Discipline, HUMAN IMMUNOLOGY 62: 869-870 (2001); D. M. Roden and A. L. George Jr., The Genetic Basis of Variability in Drug Responses, NATURE REVIEWS 1 (January 2002): 37-44. The study of population-specific differences in human responsiveness to drugs is *pharmacogenetics*; the search for insights into the causes of disease (including population level differences in disease susceptibility or resistance) is *pharmacogenomics.* For an excellent overview of the technology of functional genomics see L. Peltonen and V. A. McKusick, Dissecting Human Disease in the Postgenomic Era, SCIENCE 291 (16 February 2001): 1224-1229.

[5] S. Shifman and A. Darvasi, The Value of Isolated Populations, NATURE MEDICINE 28: 309-310 (2001); C. Bourgain et al., Search for Multifactorial Disease Suceptibility Genes in Founder Populations, ANNALS HUMAN GENETICS 64: 255-265 (2000).

[6] NIH, Sardinians Spark NIA Genetic Research Effort, National Institute on Aging press release posted on 2 February 2002 at http://www.nih.gov/news/ (last visited 5 February 2002). On this group's particularity see R. Lampis et al., The Distribution of HLA Class II Haplotypes Reveals that the Sardinian Population is Genetically Differentiated from the Other Caucasian Populations, TISSUE ANTIGENS 56:515-521 (2000).

[7] H. Lahat et al., A Missense Mutation in a Highly Conserved Region of *CASQ2* is Associated with Autosomal Recessive Catecholamine-Induced Polymorphic Ventricular Tachycardia in Bedouin Families from Israel, AMERICAN J HUMAN GENETICS 69: 1378-84 (2001).

[8] D. L. Newman et al., The Importance of Genealogy in Determining Genetic Associations with Complex Traits, AMERICAN J HUMAN GENETICS 69: 1146-1148 (2001).

messengers and catalysts.[9] A complex feedback system exists between the physiological environment (including information, nutrition and invasive pathogens), the proteome (the assemblage of human proteins), and the genome (the templates for protein construction), and this determines when particular genes are switched on, or expressed. The lab-bench approach to genomic drug discovery begins with tissues from both healthy and diseased organisms, such as laboratory mice or human clinical patients. Comparing the pattern of gene expression in healthy and diseased individuals indicates which genes are implicated in fighting disease, which genes confer resistance or vulnerability to disease, and how the disease progresses by compromising gene expression, producing symptoms. If a certain gene tends to be expressed in the early stages of a disease, it may mean that this gene is a key defender, or a crucial victim of that disease. Replacing the function of that gene, e.g. by synthesizing the protein that gene encodes and administering the synthetic to patients, can be a relatively direct, safe, and effective remedy.

The basic tool in genomic drug discovery platforms is a cDNA (expressed gene) library: a collection of DNA extracted from healthy and diseased tissues. Obviously, the interpretation of differences in gene expression within a cDNA library depends crucially on the quantity and quality of clinical data on the individual DNA donors. A secondary consideration is the size and diversity of the sample of donors, particularly if there is any reason to suspect that there are relevant differences among individuals in their resistance to the disease, their responsiveness to existing therapeutic methods, or in the course of the disease. The study of individual level differences reveal more about the biochemistry of the disease, and suggests means of individualizing future therapeutics to make them more effective.[10] In principle, it also increases the likelihood of discovering "wild" variations or alleles that confer resistance or immunity.

Another important medical and financial incentive for widespread genotyping is transplant compatibility: the first level of a search for a potential match is the population

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[9] A "gene" contains two distinct regions, the "exon" which encodes the amino acid sequence of a protein, and a "regulatory region" that contains the instructions controlling gene expression.

[10] The fact that "patients vary widely in their responses to drugs," and that this variation reflects individuals' heredity has been known since the 1940s. Roden and George, Variability in Drug Responses, *supra* note 3.

("race," ethnicity, nationality) of the patient and potential donors, or donor pools. But it is unlikely that compatibility research would focus on isolated or tribal populations since they are *less* likely to be histocompatible with predominantly urban, Northern transplant patients than other urban populations with the same European and Asian ancestries. The study of unusual immune system alleles in isolated groups is useful for understanding the diversity of immune (HLA) types within derivative cosmopolitan populations, e.g., Ami tribal people in Taiwan shed light on how highly mixed urban Chinese populations differ from the residents of south Asian or European cities.

Collecting "wild" alleles is not necessarily as rapid or cost-effective as exploring human genetic diversity through lab-bench syntheses of allele variants. Polynucleotides form a part of self-organizing and assembling systems inside living organisms; artificial self-assembling and self-selecting systems are now being designed for drug discovery.[11] There have also been promising results from the use of non-human models ranging from yeast to worms and mice; since these organisms share much of the same genetic heritage as humans, but reproduce and adapt much faster, they offer opportunities to explore and create genetic diversity within living systems.[12] Disease associations can also be inferred from statistical analyses of large pooled samples drawn from human mixed populations.[13]

Global coverage

Collection and biochemical comparisons of human tissues such as whole blood from indigenous or tribal peoples has a long history, going back to attempts to describe and compare human "races" on the basis of blood types, morphology, and intelligence in

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[11] E.g., O. Ramström and J.-M. Lehn, Drug Discovery by Dynamic Combinatorial Libraries, NATURE REVIEWS 1 (January 2002): 26-36. DCC libraries are *adaptive* in the sense that the target molecule, such as a gene of known structure, drives the assembly process; all possible chemical structures consistent with the target are generated by the target itself.

[12] Human genes or their analogs have been derived from bacteria (e.g. the G-protein coupled receptor gene, U.S. patent 5,932,702 awarded to Human Gene Sciences), for example, and the nematode worm *C. elegans* (e.g. gaf-2 gene, U.S. patent 6,225,150 awarded to Massachusetts General Hospital).

[13] E.g., H. E. Collins et al., A Simple and Accurate Method for Determination of Microsatellite Total Allele Content Differences Between Pools, HUMAN GENETICS 106:218-226 (2000).

the 1920s.[14] Although the concept of "race" retreated in the face of vehement social and scientific criticism in the 1950s and 1960s, interest in human biochemical diversity was re-energized in the 1970s by progress in structural genetics and by the heightened public attention given to endangered species, threatened peoples, and disappearing cultures and languages. Physical anthropologists and geneticists conducted hundreds of field studies of isolated communities' blood antigens and other biochemical characteristics amenable to the laboratory technologies available at that time. Three atlases of human biochemical variation had been published by 1983, with varying amounts of comparative data on more than a hundred tribal peoples as well as many ethnic and national groups.[15]

Ten years later, *The History and Geography of Human Genes* plotted the global distribution of variations in 42 marker genes based on a compilation of nearly a thousand previously published studies.[16] The authors sought to focus on "aboriginal" groups that had remained relatively isolated within their own traditional territories, in order to avoid the confounding effects of intermarriage, migration and dispersal that have affected most of the world's people since the rise of cities and empires. Nevertheless, the inconsistent quality and imprecise documentation of the available data forced them to combine tribes, linguistic groups, and geographical samples into larger constructs of debatable validity. [17] Much of the academic debate over the utility of the HGDP has been preoccupied with the ethnic classification scheme used by the authors of *History and Geography*, which poses

[14] For an early survey and critique of such studies see O. Klineberg, RACE DIFFERENCES (Harper Bros., New York and London, 1935)

[15] Tills, Kopeć, and Tills, THE DISTRIBUTION OF THE HUMAN BLOOD GROUPS AND OTHER POLYMORPHISMS, SUPPLEMENT 1 (1983); Steinberg and Cook, THE DISTRIBUTION OF THE HUMAN IMMUNOGLOBULIN ALLOTYPES (1981); Mourant, Kopeć and Domaniewska-Sobczak, THE DISTRIBUTION OF THE HUMAN BLOOD GROUPS AND OTHER POLYMORPHISMS (1976).

[16] L. L. Cavalli-Sforza, P. Menozzi, and A. Piazza, THE HISTORY AND GEOGRAPHY OF HUMAN GENES (Princeton University Press, 1994). See, also, L. L. Cavalli-Sforza, GENES, PEOPLES, AND LANGUAGES (North Point Press, New York, 2000) (transl. M. Seielstad).

[17] In Asia, for example, they used categories such as Bombay and Calcutta (cities); Pakistani (a nationality); Tagalog (a language); and various Hindu castes. In North America, all Algonquin speaking peoples appear as a single group, and in Brazil, *caboclos* (Brazilian *mestizos* or *métis*) are treated as a separate tribal group. There are also outright errors, such as treating the Chippewa and Ojibwa as separate groups, and confusing the Algonquin speaking Chippewa with Dene-speaking Chipewyans.

philosophical as well as empirical questions: in particular, critics argue, a return to racial typologies in the study of humanity.[18]

The *History and Geography* relied on previously published studies of variation in the "major histocompatibility complex" located on human chromosome six, encoding the array of human leukocyte antigens (HLA). A more powerful method of tracing historical relationships between populations based on mitochondrial DNA (mtDNA) was developed in the 1980s,[19] leading to a new round of human genetic sampling and analysis, especially in Siberia and the Americas.[20] Still another technique for population genetic comparisons using Y-chromosome haplotypes (allele sequence typologies) was developed in the 1990s when political changes in China and the former Soviet Union gave researchers access to a vastly enlarged range of collecting opportunities. Oxford University anthropologists took nearly 2,000 specimens from 49 Eurasian groups in "expeditions" mounted between 1996 and 2000,[21] and the Chinese Academy of Sciences established a national genetic diversity program, which thus far has collected more than 12,000 specimens in Chinese territory.[22]

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[18] Imprecise, overlapping population constructs would not render genetic-distance comparisons completely invalid, however; it would reduce the average genetic distance between all groups and thereby increase the risk of false negatives—i.e., failing to detect real differences between groups.

[19] A. M. Bowcock et al., High Resolution of Human Evolutionary Trees with Polymorphic Microsatellites, NATURE 368: 455-457 (1994). For a recent review, see F. Calafell, A. Pérez-Lezaun and J. Bertranpetit, Genetic Distances and Microsatellite Diversification in Humans, HMAN GENETICS 106: 133-134 (1999).

[20] A. Torroni et al., Native American Mitochrondrial DNA Analysis Indicates that the Amerind and the Nadene Populations Were Founded by Two Independent Migrations, GENETICS 130: 153-162 (1992); A. Torroni et al. mtDNA Variation of Aboriginal Siberians Reveals Distinct Genetic Affinities with Native Americans, AMERICAN J HUMAN GENERTICS 53: 591-608 (1993); A. Torroni et al., Asian Affinities and Continental Radiation of the Four Founding Native American mtDNAs, AMERICAN J HUMAN GENETICS 53: 563-590 (1993); A. Torroni et al., mtDNA and Y-Chromosome Polymorphisms in Four Native American Populations from Southern Mexico, AMERICAN J HUMAN GENETICS 54: 303-318 (1994). NIH, NSF, and the U.S. Department of Energy supported this research, which was headquartered at Emory University.

[21] R. S. Wells et al., The Eurasian Heartland: A Continental Perspective on Y-Chromosome Diversity, PROCEEDINGS NATIONAL ACADEMY SCIENCES USA 98: 10244-10249 (2001); also see the host institution's website, http://popgen.well.ox.ac.uk/eurasia/htdocs/ (last visited 1 February 2002).

[22] L. L. Cavalii-Sforza, The Chinese Human Genome Diversity Project, PROCEEDINGS NATIONAL ACADEMY OF SCIENCES USA 95: 11501-11503 (1998); B. Su et al., Y Chromosome Evidence for a Northward Migration of Modern Humans in East Asia During the Last Ice Age, AMERICAN J. HUMAN GENETICS 65: 1718-1724 (1999); B. Su et al., Y Chromosome Haplotypes Reveal Prehistoric Migrations to the Himalayas, HUMAN GENETICS 107: 582-590 (2000); Y. Ke et al., African Origin of Modern Humans in East Asia: A Tale of 12,000 Y Chromosomes, SCIENCE 292 (11 May 2001): 1151-1153. It should be noted that the vast majority of the Chinese specimens are from local groups officially identified as Han Chinese.

These recent initiatives dwarf the biological material that was available to researchers just ten years ago, but only in terms of individual rather than tribal or ethnic diversity.

Figure 1 presents a conservative estimate of the number of indigenous and tribal groups sampled by human genetic-diversity researchers since the 1960s, based upon the references in the *History and Geography*, updated through a search of biological subject databases for published studies from 1992 through 2002. More than half (54 percent) of the 489 groups included in DNA polymorphism studies were first sampled before 1985, and more than one-third (36 percent) of them have subsequently been re-sampled at least once.[23] In the Americas, for example, the *History and Geography* compared data on 94 indigenous peoples published in earlier atlases and technical journals, as well as data on pools combining at least 60 other tribes or peoples.[24] Researchers subsequently revisited at least 29 of those Amerindian groups,[25] and sampled at least 18 Amerindian groups that had not been documented previously. Although the pace of sampling "new" peoples has therefore declined there have been improvements in the preservation of samples[26] and the methods available for studying them. Once acquired by field researchers, what is the fate of human tissue specimens?

Disposition of specimens

HGDP was never a formal institution, but a network of geneticists and physical anthropologists in several countries who shared an interest in the biological origins and relationships among human ethnic and linguistic groups, and exchanged tissue samples and data. Many of the individual participants have been supported by research agencies such as the National Science Foundation (NSF) and National Institutes of Health (NIH),

[23] I have omitted tribal groups that were included in regional, ethnic, or linguistic pools such as "Ethiopian" or "Altaic", as well as European nationalities and "minorities" (such as Basques and Roma), castes in India, and dominant nationalities such as Han in China or Thai in Thailand. There are vast differences in the sizes of the tribal groups included in Figure 1, moreover, ranging from a few thousand to several million.

[24] Composites were organized by regions or linguistic families, e.g. speakers of Siouian languages, speakers of Athapascan languages, Indians of northern Mexico, Amazonian Indians, Argentine Indians.

[25] Repeat sampling is difficult to verify from publications because the sources of amples are frequently not clearly identified. All references to re-sampling in this paper should be taken as absolute minima.

[26] Ideally, cells containing target DNA can be "immortalized" by infecting them with the Epstein-Barr virus, making it possible to maintain their integrity and scientific value indefinitely in tissue cultures.

as well as European Community scientific funds, without the level of official recognition and financial commitment that was enjoyed by the Human Genome Project.[27] Indeed, the critical literature disagrees as to whether the HGDP "exists" yet.

Several collections of human DNA and genetic sequence data are freely available but mainly of unspecified European or U.S. origin (Figure 2). The GenBank depository, administered by NIH, currently holds 95 non-duplicative submissions of genetic material exclusive of overlaps with the privately maintained Coriell Cell Repository. About half (52 percent) of the GenBank accessions are pooled Europeans and Americans; 19 percent are identified as Asian nationalities such as Malaysians or Chinese; 6 percent are African-Americans; 6 percent are tribal peoples. Hispanic Americans, American Jews, and white South Africans are also included.[28] The Coriell Cell Repository currently holds 15 small samples from tribal peoples, and offers a pool of 450 U.S. individuals "designed to reflect the diversity of the human population" that includes 30 Native Americans of unspecified tribal affiliations.[29] In France, the Centre d'Etudes du Polymorphisme Humaine (CEPH) holds Amish, Utah, and Venezuelan specimens with crucial data on donors' genealogical relationships, but no specimens from tribal populations; Stanford University researchers are collaborating with CEPH to strengthen that depository's holdings of human diversity specimens.[30]

The Genome Data Base was established in 1990 as the data sharing mechanism of the Human Genome Project. It is not a repository of biological material, like GenBank or

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[27] The Human Genome Project, spearheaded by NIH, was aimed at sequencing the genome: the approximate physical sequence of genes and their constituent nucleotides, using chromosomes from a handful of human donors. Much of the resulting genome map is incompletely defined or has no known function, but like the crude maps of early explorers, it is a framework for further investigations. Celera Genomics (a division of Applera Corp.) is currently re-sequencing a larger U.S. sample (40-50 individuals) for greater precision in genomic mapping; http://www.celera.com/therapeutics/ (last visited 15 November 2001). An estimated 98 percent of the human genome is identical amongst individuals. While the remaining 2 percent accounts for many of our individual and population-level differences, it has not yet been fully described, and this is the target of the HGDP. On the initiative's financial woes see P. Smaglik, Genetic Diversity Project Fights for Life, NATURE 404 (27 April 2000): 912.

[28] One-fourth of GenBank accessions are clinical: donors were selected because they manifested symptoms of a disease such as hypertension or osteoporosis; this includes a tribal sample selected to study gout.

[29] The source of the Native American specimens was a private medical research foundation in Wisconsin; see http://research.marshfieldclinic.org/genetics/ (last visited 15 November 2001).

[30] See http://www.cephb.fr/cephb/ (last visited 10 February 2002).

Coriell, but purely a depository of gene sequence data.[31] One-fourth (25) of its 93 online genome maps represent tribal peoples. There is no accession data such as how and where specimens were collected, or the heath status of the individual donors. Another powerful online informatics tool is MITOMAP, constructed by Emory University researchers who have been involved in human genetic-diversity collecting.[32] MITOMAP offers sequence data for mtDNA polymorphisms from the literature, as well as unpublished sequence data donated by cooperating scientists including (for example) unpublished mtDNA sequences for a number of Malaysian tribal peoples. The University of Washington provides online access to a database of SNPs (single-nucleotide polymorphisms) identified in an ongoing study of African-Americans,[33] and Stanford University geneticists are building an online version of the data contained in the *History and Geography*. Researchers share cell lines as standards for genotyping[34] and share the results of gene expression research,[35] but this is ordinarily not population specific.

The growth of functional genomic drug discovery has created a market niche for companies that construct and license access to very large collections of human tissues for DNA extraction and cloning. Two of the largest and most popular commercial sources of clinical samples are Stratagene and Clontech, both of which organize their collections by tissue source (e.g. brain, lung, liver), condition (pathology), and to some extent the age of the donors, who are mainly surgical patients or cadavers, rather than ethnicity or color.[36] Similarly, an association of families with a history of Type I diabetes maintains an online

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[31] See http://www.gdb.org (last visited 2 February 2002).

[32] The access portal is http://www.gen.emory.edu/mitomap.html (last visited 10 February 2002).

[33] See http://www.pga.gs.washington.edu/data/ (last visited 5 February 2002).

[34] See e.g. http://wwwpathnet.medsch.ucla.edu/clinical-services/Immunogenetics (last visited 10 February 2002) for information on the UCLA International Cell Exchange.

[35] See e.g. the pharmacogenetics research network at http://www.nigms.nih.gov/pharmacogenetics/; genes under investigation at http://pharmgkb.org/PharmGKB/surveillance/; and Oak Ridge National Laboratories' virtual library on genetics, http://www.ornl.gov/TechResources/Human_Genome/ (all sites last visited 15 November 2001).

[36] Details are available at http://www.clontech.com/ and http://www2.stratagene.com/gc/ (both last visited 5 February 2002); both also sell informatics and laboratory tools to researchers. Other firms marketing DNA libraries containing a limited amount of ethnic diversity include Variagenics, http://www.variagenics.com; Gemini Genomics, http://www.gemini-genomics.com; and Sequenom, http://www.sequenom.com (all last visited 10 February 2002), which recently acquired Gemini.

DNA data exchange.[37] Lack of medical or commercial interest in genetic diversity data recalls the distinction made at the beginning of this paper between the aims and methods of historic and epidemiological genomics. Specimens from isolated societies mean little to researchers studying diseases in cosmopolitan countries, especially if those specimens are unaccompanied by clinical data on the donors.

For the same reasons, existing tissue and data depositories are of limited utility to historic genomics. Historic genomic research depends instead on informal exchanges of specimens and data.[38] For example the late James Neel, a pioneering albeit controversial genetic epidemiologist, collected specimens in the Americas for decades and they remain available from the University of Michigan where he worked.[39] Although there have been some recent focused sampling projects, such as the Oxford expeditions mentioned above, moreover, a much larger proportion of the new specimens described in the literature were obtained from clinical sources such as blood banks, hospital laboratories, organ donations or surgical procedures. Growth in the technological capacities of hospitals in developing countries, combined with global electronic communications and refrigerated air shipping, minimizes the need for historic genomic projects to send sampling teams abroad.

Aims and institutions

Most recent research on human genetic diversity involving non-Western peoples continues to serve intellectual rather than health interests, as indicated by an overview of scientific publications in this field over the past two years (Figure 3).[40] One-fourth of the

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[37] The Human Biological Data Interchange, http://www.hbdi.org (last visited 10 February 2002).

[38] See, e.g., the lists of academic courtesy exchanges of specimens in C. M. Bravi et al., Origin of YAP+ Lineages of the Human Y-Chromosome, AMERICAN J PHYSICAL ANTHROPOLOGY 112:149-158, at 150 (2000), and D. Smith et al., Implications of the Distribution of Albumin Naskapi and Albumin Mexico for New World Prehistory, AMERICAN J PHYSICAL ANTHROPOLOGY 111:557-572, at 561, (2000).

[39] E.g. J. T. Lell et al., The Dual Origin and Siberian Affinities of Native American Y Chromosomes, AMERICAN J HUMAN GENETICS 70: 192-206 (2002); S. R. Williams, N. A. Chagnon, and R. S. Spielman, Nuclear and Mitochondrial Genetic Variation in the Yanamamö: A Test Case for Ancient DNA Studies of Prehistoric Populations, AMERICAN J PHYSICAL ANTHROPOLOGY, 117:246-259 (2002); NSF award # 9816394 (1999) to Mark Weiss (University of Michigan) for re-analyzing Neel's Yanomamö specimens.

[40] The data in Figure 5 were drawn from the bibliographies of human genetic diversity research published electronically by Oxford and Stanford University researchers, and from the tables of contents of six major English language journals in the field: American Journal of Human Genetics, American Journal of Physical Anthropology, Annals of Human Genetics, Human Genetics, Human Immunology, and Tissue Antigens. I have omitted recent studies of "racial" and ethnic groups or "minorities," such as African-Americans, Afro-

published studies had implications for human health, but only 12 were specially designed to address the health concerns of the donor communities[41] and only three had community organizations as study partners.[42] It should also be noted that while 18 novel alleles were discovered as a result of the studies listed in Figure 5,[43] the University of Washington has thus far identified 3,325 SNPs from just 47 white and African-American donors.[44]

A very large number of institutions worldwide are currently involved to varying degrees in human genetic diversity studies (Figure 4).[45] More than half of the institutions involved in this field are universities; about one-fifth are hospitals and blood banks. Half of this global technological capacity is concentrated in 16 industrialized countries (which is to say in the "North") and the rest is distributed amongst 52 developing and transitional states, led by Argentina, Brazil, China, India, Mexico, and South Africa. For any agency attempting to monitor and manage the flow of specimens and data, this would represent a formidable challenge. As shown in Figure 5, furthermore, a wide variety of governments sponsor this kind of research—as many in the South as in either the U.S. or the European Community.

In the U.S., NSF and NIH account for most government funding of human genetic diversity research. Over the past five years, NSF awards represent a public investment of

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Caribbean groups, Basques, Roma, Sardinians, Finns, regional sub-groups of Han Chinese, castes in India, Latin American *mestizos* and "white" Brazilians, although they employed the same methods and addressed the same kinds of research questions.

[41] Disease targets of the health-related studies in Figure 5 included diabetes, breast cancer, cystic fibrosis, malaria, leishmaniasis, schizophrenia, Chaga's Disease, Werner's Syndrome and hereditary ataxias.

[42] Viz., Busfield et al., A Genomewide Search for Type 2 Diabetes-Susceptibility Genes in Indigenous Australians, AMERICAN J HUMAN GENETICS 70:349-357 (2002); H.-J. Tsai et al., Type 2 Diabetes and Three *Calpain-10* Gene Polymorphisms in Samoans: No Evidence of Assocation, AMERICAN J HUMAN GENETICS 69:1236-1244 (2001); M. Toneva et al., Genomic Diversity of Natural Killer Cell Receptor Genes in Three Populations, TISSUE ANTIGENS 57:358-362 (2001).

[43] E.g., D. Ramon et al., HLA-A*6817, identified in the Kolla Amerindians of North-West Argentina Possesses a Novel Nucleotide Substitution, TISSUE ANTIGENS 55:453-454 (2000); S. A. Scheltinga et al., A Novel HLA-A24 (A*2420) Allele Identified in the Atayal Tribe of Taiwan, TISSUE ANTIGENS 55: 65-67 (2000).

[44] Statistics and details of SNPs are available at http://pga.mbt.uwashington.edu/finished_genes.html and at the Fred Hutchinson Cancer Center site, http://fhcrc.org/labs/krugylak/pga.htm (both last visited 5 February 2002).

[45] Institutions with which the authors of human genetic diversity publications (2000-2002) were identified: a conservative since not all publications and unpublished research could be located and examined.

$2.7 million in 12 universities[46] about equally divided between collecting new specimens and re-analyzing existing collections. Three universities also received annual support for genetic diversity research from NIH, although only three of their projects focused on the health problems of the studied populations.[47] Other U.S. government agencies mentioned in published acknowledgments as contributors to recent human genetic-diversity research include the National Institutes of Mental Health (NIMH), the Smithsonian Institution, and the Department of Defense.

It is worth noting that a considerable amount of recent genetic diversity work has focused on the origins, migrations and interrelationships of European ethnic groups; not only of relatively unusual groups such as the Roma ("gypsies"),[48] but also, for example, the Greeks, whose immunological (HLA) profile is consistent with their strong political and commercial relationships with Egypt and Ethiopia 2,500 years ago.[49] Studies of the genetic diversity of Europe are conducted by many of the same institutions as studies of isolated or tribal groups.[50]

Who benefits?

Human genetic-diversity research has thus far contributed relatively little to drug discovery. While there continue to be studies of genetic polymorphisms associated with

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[46] Data obtained from http://www.fastlane.nsf.gov/ and from http://commons.cit.nih.gov/crisp3/ (both last visited 5 February 2002). Top NSF beneficiaries in terms of number and size of awards were Pennsylvania State University and the University of Arizona, which represented nearly half of the funds distributed. NIH gave most of its support to the University of Arizona and Stanford University. Figure 3 does not include 8 NIH awards for the study of the genetic diversity of *pathogens* collected from diverse human populations.

[47] Two NIH studies of the genetic bases of hypertension in West African populations, and an NIH study of the comparative AIDS susceptibility of African-Americans and white Americans.

[48] E.g. D. Gresham et al., Origins and Divergence of the Roma (Gypsies), AMERICAN J HUMAN GENETICS 69: 1314-1331 (2001).

[49] A. Arnaiz-Villena et al., HLA Genes in Macedonians and the Sub-Saharan Origin of the Greeks, TISSUE ANTIGENS 57: 118-127 (2001). Similarly, see C. R. Guglielmino, A. de Silvestri and J. Beres, Probable Ancestors of Hungarian Ethnic Groups: An Admixture Analysis, ANNALS HUMAN GENETICS 64: 145-159 (2000).

[50] See e.g., P. Malaspina et al., A Mutlistep Process for the Dispersal of a Y Chromosomal Lineage in the Mediterranean Area, ANNALS HUMAN GENETICS 65: 339-249 (2001); P. Malaspina et al., Patterns of Male-Specific Inter-Population Divergences in Europe, West Asia, and North Africa, ANNALS HUMAN GENETICS 64: 395-412 (2000).

disease,[51] commercial genomic medicine continues to rely almost exclusively on clinical populations (human and non-human) as sources of DNA for study. This is apparent from the collaborations maintained by leading pharmacogenomics companies such as Amgen[52] and Myriad Genetics,[53] from patent applications (Figure 6), and from a re-examination of the examples of abuses of human genetic-diversity research most often cited by its critics: Iceland, Tonga, and Tristan da Cunha.[54]

Despite published accusations that Iceland "sold the genetic heritage of its entire population" to DeCode Genetics,[55] it appears that Icelandic authorities awarded DeCode a 12-year license to construct and operate a national health services database, in Iceland, under the direct supervision of national ministries.[56] Individual Icelanders may consent to the anonymous inclusion of their genotypes with their medical records in the database, and DeCode is authorized to use the database for drug discovery research until its license expires, at which time Iceland retains the database and software. DeCode cannot disclose information from the database without special authority from the government, restricting the company's ability to acquire derivative patents or copyrights. DeCode has not sought nor received any U.S. patents clearly associated with its Icelandic database license.[57]

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[51] E.g. T. Niimi et al., A Polymorphism in the Human UGRP1 Gene Promoter that Regulates Transcription is Associated with an Increased Risk of Asthma, AMERICAN J HUMAN GENETICS (in press for March 2002, already published electronically at http://www.journals.unchicago.edu/AJHG/journal/), a cooperative effort of U.S. and Japanese universities, private companies, and the NIH.

[52] See their Research Center and Product pages at http://www.amgen.com (last visited 12 October 2001).

[53] See their Partners & Collaborator page at http://www.myriad.com (last visited 16 January 2002).

[54] The New Genomics Agenda, ETC Group Communiqué (September/October 2001); Phase II for Human Genome Research—Human Genetic Diversity Enters the Commercial Mainstream, RAFI Communiqué (January/February 2000), both available at http:// www.etcgroup.org (last visited 10 February 2002). Also Andrews and Nelkin, BODY BAZAAR, *supra* note 1. The ETC (Action Group on Erosion, Technology and Concentration) was formerly known as RAFI (Rural Advancement Foundation International), and has been the most visible North American opponent of human and plant genetic-diversity research.

[55] The New Genomics Agenda, op. cit., at 5.

[56] Legal documentation of the transaction is available at http://www.decode.com/resources/ (last visited 10 February 2002) with links to the Government of Iceland.

[57] DeCode applied for a parent on the human narcolepsy gene (US patent no. 6,319,710) on 7 January 2000, two weeks before Icelandic authorities approved DeCode's database operation license, apparently relying on GenBank accessions. It is possible DeCode's Icelandic subsidiary was already collecting and analyzing Icelandic DNA, however.

Autogen, an Australian genomics enterprise, recently announced a similar kind of database arrangement with the Tongan Ministry of Health.[58] Autogen reportedly will not only construct the database and requisite laboratory facilities in Tonga but pay an annual fee for access to the data and royalties on the development of any derivative patents. The company's promotional literature states that it also holds collections of DNA from Nauru and Mauritius, and is seeking collecting and database arrangements with other Polynesian island nations. Autogen's disease targets, obesity and diabetes, are of considerable public health interest in Oceania. No U.S. patents have resulted thus far, however.[59] It is worth noting that RAFI/ETC has accused the U.S.-based genomics company DNA Sciences of using its website to solicit DNA samples from the public for its commercial research, but in actuality the company is offering genome banking services to health care providers, i.e. Iceland-style genomic database contracts with hospitals and HMOs.[60]

Published results of genetic polymorphism research on the residents of Tristan da Cunha[61] appear to have provided Axys Pharmaceuticals with a lead for the development of a patent on two human asthma-related genes.[62] Axys compared the published Tristan da Cunha data with a Canadian clinical sample and GenBank accessions, and identified the "wild" (naturally occurring) allele responsible for at least some asthmatic conditions. As far as I can determine, this is as close as industry has come to commercializing leads from the genetic sampling of isolated indigenous or tribal populations, as opposed to the study of U.S., European and Japanese clinical populations.

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[58] A project description and ethics policy are available at http://www.autogenlimited.com.au (last visited 10 February 2002).

[59] Autogen's corporate website contains the recent announcement of applications for U.S. patents on genes related to diabetes and derivative of the Tongan project, but I have not found the applications in the USPTO patent application database.

[60] The New Genomics Agenda, *supra* note 53, at 5; "Commercial Products and Services" on the home page of DNA Sciences, http://www.dna/com (last visited 10 February 2002).

[61] The original published report was N. Zamel et al., Asthma on Tristan da Cunha: Looking for the Genetic Link, AMERICAN J RESPIRATORY & CRITICAL CARE MEDICINE 153: 1902-1906 (1996).

[62] U.S. patent no. 6,087,485. Celera Genomics (a subsidiary of Applera Corp.) subsequently acquired Axys Pharmaceuticals for $174 million.

More than 600 human genes have been the subjects of U.S. patents since 1996.[63] Incyte Genomics alone accounts for half of these patents, mainly developed from clones of cells from clinical samples, such as diseased tissue from hospital procedures. Incyte rushed genes to the patent office in order to protect its commercial interests in LifeSeq®, a proprietary genome map and reagent service for other researchers.[64] Celera Genomics, the second largest holder of U.S. patents on human genes, is also primarily a distributor of proprietary databases and informatics tools, rather than a developer of new drugs.[65] In third place is Human Genome Sciences, an emerging pharma company that has worked in partnership with a number of universities on drug discovery. Smaller numbers of human gene patents are held by companies such as Myriad Genetic Laboratories, which works in collaboration with ten Big Pharma corporations such as Eli Lilly, to which it licensed its BRCA1 gene discovery for $4 million plus royalties, and Bayer, with which it is working on genes related to asthma, obesity, osteoporosis, and depression.[66]

Figure 6 summarizes a sample of recent U.S. patents and the sources of the DNA used to develop the claims. It includes human gene sequence patents awarded to most of the leading U.S., European and Japanese functional genomics companies[67] and university laboratories;[68] a 15 percent random sample of gene patents awarded to Incyte Genomics and Human Gene Sciences; and the results of a search of the U.S. Patent and Trademark Office (USPTO) online database for the keywords *human* and *polynucleotides* in patent claims. Alliances between universities and corporations are shown separately.[69] Figure 6

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[63] D. Malakoff and R. F. Service, Genomania Meets the Bottom Line, SCIENCE 291 (16 February 2001): 1193-1203, at 1194.

[64] See Research Solutions at http://www.incyte.com/sequence/index.shtml (last visited 10 February 2002). Patent applications indicate that Incyte frequently uses the Mayo Clinic, the University of California-Davis, and commercial tissue suppliers such as Stratagene and Colonetics to provide diseased tissue for cloning.

[65] Malakoff and Service, Genomania Meets the Bottom Line, *op. cit*.

[66] See http://www.myriad.com (last visited 16 January 2002).

[67] AmGen, Applera (Axys Pharma and Celera Genomics), DeCode Genetics, Gene Logic, Genentech, Hoffman-La Roche, Myriad Genetics, Novartis, Otsuka Pharmaceuticals, Roche Bioscience, SmithKline Beecham.

[68] Columbia University, Emory University, Johns Hopkins University, New York University, St. Louis University, Stanford University, University of California, University of Massachusetts, and University of Washington.

[69] Human Gene Sciences with Johns Hopkins, McGill, University of Michigan, and University of North Carolina; SmithKline Beecham with Yale and Monash University; Amgen with Rockefeller University.

is not exhaustive, since many patent applications may be framed in obscure language and do not respond to logical searches.

There is little evidence in Figure 6 for the use of population-level DNA sampling. As mentioned above, AxyS Pharmaceuticals took advantage of published research on the Tristan da Cunha polymorphism data as a lead in developing its patent on asthma-related genes, and it is possible that DeCode Genetics used Icelandic DNA—albeit not under the company's database license in that country—for its isolation and description of the gene responsible for narcolepsy.[70] I can find no other examples among recent U.S. patents.[71] Roche Bioscience has participated in publicly funded published human genetic diversity work, but does not appear to have acquired any derivative patent rights.

On the other hand, industry clearly benefits from government investments in the construction of general tissue collections and databases, as indicated by the "repository" column in Figure 6. The leading public source of patent leads has been GenBank, which contributed to one-fifth of the patents shown in Figure 6, followed by CEPH (10 percent) and standardized commercial sets such as LifeSeq® (7 percent). Many patents also made references to universities' online databases.[72]

HGDP scientists have generally not benefited commercially from their research. Two of the Stanford partners have patented some laboratory methods,[73] but not genes as such. They were instrumental in developing ways of using Y chromosome haplotypes to trace human phylogeny, but a New Jersey agricultural biotechnology company, Fitolink,

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[70] A method for detecting the mutations associated with Parkinsons and Alzheimers Disease was developed by DeCode Genetics (U.S. patent no. 5,494,794) using HGDP data only as a control group against a clinical sample of diseased patients.

[71] H. Shand, Where New Genes Come From, MOTHER JONES (May/June 1998), identified two patents on HLTV-1 (human T-cell lymphotropic virus type 1) resistant alleles from Melanesia populations, both obtained by NIH or it parent department, DHHS, in the 1990s and subsequently withdrawn for technical and political reasons. DHHS has proceeded with lab-bench research on HLTV-1; see e.g. U.S. patent no. 5,695,762 (1997).

[72] E.g. online tools available from the University of Washington Department of Molecular Biotechnology, http://www.mbt.washington.edu (last visited 12 October 2001), and the Wellcome Center at the University of Oxford, http://www.well.ox.ac.uk (last visited 29 January 2002). Nearly 70 percent of Incyte's human gene patent applications (100 percent sample) make some reference to GenBank.

[73] U.S. patents 5,585,236 (1996); 5,795,976 (1998); 5,846,832 (1998).

has obtained the only U.S. patent related to this methodology.[74] Fitolink even referenced Stanford geneticists' publications in its patent application, and the only colorable novelty is Fitolink's claim that the technique can be used to determine the relatedness of families within a small geographic area (the example given was the city of Trieste, in Italy), rather than the relatedness of larger populations such as tribal or ethnic groups!

In reality, then, the motivation behind most human genetic-diversity research has been intellectual curiosity and academic career promotion rather than profit, just as I have shown elsewhere to be true of research on indigenous peoples' traditional medicines.[75]

Bioethical standards

The United Nations recently called upon governments and industry to ensure free access to information about the human genome, while respecting the fundamental rights of individual gene donors to their privacy, dignity, and identity.[76] Some of the research reviewed here does raise ethical suspicion insofar as it involved the sampling of clinical or institutionalized (and therefore vulnerable) populations of marginalized or oppressed peoples: Chinese hospitals obtaining specimens from Tibetans,[77] for example, or Israeli hospitals obtaining specimens from Palestinians.[78] Is this merely an issue of individuals' freedom of consent, or does it implicate the rights and interests of groups?

An evaluation of the benefits and ethical dimensions of human genetic diversity research by the National Research Council concluded that it is more important to shield individuals than groups from the potential harm of improper disclosure.[79] The Council

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[74] U.S. patent 6,277,567 (2001).
[75] Barsh, Who Steals Indigenous Knowledge, *supra* note 2.

[76] UNESCO General Conference, Universal Declaration on the Human Genome and Human Rights (11 November 1997), endorsed by the UN General Assembly, res. 53/152 (9 December 1998); United Nations Millennium Declaration, UNDOC A/RES/55/2, par. 23 (8 September 2000); UN Commission on Human Rights res. 2001/71, Human Rights and Bioethics (25 April 2001).

[77] Note 19, *supra*.

[78] E.g. A. Nebel et al., High-Resolution Y Chromosome Haplotypes of Israeli and Palestinian Arabs Reveal Geographic Substructure and Substantial Overlap with Haplotypes of Jews, HUMAN GENETICS 107:630-641 (2000); the acknowledgments imply that the samples were collected by Palestinian physicians working in the territory administered by the Palestinian Authority.

[79] National Research Council, COMMITTEE ON EVALUATING HUMAN GENETIC DIVERSITY (National Academy Press, Washington D.C., 1997), at 4, 63-65; available at http://books.nap.edu/books (last visited 15 November 2001).

recommended against sampling by lineages, or including family or medical history data in accessions, due to the risk of subsequent unauthorized disclosures of the identities of the donors. Instead, the Council suggested the use of pooled samples of several hundred anonymous individual members of groups, and accessioning the pool with nothing more than "basic group identification" to minimize the risk of compromising individual tissue donors' privacy. Informing and seeking the formal approval of the group was described as "useful" rather than necessary.

The NRC proposal is an interesting albeit highly debatable trade-off between the utility and risks of genetic diversity research. Without lineage and medical-history data, researchers are hampered in associating any unusual genetic characteristics of the sample with gene functions. This obstacle is not insurmountable, however, because the variation can be explored through laboratory cloning and expression of the target genes. The cost to researchers is difficult to estimate; the only commercial laboratory that has access to a lineage-specific genetic diversity library has not won significantly more U.S. human gene patents than its competitors.[80] On the other hand, the NRC arguably underestimated the potential harm of disclosure to groups. Its panel assumed that genetic diversity within groups is nearly as great as the differences that exist between groups—in effect, that there is little danger of individuals being seriously stigmatized by virtue of their membership in particular groups. That might be true in a rational world populated by geneticists, but we live in an irrational world that seizes upon "scientific" evidence to justify discrimination.

Stanford University HGDP researchers have prepared an admirable model ethical protocol for the collection of human tissue samples.[81] It stresses respect for the privacy, interests, and freedom of choice of individual genetic donors as well as the communities and countries to which they belong, drawing upon the familiar bioethical requirement of genuine informed consent. While it does not refer to the self-determination or territorial sovereignty of indigenous peoples, the HGDP model protocol is consistent with standards

[80] Myriad Genetics, based at Salt Lake City, frequently uses data from Utah (Mormon) kindreds.

[81] HGDP North American Regional Committee, Model Ethical Protocol for Collecting DNA Samples, at http://www.stanford.edu/group/morrinst/hgdp (last visited 22 April 2001), the home page of the HGDP at the Morrison Institute for Population and Resource Studies of Sanford University.

advocated by its critics, such as the Indigenous Peoples Council on Biocolonialism.[82] The model protocol lacks enforcement machinery, however. An aggrieved community could presumably complain to national HGDP oversight committees, or to funders such as NIH and NSF. If a patent resulted from the research, an aggrieved community could plausibly sue the collector to relinquish its patent rights or pay compensation on a theory of implied contract or unjust enrichment.

Individual consent is considerably easier to secure than group consent. Consent to genotyping can be included routinely in the set of standardized consent and release of liability forms supplied to blood donors, hospital admissions, and patients scheduled for tests or surgical procedures.[83] Questions may be raised as to whether blanket consent to genotyping given by a trauma patient at the time of initial admission, can be genuinely informed or voluntary, especially with respect to research projects that have not yet been designed.[84] Indeed, consent to a specific existing research project does not meaningfully cover any research that may be conducted in the future. As a practical matter, however, preserving the anonymity of specimens as a protection of individual donors, also has the effect of depriving donors of any knowledge of the future disposition of their specimens. A suspicious donor would simply be unable to confirm the identity of a specimen used in subsequent research without submitting to a further sampling for genetic comparison. A tribal or ethnic group would be better able to monitor the technical literature and patents, and to intervene effectively without compromising the identities of individual donors.

I have been able to document at least one case in which indigenous peoples have challenged a genetic diversity project. In 1993, University of Pennsylvania arranged for the use of blood samples collected by Argentine public health clinics from the Tobas and Matacos; national indigenous organizations demanded that the Argentine state put an end to such studies.[85] The allegedly covert sampling activity reportedly ceased, but Mapuche

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[82] Indigenous Research Protection Act, available at http://www.ipcb.org (last visited 16 February 2002).

[83] See, e.g., the detailed list of sample sources in Smith, Distribution of Albumin Naskapi, *supra* note 37, which includes several hospitals operated by U.S. Indian tribes or the U.S. Indian Health Service.

[84] I have found two examples of blood obtained from police laboratories, which raise additional problems of an ethical and legal nature: Basque samples used in Malaspina et al., Multistep Process, *supra* note 49, and Ojibwa (Chippewa) samples used in Torroni et al., Asian Affinities, *supra* note 19.

[85] Interview of Jorgue Neuel, Coordinadora de Organizaciones Mapuche (1 August 1997) [author's files].

DNA sequences have been widely published,[86] and no patents appear to have resulted, at least in the United States. Researchers have generally not experienced any difficulties re-sampling communities that were sampled in the past. The Yanamamö, for example, were sampled repeatedly the 1960s to the 1990s by many of the same researchers.[87]

Unfortunately, most of the harm has already been done, from a community-level perspective. Samples taken in the 1970s-1980s do not identify individuals, but identify groups, and there was generally no documented group-level consent. Group privacy and property interests have already been compromised, and most of the material is probably already in the hands of third parties who can allege ignorance in their defense, including, in a small number of cases, patent assignees. There are relatively few virgin populations to be studied. Nevertheless, the sample size in most instances was very small, generally fewer than ten individuals and frequently only a single exemplar. Researchers returning for additional, better-preserved and better-documented DNA specimens could be required to observe the model protocol, and even to pay compensation for the past improprieties of other researchers. This assumes a substantial financial incentive for additional sampling, which is questionable.

Future collecting

The pharmaceutical payoff from functional genomics generally has thus far been commercially disappointing.[88] New drugs have not been produced any faster than before. On the contrary, while there have been more leads and patents, more have had "off-target effects"—that is, adverse reactions or side effects in clinical trials and failed at late stages of development.[89] As the editors of *Nature* concluded after hosting a conference on drug discovery and biotechnology, "most new targets still lack both a known function and any

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[86] E.g. A. S. Goicoechea et al., Genetic Relationships Between Amerindian Populations of Argentina, AMERICAN J PHYSICAL ANTHROPOLOGY 115:133-143 (2001); M. L. Moraga et al., Mitochondrial DNA Polymorphisms in Chilean Aboriginal Populations: Implications for the Peopling of the Southern Cone of the Continent, AMERICAN J PHYSICAL ANTHROPOLOGY 113:19-29 (2000).

[87] Williams, Chagnon and Spielman, Nuclear and Mitochondrial Genetic Variation, *supra* note 38.

[88] J. Carey and E. Licking, Nice Job on the Genome. Now, Let's See Some Profits, BUSINESS WEEK (26 February 2001): 34; Malakoff and Service, Genomania Meets the Bottom Line, *supra* note 62.

[89] R. Ulrich and S. H. Friend, Toxicogenomics and Drug Discovery: Will New Technologies Help Us Produce Better Drugs? NATURE REVIEWS 1 (January 2002): 84-88.

specific chemical modulators" because researchers have failed to give adequate attention to the fact that "drugs act on targets *within a biological context*."[90] In other words, there has been too much stress on the chemistry of individual genes, and not enough on genes as part of complex biological systems.

This might seem like good news for proponents of more human genetic-diversity research, since clinical observation and sampling of living populations could tell us more about the functioning of polymorphic genes in real people under varied conditions. Cost, time, ethical and political considerations make it unlikely that naturalistic experiments on isolated human societies will be contemplated, I suggest, unless those societies have their own reasons for encouraging such research. Sufficient information on gene variation and expression *in vivo* can be generated by a combination of new lab-bench technologies and clinical research with hospital populations; indeed, hospital populations in relatively rich countries represent the most profitable market for any drugs that result from the research. To the extent that comparisons with "founder" societies are still desirable, a large number of tissue specimens originally collected for historic genomic studies remain available for re-analysis. As indicated in Figures 3 and 5, moreover, nuclear and mitochondrial DNA has also been extracted from skeletal remains,[91] and this technology may eventually help expand the breadth of genetic diversity collections without recourse to living donors.

There is a different issue, which falls closer to the concerns raised by WHO in the context of the AIDS crisis in developing countries: affordable and effective drugs. Very little genetic-diversity research has focused on the health of indigenous peoples. Across populations, different genes may be implicated in what appears to be the same syndrome such as NIDDM.[92] There is increasing evidence of the extent to which humans are not

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[90] Navigating the Evolving World of Drug Discovery, NATURE REVIEWS 1 (January 2002): 1 [emphasis supplied].

[91] See, e.g., C. K. Kolman, Ancient DNA Analysis of Human Populations, AMERICAN J PHYSICAL ANTHROPOLOGY 111:5-23 (2000); also see US Patent 6,329,149 (2001) for a non-destructive methods of salvaging DNA from human teeth.

[92] See Busfield et al., Type II Diabetes-Susceptibility Genes, *supra* note 41; R. L. Barsh, Chronic Health Effects of Dispossession and Dietary Change: Lessons from North American Hunter-Gatherers, MEDICAL ANTHROPOLOGY 18:135-161 (1999).

only adapted to local dietary possibilities, but also to local pathogens.[93] This means that diversity research can play a very important role in ensuring that therapeutic methods are effective on diverse populations. It also means that there is a real danger that functional genomics research focused on Western clinical samples will simply overlook the genetic bases of disease among relatively isolated, traditional communities.

A brief glance at the pipelines of major pharmacogenomic companies shows that some of their work is relevant to the specific health concerns of indigenous peoples such as diabetes (NIDDM) and osteoporosis (a significant and growing problem among Inuit). Most recent pharmacogenomic research has been directed at cancer, asthma and allergy, cardiovascular disease, and neurodegenerative conditions such as Parkinsons Disease and Alzheimers, which is to say the priority concerns of relatively wealthy Western peoples.[94] Indigenous peoples' own priority for the future should be assuring the responsiveness of pharmacogenomic research to the needs of genetically distinct but marginalized societies, so that they fully benefit from new medical technologies, rather than remaining—insofar as genetic research is concerned—an academic sideshow.

[93] D. Meyer and G. Thomson, How Selection Shapes Variation of the Human Major Histocompatibility Complex: A Review, ANNALS HUMAN GENETICS 65:1-26 (2001).

[94] Based on the disease targets identified in the patent applications included in Figure 5.

Figure 1. Tribal Groups Sampled by Genetic-Diversity Researchers

Regions		New groups documented			Groups re-sampled*
		Before 1985	*Since* 1985*	**Total**	
Africa	North	4	1	**5**	1
	Sub-Saharan	38	25	**63**	13
Americas	North	25	19	**44**	9
	Central-South	69	45	**114**	20
Asia	East-Southeast	16	68	**84**	14
	Central	8	8	**16**	2
	Siberia-Amur	11	10	**21**	10
	South	28	18	**46**	4
Europe	Northern	1	2	**3**	1
Pacific	Australia-PNG	43	19	**62**	5
	Polynesia	20	11	**31**	17
World		**263**	**226**	**489**	**96**

*Some groups were originally included in pooled samples, and only reported separately after 1985. Clearly identified instances of re-sampling after 1985 probably underestimate the actual number. A referenced list of tribal groups included in this figure is available from the author.

Figure 2. Tribal Peoples in Major DNA Collections and Databases

Regions		Number of groups documented			
		GenBank	**Coriell**	**GDB**	**Total**
Africa	North	-	-	1	**1**
	Sub-Saharan	3	2	6	**11**
Americas	North	1	2	3	**6**
	Central-South	1	5	4	**10**
Asia	East-Southeast	-	2	-	**2**
	Central	-	-	-	**-**
	Siberia-Amur	-	1	-	**1**
	South	-	-	1	**1**
Europe	Northern	-	-	-	**-**
Pacific	Australia-PNG	1	2	2	**5**
	Polynesia	1	1	3	**5**
World		**7**	**15**	**20**	**42**

Figure 3. Published human genetic-diversity studies (1999-2002)*

Target region		Studies, by DNA source			Health related	Novel alleles
		Living	Dbases	Skeletal		
World		3	4		3	
Africa	North	6	1		1	
	Sub-Saharan	16	4		6	3
Americas	North	4	2	3		1
	Central-South	17	5	1	6	5
Asia	East-Southeast	14	5		5	4
	Central-Siberia	5	2		1	1
	South	6	1		3	
Europe	Arctic	1				
Pacific	Australia-PNG	4	2		3	
	Polynesia	4			2	
Total		**80**	**26**	**4**	**30**	**14**

* Sources are described in the text. Groups are non-duplicative totals.

Figure 4. Institutions handling human genetic-diversity samples (2000-2002)

Locations		States	Number of institutions				
			Academic	Medical	Science	Corporate	**Total**
North	United States	1	31	11	1	4	**47**
	Europe (West)	11	33	16	2		**51**
	CANZ	3	9	3			**12**
	Japan	1	12	3	1		**16**
Africa	North	2	3	5			**8**
	Sub-Saharan	10	8	9			**17**
Americas	Central-South	10	15	8	5	1	**29**
Asia	China	1	5	2	3		**10**
	Middle East	4	4	3	1		**8**
	South Asia	2	5	3	8		**16**
	Southeast Asia	7	10	3	1		**14**
Europe	Russia-Eastern	13	10	9	2		**21**
Pacific	PNG, Polynesia	3		3			**3**
World		**68**	**145**	**78**	**24**	**5**	**252**

Key to institutional types: Academic (universities, medical schools); medical (public and private hospitals, clinics, blood banks, public health departments, government medical research institutes, health promotion NGOs); science (non-medical government research agencies and institutes including museums); corporate (for-profit businesses).

Figure 5. Funding for published human genetic-diversity studies (2000-2002)*

Funding source by type and region		Studies funded, by DNA Source			Health-related
		Living	Dbases	Skeletal	
Government	World (UN)	1			1
	Europe-EEC	23	5	1	8
	United States**	24	11	6	8
	Japan	2	3		2
	CANZ	4			3
	Russia	1			
	China	4			
	South	17	9	1	6
Foundations	World	2	6	1	7
Corporations	United States	1	1		2
Total awards = 123		79	35	9	37

*Sources are described in the text. Column totals exceed those in Figure 5 because some studies were founded from multiple sources.