

Genes, Culture, and Health

Ensuring the Best Health Outcomes for All



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A report of the
National Alliance for Hispanic Health
and the Healthy Americas Institute

FEBRUARY 2015

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Executive Summary

In 2004, the National Alliance for Hispanic Health released *Genes, Culture, and Medicines: Bridging Gaps in Treatment for Hispanic Americans*, and brought together for the first time the body of scientific research demonstrating the role of genetic factors in medication effectiveness for Hispanic communities. Since that report, the pace of knowledge and clinical application of genetic findings has been breathtaking. The growth in genetic technologies and knowledge has been exponential. The costs of genetic testing, including genome-wide association studies (GWAS) and next-generation genome sequencing have dropped significantly and technologies improved. The number of disease areas for which genetic testing has shown utility has increased; and, in areas such as cancer, personalized therapies have become more available.

Despite developments in genetics and clinical applications, the promise of personalized medicine is not reaching all. There are limits to health access and quality for underserved communities. Consider these findings —

- **Major racial and ethnic U.S. populations are underrepresented in genetic studies.** As of 2011, only 4% of GWAS, included subjects of non-European descent.¹
- **Without diversity in study populations, genetic variants important to disease and therapy responses may go undiscovered.** Some of the latest research has shown common genetic variants have different effects in different ethnic groups and variants found in less than 5% of the population may be the most significant in terms of understanding risk of disease and response to particular therapies.
- **Attention to issues of inclusion and access will advance personalized medicine by driving genetic discovery that will benefit all.** Advances in Personalized Medicine (PM) hold the promise of improved quality in areas such as determining the most effective medicine and dose — based on pharmacogenomic studies of drug effectiveness and metabolic differences — to tailoring treatment to the individual through biologies and other advances.²

There is a clear scientific and health quality case for improving the diversity of our genetic research and understanding of clinical applications. There is also a clear legislative and regulatory mandate to show improvement. Three key recommendations are:

1. **Improve the Science.** Fully implement federal research guidelines for inclusion of underrepresented groups in all study and grant applications, including pilot studies, and encourage non-federal granting bodies to do the same.
2. **Enhance Quality of Care.** Initiate a translational effort, based on new knowledge from genetic studies, that will deliver enhanced guidance to providers on applicability to specific populations of current clinical recommendations and prioritize new studies to fill in knowledge gaps.
3. **Support Consumer Health Decision-Making.** Launch a consumer support effort on using genetic information to inform health decision-making and ensure access to testing, counseling, and companion diagnostics.



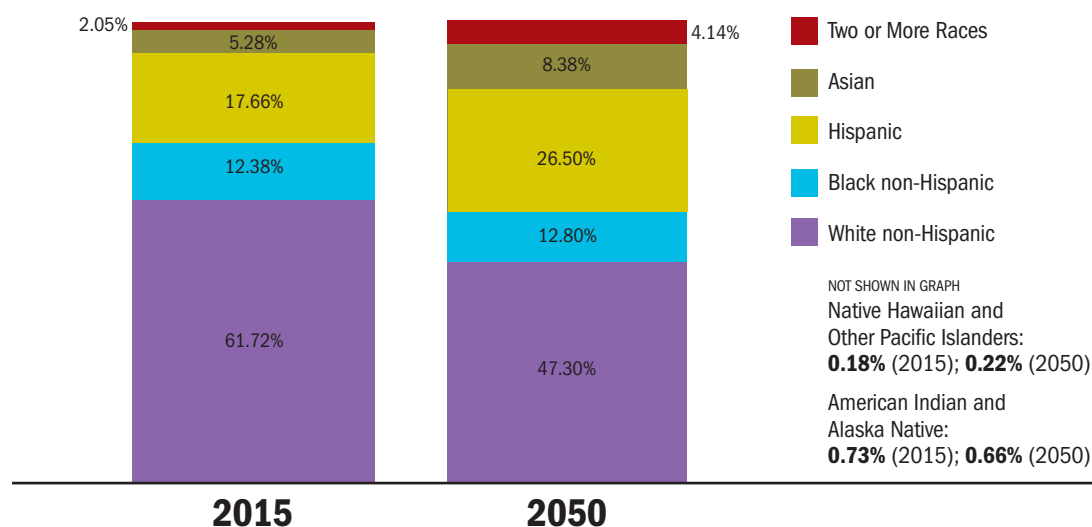
Genetic considerations for understanding health

Today, one in six persons in the U.S. is Hispanic, with a total population of 57.6 million (54 million residents in the 50 states and DC and 3.6 million residents in the Commonwealth of Puerto Rico).³ The U.S. Hispanic population is projected to comprise 27% of the total US population by 2050.⁴

However, significant differences in health care, pharmaceutical treatment and medical outcomes persist for Hispanic communities. These differences are attributable to a combination of factors including socioeconomic status, cultural and social determinants of health, environmental exposures, dietary practices, and genetic variations in disease susceptibility and drug metabolism. Additionally, 24.3% of U.S. Hispanics do not have health insurance.⁵

The understanding of the role of genetics in health has increased and is helping to shape the rise of personalized medicine. This new frontier tailors medical treatment to the individual characteristics, needs, and preferences of the health care consumer during all stages of care (prevention, diagnosis, treatment, and management).⁶ These advances,

U.S. Population by Race and Ethnicity, 2010 and 2050



Source: U. S. Bureau of the Census, Population Division. Percent Distribution of the Projected Population by Hispanic Origin and Race for the United States: 2015 to 2060, December 2014. Note: Data do not include the Commonwealth of Puerto Rico. American Indian/Alaskan Native and Native Hawaiian and Other Pacific Islander proportion is less than 1%.

however, are not being fully realized for everyone. Little is known about the role of genetics in Hispanic health and well-being. The literature that does exist, however, points to an urgency for those involved in the delivery of health care and health care policy to understand the implications of genetics for Hispanic health and well-being.

The genetic roadmap

It is extraordinary that each of our cells holds the blueprint to our makeup — our DNA. Each of our cells has the long, ladder-shaped, twisted molecule of DNA that is the blueprint for our makeup, and is also a roadmap of humankind's history. Our

long DNA molecules are organized into pieces called chromosomes. Chromosomes are further organized into short segments of DNA called genes. It is variations in these genes, or alleles, that drive our understanding of why one person may have a disease but not another person even when these same two person are related. Variations also explain why a medication may work for one person but not another with the same disease. Studies of genetic variation have also led us to a deeper and critical understanding of the interaction of our genes with environmental factors such as a healthy diet or pollution in our air or water. Environmental factors affect whether or not genes are switched on or off, including genes that when switched on may cause a disease or make a medication less effective in treating an illness.

“...the remaining 0.5% of our genes that makes us genetically different from one another that is critical to understanding genetics and environmental triggers and their role in health.”

All human beings are 99.5% genetically similar. It is the remaining 0.5% of our genes that makes us genetically different from one another that is critical to understanding genetics and environmental triggers and their role in health. The primacy of understanding gene

variations, or alleles, also means that it is critical that scientific efforts to catalogue such variations draw from a large and diverse study population.

Genome-wide sequencing, which has become faster and less expensive in recent years, is finding that accelerated world-wide population growth has been accompanied by a growth in rare variants.⁷ The population groups in the U.S. of a majority non-European descent are more likely to have rare genetic variations due to their ancestry than those of a majority European ancestry. For example, investigators in the 1000 Genomes Project study found that populations of African ancestry had three times as many rare variants compared with those of European and Asian origin.⁸ This finding underscores the importance of diversity in genetic studies.

Scirica and Celedón detailed four areas where understanding the genetics of complex diseases in diverse populations would help to improve health for all communities⁹:

- Rare disease susceptibility alleles (frequency <2%) may be found only in certain ethnic subgroups. For example, a rare mutation associated with inherited deafness was identified in an isolated population in Costa Rica.¹⁰
- Knowledge of the frequencies of variants in disease susceptibility genes within ethnic groups may be important in designing strategies for effective disease screening and diagnosis.
- Knowledge of the risk of disease that is attributable to a particular allele in an ethnic group or subgroup may be important in disease prevention and treatment.
- Genetic variants and their interaction with other genetic and environmental factors may impact the response to and side effects from therapy, including drug metabolism and effectiveness.
- A number of areas of health research in racial and ethnic groups demonstrate the growing importance of understanding the role of genetics in assessing health risk and effective diagnosis, treatment, and management of disease.

Understanding Genetic Admixture

The terms “Hispanic” and “Latino” describe a racially diverse group of peoples who have descended from areas with historical Iberian (Spanish and Portuguese) colonization, and who either speak Spanish or have a cultural Spanish-speaking heritage. The five largest groups, comprising 84% of the total U.S. Hispanic population, are Mexican Americans, Puerto Ricans, Cubans, Salvadorans, and Dominicans with another 16% of the population representing all other countries of Latin America and the Caribbean. The various Hispanic subgroups exhibit a high degree of admixture (mixed ancestry) —their unique population history has been characterized by a substantial mixture of European, West African, and Native American ancestry, and a multitude of other peoples from other distinct geographic regions.¹¹ Rather than being homogenous, the genetic diversity among Hispanics is quite broad.

Ancestry Markers and Statistical Innovations

Along with the remarkable advances in genomic technologies in recent years, there has been a much less-publicized but equally important boom in the development of statistical tools needed to analyze and interpret the “tsunami” of data being produced. With newfound abilities, informatics experts are developing increasingly sophisticated strategies. It is becoming evident that this toolbox will enable researchers to take advantage of racial and ethnic differences to enhance personalized medicine and quality of care.

Ancestry informative markers (AIMs) are sets of DNA sequence variations that appear in substantially different frequencies between populations from different regions of the world. They are powerful tools for unlocking the secrets hidden in the compartments of our genomes that reveal where we came from and which can shed vitally important light on medically relevant associations linked with specific variants.¹² For example, in 2005 Choudhry *et al* used 44 AIMs among Mexican and Puerto Rican subjects participating in case-control studies of asthma. The study showed that among Mexican Americans there was a strong association between higher levels of European ancestry and increased asthma severity, and conversely an association between higher levels of Native American ancestry and decreased asthma severity. Among Puerto Ricans, however, there was no association between measures of asthma severity and ancestry. At that time, the use of AIMs was still relatively new, and the authors cautioned that confounding due to population stratification was still a cause for much concern.¹³

Subsequent development of the techniques has alleviated some, or perhaps all of that concern, especially when compared to past techniques such as racial and ethnic self-reporting. “The use of AIMs ... is becoming more and more popular among biomedical researchers who understand that self-reporting is not a strong proxy for biology ... While race may be an important determinant to monitor health status and health care quality, it lacks biological integrity,” reported Kittles *et al*.¹⁴ In 2005, Burchard *et al* made the crucial connection: “The unavailability of self-report of ancestry and the genetic complexity among Latinos may complicate biomedical research studies in this population,” they wrote in 2005. “On the other hand, precisely because of this complexity, Latinos also present a unique opportunity to disentangle the clinical, social, environmental and genetic underpinnings of population differences in health outcomes.”¹⁵

In a 2012 article, Seldin described how “advances in statistical methodologies that can infer

Talking Genetics

Listen to a brief talk on Ancestry Informative Markers (AIMS) and learn more about genetic terms from scientists at the National Human Genome Research Institute

www.genome.gov/glossary

Genetic Atlas

Go online to view an interactive atlas of
ancestral population groups
and see their genetic contribution to
populations around the world today.

admixturemap.paintmychromosomes.com

genetic contributions from ancestral populations may yield new insights into disease and may contribute to the applicability of genomic medicine in diverse population groups.”¹⁶ Galanter and colleagues have developed a panel of genome-wide AIMS to study admixture (multiple ancestries) throughout the Americas.¹⁷ They developed a panel of 446 AIMS well-distributed throughout the genome and used the panel to genotype 18 populations throughout Latin America. “Once determined, these ancestral proportions can be correlated with normal phenotypes, can be associated with disease, ...or can inform on the history of admixture in a population,” they wrote in their 2012 paper.¹⁸ AIMS have now been used in a wide variety of studies exploring the relationship between admixture and disease prevalence, looking at associations with conditions such as diabetes, obesity, cardiovascular disease, depression, and breast cancer.^{19,20,21}

The innovation of admixture mapping could potentially translate into advances in personalized medicine for consumers. As reported in 2008 by Drake *et al*, admixture mapping at that time had already been used to identify genetic variants that contribute to multiple sclerosis, hypertension, and circulating levels of inflammatory markers.^{22,23,24} Specifically, in the case of hypertension, in 2005 Zhu *et al* used the technique to assess genetic variants related to the condition and concluded that “chromosome 6q24 and 21q21 may contain genes influencing the risk of hypertension in African Americans”;²⁵ for multiple sclerosis (MS), Oksenberg *et al* reported an association of the HLA-DRB1 gene with MS in African Americans,²⁶ and finally, Reich and others used admixture mapping to search for regions in the genome associated with inflammatory markers that “can predict cardiovascular disease risk”.²⁷

Emerging Genomic Approaches

With the Human Genome Project and the HapMap Projects having been completed, since 2008 the international collaborative scientific community has turned its attention to the 1,000 Genomes Project. This effort builds upon the previous achievement by deep sequencing the whole genomes of individuals from different worldwide populations, with the central goal being to describe most of the genetic variation that occurs at a population frequency greater than 1%. This bold, ambitious initiative will allow researchers to identify genetic variation at an unprecedented degree of resolution. By identifying novel or rare functional genetic variants, scientists will be able to pinpoint disease-causing genes in genomic regions initially identified by association studies. Ultimately, the identification of those variants will enable the development of new population-specific genotyping arrays.²⁸

Milestone Efforts in Genetic Mapping

Human Genome Project. Began in 1990 led by an agreement between the National Institutes of Health (NIH) and the Department of Energy to develop the first map of the human genome. A parallel project outside of government was launched in 1998 by the Celera Corporation headed by Dr. Craig Venter. In 2000, Dr. Francis Collins of the NIH and Dr. Venter jointly announced the completion of a draft of the first human genome map; completed in 2003.

HapMap Project. International collaboration to describe the most common patterns of human genetic variation with a third phase of mapping completed in 2009 with data from 11 global populations that included an expanded sample size of U.S. non-European ancestry populations.

1000 Genomes Project. Began in 2008, this international effort in October 2012 announced the sequencing of 1092 genomes and is the most detailed catalogue of human genetic variation.

Cancer Genome Atlas. An NIH effort begun in 2005 to catalogue genetic mutations responsible for cancer with plans to complete by the end of 2014 the sequencing of 20-25 different tumor types.

Recent results from the consortium, published in *Nature* in November 2012, describe an integrated map of genetic variation from 1,092 human genomes from 14 populations, including people with Mexican ancestry in Los Angeles, Iberian populations in Spain, and Puerto Ricans in Puerto Rico. The investigators show that individuals from different populations carry different profiles of rare and common variants, and that low-frequency variants show substantial geographic differentiation.²⁹

In 2010, Gravel and colleagues presented an approach combining complementary aspects of whole-genome sequencing, low-coverage data and targeted high-coverage data, applying it to data from the pilot phase of the 1,000 Genomes Project. They found that “the majority of human genomic variable sites are rare and exhibit little sharing among diverged populations,”³⁰ implying that ancestral genomic information will be useful.

De La Vega *et al* may have pointed the way forward in their 2010 publication, *Genome sequencing and analysis of admixed genomes of African and Mexican ancestry: Implications for personal ancestry reconstruction and multi-ethnic medical genomics*.³¹ The team performed deep sequencing on two genomes from the Phase HapMap. These were the first admixed genomes to be sequenced to high coverage. They combined the sequencing data with other genetic variation data, including from the 1,000 Genomes Project, “to quantify the relative proportions of private, rare, and common functional and neutral alleles within and among populations ... Our results suggest that there are many new variants to be discovered in populations from African and American descent, some of potential disease relevance.” By integrating data from several sources, this group and others have provided examples of innovative methods that promise to yield important new information about how ancestry and populations may be the previously missing links in the quest for truly personalized medicine.



Hispanic Inclusion in Genetic Studies

As NIH Director Dr. Francis Collins noted upon the tenth anniversary in 2010 of the completion of the Human Genome Project, “Human genome research is an epic drama being played out year after year, in sequel after exciting sequel... It is my hope and expectation that over the next one or two decades—or however long it takes—genomic discoveries will lead to an increasingly long list of health benefits for all the world’s peoples.”³²

That promise, however, is diminished by a lack of diversity, including inclusion of Hispanic populations, in genetic studies. For example, as of 2011, only 4% of GWAS were being conducted with subjects of non-European descent.³³ There has certainly been breathtaking progress in the epic drama that is the genetics/genomics discipline since 2004, with sequencing technologies and the computational tools needed to interpret the “big data” they generate gaining rapidly in firepower and sophistication. But attention to diversity has lagged, and unless there is a dramatic paradigm shift in the research agenda and research practices, Dr. Collins’s expectation that genomic discoveries will benefit “all the world’s peoples” will likely remain unfulfilled.

Current Status

As Bustamante *et al* pointed out in their influential comment in *Nature*, 96% of GWAS, the sequencing technology used to research common genetic variants, have been conducted in subjects of European descent, introducing a troubling bias. The authors argue this bias is likely to continue as the field evolves to use newer technologies such as NextGen sequencing to discover rare variants.³⁴ “Geneticists worldwide must investigate a much broader ensemble of populations, including racial and ethnic minorities. If we do not, a biased picture will emerge of which variants are important and genomic medicine will largely benefit a privileged few.”³⁵

“Geneticists worldwide must investigate a much broader ensemble of populations...if we do not...genomic medicine will largely benefit a privileged few.”

The issue of which variants are important is far from trivial—it is central to the promise of genomic medicine and personalized pharmaceutical treatments. Although they were quite valuable in identifying loci for candidate genes thought to be involved in some common diseases, the common variants brought to light by GWAS only accounted for approximately 5-50% of heritable factors, highlighting the famous “missing heritability.” That missing heritability lies in rare genomic variants, those that occur in less than 5% of the world’s population.

Rare variants “may be disproportionately important both in determining a person’s risk of getting a complex disease and in predicting their response to a particular drug.” Importantly, they tend to be population specific. “So if they do play a key part in disease, the lack of diversity in genetic studies will be severely skewing our understanding of which are important,”³⁶ Bustamante *et al* conclude, “Those most in need must not be the last to receive the benefits of genetic research.”³⁷

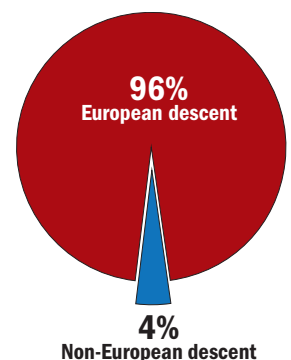
Mandates for Inclusion

Given the ongoing issue of lack of inclusion of racial and ethnic minorities in clinical research despite federal regulations mandating inclusion and reporting, changes to the status quo of research are necessary. The National Institutes of Health (NIH) Revitalization Act of 1993 requires that NIH-funded clinical trials include women and minorities as participants. The Agency for Health Research and Quality (AHRQ) and the Centers for Disease Control and Prevention (CDC) adopted similar guidelines soon after the enactment of the NIH Revitalization Act, and in 1998 the FDA issued its Demographic Rule followed by the 2005 Guidance for Industry on Collection of Race and Ethnicity Data in Clinical Trials. In 2001, the NIH amended its policy, providing additional guidelines and definitions for the clinical research community.

The NIH was directed to ensure that women and minorities were included as subjects, unless their exclusion was justified due to circumstances specified by NIH guidelines. Furthermore, clinical

Sampling Bias

Most-genome-wide association studies have been of people of European descent.



Bustamante CD, De La Vega FM, González-Burchard E. Genomics for the world. *Nature*. 2011 Jul; 475: 163-165

Inclusion of Women and Minorities as Subjects in Clinical Research

It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-funded clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.

—NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research Effective, March 1994; Amended, October 2001

trials were to be designed and carried out in a manner that would elicit information about individuals of both genders and diverse racial and ethnic groups to examine differential effects on such groups. Despite these federal mandates, there remains a need to increase participation by underrepresented racial and ethnic groups in clinical research, including Hispanics. Lack of inclusion of Hispanics and other underserved populations in clinical research diminishes the quality of the science by introducing inherent bias in investigations, and perpetuates a long-standing and troubling pattern by which effective translation of research results may be compromised with respect to relevance for racial and ethnic groups.

In 2011, Geller *et al* published a study examining whether progress had been made in inclusion, analysis and reporting of sex and race/ethnicity in randomized controlled trials (RCTs) in the period from 2004-2009. The study assessed the impact of the federal mandates in the context of increasing emphasis from the FDA on reporting over the five-year period. Of the 86 studies included, “one-fifth of the studies we reviewed failed to report the racial/ethnic distribution of their participants, and when reported, black and Hispanic subjects remain underrepresented in clinical studies relative to their distribution in the U.S. population.”

Overall, the authors concluded, “given the ongoing focus by NIH and others over the past 5 years for inclusion of women and underrepresented minorities in clinical trials, we expected to see greater compliance with the guidelines, but for these nine influential journals, we found little improvement.”³⁸ The authors did note, however, that one of the notable changes they saw since the earlier study was an increase in the number of studies that considered “Hispanic” as an ethnic rather than a racial category, in accordance with Office of Management and Budget census categories (also followed by the FDA) that allow for a question on ethnicity in which the choices are “Hispanic or Latino” and “Not Hispanic or Latino.”

“...black and Hispanic subjects remain underrepresented in clinical trials...given the ongoing focus by NIH and others...we expected to see greater compliance with the [inclusion] guidelines...but...we found little improvement.”

FDA Safety and Innovation Act

On July 9, 2012, the FDA Safety and Innovation Act (FDASIA) was signed into law, which among many other provisions directs the FDA to publish a report “addressing the extent to which clinical trial participation and the inclusion of safety and effectiveness data by demographic subgroups including sex, age, race, and ethnicity, is included

in applications submitted to FDA.” The agency was also directed to post an action plan with recommendations on how to improve analysis of data on demographic subgroups in summaries of product safety and effectiveness and in labeling, along with recommendations on how to improve public availability of such data.³⁹ In response to this requirement of FDASIA, the FDA published their report in August 2013.

The report was based on the findings of an FDA workgroup that reviewed 72 applications approved during 2011. These applications involved drugs, biologics and medical devices.⁴⁰ The three FDA centers involved in the approval of the analyzed applications were the Center for Drug Evaluation and Research (CDER) for drugs, Center for Biologics Evaluation and Research (CBER) for biologics, and the Center for Devices and Radiological Health (CDRH) for medical devices.⁴¹ The findings were:

- Drugs. CDER approved 30 applications in 2011. Hispanic data could not be analyzed because some applications reported race and ethnicity as one item, rather than separately.⁴²
- Biologics. CBER approved five biologics. The FDA analysis found that the percentage of Hispanics/Latinos in the efficacy trial composition for the five submissions ranged between 5-35%.⁴³
- Medical devices. There were 37 premarket approval applications (PMA) analyzed by the FDA team. Hispanic representation in the study populations of the studies submitted to support the applications ranged from 0.3% to 35% by PMA application. PMAs for hepatitis B virus and HPV (applications for diagnostic tests) had the highest percentages of Hispanics.⁴⁴

Following that report the FDA in August of 2014 issued its Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data. The plan focuses on three overarching priorities—quality, participation and transparency.

- Priority One: Improve the completeness and quality of demographic subgroup data collection, reporting and analysis (**Quality**).
- Priority Two: Identify barriers to subgroup enrollment in clinical trials and employ strategies to encourage greater participation (**Participation**).
- Priority Three: Make demographic subgroup data more available and transparent (**Transparency**).

To carry out these priorities the action plan details a list of 27 action items along with a projected timeframe for completion: short-term (within one year), intermediate-term (within 1 to 3 years) or long-term (within 3 to 5 years).

Knowing the situation the FDA has been exploring ways to improve its data. for example, an enrichment strategy was detailed in the December 2012 draft guidance *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*. Enrichment is prospective use of any patient characteristic, including demographic or genetic, to select patients for study to obtain a study population in which detection of a

drug effect is more likely than it would be in an unselected population. and a model for the future

Conclusion

There appears to be a complex variety of reasons for the ongoing, persistent lack of inclusion of racial and ethnic groups in clinical research, including lack of focus and enforcement of mandates for racial and ethnic inclusion; lack of inclusion of a diverse group of investigators, especially in the genetics/genomics disciplines; and lack of resources dedicated to community education about clinical research, inclusion in design of studies, and elimination of access barriers to participation.⁴⁵

Addressing these issues is not only necessary to comply with legislative and regulatory mandates, it is critical to improving the science base and achieving the promise of personalized medicine. It has been shown it can be done with the NIH Hispanic Community Health Study/Study of Latinos (SOL) reporting in 2014 that it had enrolled an active study population of 16,415 Hispanic participants in four study centers around the country, the largest Hispanic study of its kind to date.



Genetics and Personalized Medicine

“It’s far more important to know what person the disease has than what disease the person has.” – Hippocrates

While we know that genes are not destiny but a blueprint that is influenced by many factors the era of truly personalized medicine and Pharmacogenomics (PGx) has begun its march into the clinical setting.⁴⁶ The use of genome sequencing will become increasingly common in clinical settings to diagnose rare conditions just as sequencing of tumor samples is now used to help guide care.”⁴⁷ In fact, the FDA in its October 2013 *Paving the Way for Personalized Medicine* reported, “In just the last two years, the FDA approved four cancer drugs for use in patients whose tumors have specific genetic characteristics that are identified by a companion test. Last year, FDA approved a new therapy for use in certain cystic fibrosis patients with a specific mutation.”⁴⁸

The President’s Council of Advisors on Science and Technology (PCAST) defined PM as “the tailoring of medical treatment to the individual characteristics of each patient.” The Council

noted that the promise of PM is “the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.”⁴⁹ Although clinical benefits are still evolving, five areas of PM development show great promise:

- Diagnosis/Prognosis — to assess particular subtypes of a disease or the unique characteristics of a condition;
- Treatment Prediction — to analyze whether a patient, infectious agent, or tumor with particular characteristics will respond to a certain treatment;
- Dosing — to determine appropriate amounts or strengths of treatment to administer to a particular individual;
- Safety — to anticipate adverse treatment reactions in certain subpopulations; and,
- Monitoring — to track and observe a patient’s response to a course of treatment, in part to evaluate any necessary modifications to the chosen treatment course.

In an April 2013 issue of *JAMA* devoted to genomics, a lead *Viewpoint* article on access argued that, “if molecular-based innovations are to be effectively and equitably introduced into delivery systems, all stakeholders will need to work diligently to address,” three issues. These issues are:⁵⁰

- Value Demonstration — There has to be adequate information across population groups regarding its accuracy and reliability, clinical utility, and the way it will be coded within the medical coding system.
- Clinical Management — There is a need for increased attention to how molecular discoveries will later be integrated into clinical settings, how providers will receive education on them, and services integrated into reimbursement.
- Patient Engagement — There must be engagement that should include patient education (with special attention to genetic literacy and informed consent), more training of personnel involved in care in genetic counseling, and, above all, a decision-making process in which providers and patients participate.

Clinical Implications of Genetics and Drug Metabolism

Pharmacogenomics is an intrinsic element of personalized medicine, and is defined as the study of how genetic factors relate to interindividual variability of drug response.⁵¹ People vary in their capacity to eliminate drugs because of differences in their drug metabolism systems. Increased or decreased metabolism changes the concentration of the drug.⁵² Persons with reduced ability to metabolize a specific drug are termed poor (slow) metabolizers of that drug; those with enhanced metabolic activity are termed ultrarapid (fast) metabolizers. Failure to recognize an individual as an ultrarapid or poor metabolizer and to adjust the dose accordingly may potentially result in therapeutic failure or unexpected toxicity, respectively.^{53,54}

Genes and Drug Metabolism Variation in Hispanic Populations

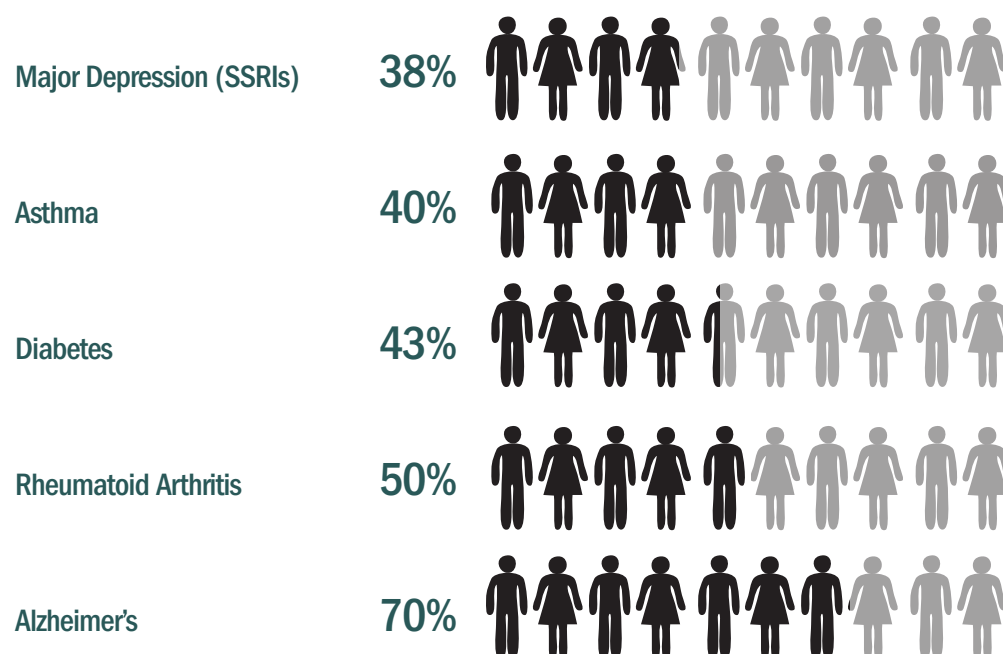
| Gene | Hispanic Variation | Major Drugs Regulated |
|--------|--|--|
| CYP3A4 | Slower metabolism/higher blood levels in Mexicans (metabolism in U.S. Hispanics not yet studied) | <ul style="list-style-type: none"> • nifedipine (cardiovascular) • cyclosporine (immunosuppressive) • midazolam (anesthetic) • sildenafil (erectile dysfunction) |
| CYP2D6 | Faster metabolism in Mexican Americans Slower metabolism in Dominicans and Puerto Ricans | <ul style="list-style-type: none"> • many cardiovascular drugs • many psychotropic drugs |
| CYP2C9 | Slower metabolism in Spaniards (metabolism in U.S. Hispanics not yet studied) | <ul style="list-style-type: none"> • warfarin (stroke prevention) • phenytoin (epilepsy) • many diabetes medications |

Drug metabolism and deactivation proceed via a process of chemical modification (e.g., oxidation, dealkylation, reduction, acetylation, sulfation).⁵⁵ Cytochrome P450 is a super-family of iron-containing enzymes that are named after the genes that encode them (e.g., CYP3A4, CYP2D6, CYP2C9). The majority of drugs in common clinical uses are converted (oxidized) in the liver by metabolic enzymes of the cytochrome P450 group.⁵⁶ This conversion makes the drugs more soluble in water, which facilitates their elimination from the body.^{57,58} Over 50 different forms of CYP450 have been characterized in humans, each encoded by a different gene.⁵⁹

Genetic variations in drug-metabolizing enzymes differ in frequency among ethnic groups.^{60,61,62,63} These variations can result in reduced or enhanced capacity of the corresponding enzymes to metabolize drugs. “It is interesting to note, that, almost without exception, wherever genetic polymorphism is identified, the allele frequency of mutations typically varies substantially across ethnic groups.”⁶⁴ In addition, environmental factors influence the activity of these metabolic enzymes.^{65,66,67} The activity of drug metabolizing enzymes can be increased or decreased by numerous substances, including foods, alcohol, tobacco, herbal medicines, as well as medications. As immigrant groups change their lifestyles and their exposure to these substances, their metabolic profiles can also change.⁶⁸

Decisions regarding the availability, selection, and dosages of drugs for patients from a given ethnic or racial group can be informed using available information on the likelihood of slow or fast metabolizers in that group. Relatively few studies have compared frequencies of genetic variations affecting metabolism in Hispanics compared with other population groups.⁶⁹ However, those studies that are available of the CYP2D6 and CYP2C9 forms of the CYP450 enzyme series have reported different frequencies of variants of these genes in some Hispanic groups, compared with other U.S. population groups or in some cases for Spain, Mexico, and some Central and South American populations compared to the U.S. population overall.^{70,71,72,73} In addition, CYP3A4 enzyme

Percentage of the patient population which does not respond to a major drug, by condition



Source of data: Brian B. Spear, Margo Heath-Chiozi, Jeffery Huff, "Clinical Trends in Molecular Medicine," Volume 7, Issue 5, 1 May 2001, pages 201-204.

activity is highly sensitive to environmental factors and varies substantially across ethnic groups with distinct diets. Foods such as corn, grapefruit juice, and charbroiled beef featured in the Hispanic diet, have been shown to alter the efficiency of the CYP3A4 gene.⁷⁴

As the availability of pharmaceutical products with known genetic variabilities becomes more commonplace, PGx will become integral to the practice of good medicine. Understanding and tailoring available treatments to those patients for whom they will be effective saves both expense and unnecessary risks from toxicity and side effects of a treatment for patients for whom that treatment will not be effective. In fact Duconge and Ruaño see a future in which the standard of good practice will be a "Genetic Prescription Model" that untangles the clinical utility of knowing an individual's genotype before initiating drug treatment by taking admixture into account, resulting in more effective healthcare in admixed people.⁷⁵

Companion Diagnostics

Companion diagnostics are laboratory tests and professional services that identify or measure genes, proteins or other substances that can help inform the proper course of treatment for a particular patient.⁷⁶ In 2014, the FDA's CDER, CDRH, and

CBER issued a joint draft guidance document that defined a companion diagnostic device as “an in vitro diagnostic device that provides information essential for the safe and effective use of a corresponding therapeutic product.”^{77,78} The intent of the guidance is to assist (1) sponsors who are planning to develop a therapeutic product that *depends on* the use of an *in vitro* companion diagnostic device (or test) for its safe and effective use and (2) sponsors planning to develop an *in vitro* companion diagnostic device that is intended to be used with a corresponding therapeutic product.

The genetic test accompanying the breast cancer drug Herceptin® (trastuzumab) is probably the best-known companion diagnostic product. The era of companion diagnostics can be said to have begun with the introduction of the HercepTest - a first-of-a-kind diagnostic tool developed by DakoCytomation in 1998 to select patients for therapy with Herceptin. Herceptin and the paired test proved that companion diagnostics can help guide patient-tailored therapies.⁷⁹ Herceptin targets the approximately 25% of breast cancer patients who have HER-2 gene amplification and over-express HER2/neu, a protein that makes breast cancer cells grow quickly. These tumors are associated with poor prognosis, but Herceptin is quite effective when patients are screened for the presence of HER2/neu. Progress in this area continues. In March 2013, the FDA approved two new assays from the Danish company Dako as companion diagnostics to Genentech’s new medicine for HER-2-positive metastatic breast cancer patients, Kadcyla™ (ado-trastuzumab emtansine).⁸⁰

The use of validated biomarkers to generate companion diagnostics has progressed rapidly in recent years, as has the entire PM sector. According to the Personalized Medicine Coalition, in 2006 there were 13 prominent examples of PM drugs, treatments, and diagnostic products available. By 2011, that number had ballooned to 72.⁸¹ As of March 2013, the FDA listed fully 117 instances of pharmacogenomic (PGx) biomarkers in drug labels, a list that will undoubtedly continue to grow as research evolves.⁸² PGx continues its advance into the mainstream of clinical medicine.

The antiretroviral drug Abacavir, is an important example of the power of PGx to definitively guide patient therapy. Approximately 5-8% of HIV-infected patients treated with abacavir experience a severe, life-threatening reaction known as abacavir hypersensitivity.⁸³ When the phenomenon was recognized, researchers discovered that there was a strong association between abacavir hypersensitivity and the major histocompatibility complex class I allele HLA-B*5701. Today, the genetic test for that allele, which took six years to develop and validate, is now a routine companion diagnostic procedure, and has certainly saved many lives.⁸⁴

“ Recently, the development of therapeutic products that depend on the use of a diagnostic test to meet their labeled safety and effectiveness claims has become more common... These technologies are making it increasingly possible to individualize, or personalize, medical therapy by identifying patients who are most likely to respond, or who are at lower or higher risk for a particular side effect. ”

—Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices, August 6, 2014.

Although they are not companion diagnostics, the approval by the FDA of 4 “next generation sequencing” devices deserves mention. In November 2013, the FDA approved 2 devices to aid in the detection of changes on the CFTR gene associated to the development of cystic fibrosis. The other set of devices allows for the sequencing of any of a person’s genes and then compares it to a reference genome and reports back any differences between the two.⁸⁵ This development is a glimpse into the future of personalized medicine and development of tools that will make genetic testing for disease and treatment utility a commonplace clinical occurrence.

Direct-to-consumer (DTC) testing

The DTC genetics testing industry has grown rapidly, with more than 60 companies now offering various types of tests directly to the public.⁸⁶ In 2011, the FDA Molecular and Clinical Genetics Panel meeting recommended that at least some categories of DTC genetic tests should be offered solely upon prescription, necessitating the involvement of a medical professional in the process. Following the panel’s deliberations, Alberto Gutiérrez, Ph.D, director of the FDA’s Office of In Vitro Diagnostics, noted that the outcome will likely depend on the type of test involved: “We’re not going to be able to take one approach to all types of tests. Some may not require a doctor at all and some might require that a qualified health professional be involved, and some might involve the doctor to order the test.”⁸⁷

To support the advancement of improved health outcomes for all, the FDA is playing a leading role in convening stakeholders on how to improve the process.⁸⁸ Streamlining the regulatory process is critical and requires stakeholder leadership to reach a common ground that will facilitate innovation in the field of personalized medicine and make available these innovations to improve health and well being while maintaining standards for safe and effective use.

Prenatal genetic testing

This category of diagnostic methodologies is poised to have a major impact in the clinic, as it is an enormously improved approach to detecting fetal abnormalities. Amniocentesis, the invasive insertion of a needle into the womb to collect amniotic fluid for analysis, is the current gold standard. As new tests advance, including those of fetal DNA collected from a mother’s blood, amniocentesis is expected to eventually serve only to confirm problems detected by fetal DNA screening procedures. The new, substantially safer prenatal genetic tests have been shown to accurately detect the presence of Down syndrome in fetal DNA, as well genetic blood disorders such as beta-thalassemia and hemophilia.⁸⁹ Another advantage of the new blood tests is that they can be performed earlier in a pregnancy—as early as nine weeks.

Researchers anticipate that as genomic technologies become cheaper and more accessible, more noninvasive tests will be developed to detect other inherited conditions such as cystic fibrosis and sickle cell disease.⁹⁰ However, it should be noted in this context that as those capabilities progress, perhaps to the point in the foreseeable future that fetal

genomes could be routinely sequenced, many thorny ethical, legal, and practical issues will inevitably arise.

Bioethical debates on prenatal diagnosis have continued for many years since the advent of amniocentesis itself (first performed in the U.S. in the early 1970s). A 1999 study of attitudes toward amniocentesis among women of Mexican origin and their partners enrolled in California's state-administered program for prenatal diagnosis sheds light on the potential contemporary implications of the newer fetal DNA blood tests among Hispanics. Between 1995 and 1997, 66.1% of Hispanic women and 70.5% of African American women accepted amniocentesis after testing positive for potential fetal defects after a maternal serum α -fetoprotein (AFP) screening, the non-invasive screening method in use at the time, compared to 75.8% of White women.⁹¹ Interestingly, the authors concluded that health care providers tend to have largely erroneous assumptions about Hispanic women's willingness to undergo amniocentesis, centering on assumptions about ethnic norms. The authors report "our findings suggest that the most important factors include the women's understanding of the risks of amniocentesis, their fear of birth defects, their faith in medicine, and their relationships with their doctors."⁹²

With the advance of science, it is incumbent on the health system to ensure access and that advances in personalized medicine and genetic testing do not exacerbate existing inequities in providing care to diverse racial and ethnic communities. Kiros *et al* concluded that, "new genetic technologies are likely to increase...disparities as access to expensive genetic tests further widens the gap."⁹³ The authors identified several barriers to genetic testing, including knowledge about genetic testing, type of health insurance coverage, concerns about the potential misuse of genetic testing, and lack of trust in a medical doctor to keep medical information private.⁹⁴ They note that, "previous studies have found that African Americans⁹⁵ and Hispanics⁹⁶ are less likely to know about the availability of genetic testing for risk of the disease."^{97,98}

Efforts to Introduce Health Providers to Personalized Medicine

Key to moving the promise of personalized medicine from the laboratory to the patient are health care providers armed with the latest science and commitment to working with patients to personalize care. Personalized medicine and genomics is a new field even for recently graduated health providers. Even the greatest advances in personalized medicine will not be as significant if they do not reach clinical providers which, in turn, will use them to improve treatments for their patients. That is why a number of health centers and universities are striving to help their providers see the relevance of personal medicine in their practices. For example, El Camino Hospital in California organized a 10-month long series of lectures on the topic offering Continuing Medical Education (CME) credits. The Mayo Clinic and Vanderbilt University Medical Center have integrated alert systems into their electronic medical records that let physicians know if they are prescribing a medicine with genetic interactions. The University of Utah offers a graduate certificate in personalized health care and Ohio State University has a summer program for first and second year medical students on personalized medicine.⁹⁹

All of these efforts make it easier for the clinician to apply personalized medicine to their practices by including the interventions as part of what they already do; either by including them in electronic records or offering continuing education credits which all providers have to take to maintain licensure. Despite these examples of progress, Roxanne Young, in her 2013 Viewpoints piece in JAMA,¹⁰⁰ finds that health professionals are not yet prepared for “the 21st Century Patient” and that a “lack of training has implications for patients and physicians dealing with genetic data.”

Family Health Histories

Although the era of PM may not quite be with us yet, it could be argued that medicine has always largely been about tailoring available treatments to individual needs, and that that will continue to be true even as PM becomes more a part of the clinical setting. Regardless of where the technology takes us, medical care, particularly primary care, relies upon strong relationships, communication, trust, intuition, and intimate knowledge to work most effectively. Thus, patients should ensure that their physicians have complete and accurate records regarding their family history. Duconge and Ruaño in their 2010 article on *The Emerging Role of Admixture in the Pharmacogenetics of Puerto Rican Hispanics*,¹⁰¹ find that this particularly holds for Hispanic individuals, who are the products of generations of admixing and that Hispanics “stand to gain the most from the revolution in personalized medicine, given longstanding disparities in healthcare.”¹⁰²

A section of the statement that emerged from the 2009 NIH state-of-the-science conference, Family History and Improving Health, made the connection explicit: “Many common diseases have genetic, environmental, and lifestyle antecedents that family members share... A person’s family history has the potential to capture information about shared factors that contribute to that person’s risk for common diseases [and] *makes the systematic collection of family history a potentially important step in personalizing health care* [emphasis added].”¹⁰³

To encourage families and health professionals to gather and utilize family health histories, every Thanksgiving Day is now observed as National Family History Day under the Surgeon General’s Family Health History Initiative. The family history has been shown to help predict the risk of such varied health concerns as heart disease, colorectal cancer, breast cancer, ovarian cancer, osteoporosis, asthma, type 2 diabetes, and suicide, among many others. Yet many patients are unaware of the medical histories of their

Family History

Go online create a family health portrait
to share with your family and
your health provider.

<https://familyhistory.hhs.gov/>

relatives, and many health professionals underuse this information in advising patients about how to maintain good health.”¹⁰⁴

This is one area where individuals can have a positive and practical impact on their own treatment by arming providers with vital information to help them assess disease risk appropriately (it may also work to counteract potential biomedical racial and ethnic stereotyping, which is known to exist).¹⁰⁵ Families can easily create their own family health history records to present to their doctors by using the online tool provided as part of the Surgeon General’s Family Health History Initiative.

To support taking family health histories, in 2013 the Genetic Alliance launched Genes In Life. This resource helps families learn about genetic testing and the role of family history and lifestyle in health. Also in 2013, the Personalized Medicine Coalition conducted a study to learn about the public’s opinion on personalized medicine. The study consisted of 6 focus groups with a total of 52 participants considered “opinion leading consumers”.¹⁰⁶ This work found that consumers had low awareness about PM. However, after being given examples of PM and its applications, consumers were interested in PM’s potential to help in earlier prevention, reducing trial and error, and its ability to bring to the table less invasive procedures and treatments with reduced side effects. One big issue brought up by consumers is lack of access to PM either because of cost or because of limits by insurers on what they will cover.

These findings are a first step in the critical process of making sure consumers are a part of efforts to bring personalized medicine to the clinical setting and should be the first of ongoing efforts. As a new field, personalized medicine offers an opportunity to design consumer engagement in a way that will bridge rather than continue inequities in other areas of medicine. It is not hard to imagine the coming years being one where genetics and an individual’s unique genetic and environmental profile is the starting point for prevention, diagnosis, management, and treatment. That future, however, will only be fully realized if all are included in genetic research and findings cover diverse population groups, the science is adequately translated into clinical findings that reach all clinical settings, and consumers empowered with the information and the access to support the best health outcomes for all.



Recommendations for Action

There is a clear case based on science and achieving the best health outcomes for all for improving the diversity of the genetic database and understanding the clinical applications of the evolving science. Some key recommendations to meet this challenge, include:

I. Improve the Science. Fully implement federal research guidelines for inclusion of underrepresented groups in all study and grant applications, including pilot studies, and encourage non-federal entities to do the same.

Efforts to diversify genetic studies and define genetic variations, such as the 1,000 Genomes Project, hold the promise of expanding our understanding of the role of genetics in health. However, those efforts require that research meet federal standards for inclusion and reporting by gender, race, and ethnicity including Office of Management and Budget Directive 15 on Race and Ethnic Standards for Federal Statistics, the NIH Policy on the Inclusion of Women and Minorities in Clinical Research, and the FDA Guidance on Collection of Race and Ethnicity Data in Clinical Trials. While these policies have been long-standing, with the OMB standard issued in 1977, the NIH Policy since 1985 (women) and 1987 (racial and ethnic minorities), and the FDA since 1993 (women)

and 1997 (racial and ethnic minorities), the standards are not being met. A recent analysis by the FDA of research supporting drug, biologics, and device approval applications, in response to requirements under the Food and Drug Administration Safety and Innovation Act, points to the exclusion of women and racial and ethnic groups in medical product applications submitted to the FDA. The analyses also point the way to steps that can be taken to improve the situation. These include:

- Emphasize efforts to inform researchers of requirements for collection and reporting of data including by gender, race, and ethnicity.
- Ensure all research applications to the NIH and drug and device approval applications to the FDA meet standards of inclusion and meaningful analysis (including by gender, race and ethnicity).
- Conduct a review and report by the NIH of currently funded research and analysis plans and by the FDA of post-marketing surveillance measured against inclusion policies and where appropriate establish study enrichment strategies.

II. Enhance Quality of Care. Initiate a translational effort, based on new knowledge from genetic studies, that will deliver enhanced guidance to providers on applicability to specific populations of current clinical recommendations and prioritize new studies to fill in knowledge gaps.

While product labeling and peer-reviewed clinical study reviews play a critical role in communicating to providers, there is a need to inform providers of variations in population groups brought to light by new analyses and findings from genetic science. To enhance current approaches and establish new avenues for moving science from the bench to the bedside, a series of new collaborations would be helpful, including:

- Enhance partnerships between the NIH National Center for Advancing Translational Sciences (NCATS) and the FDA Office of Translational Sciences (OTS) to ensure a pathway to review and inform providers of the FDA post-approval findings, findings from enrichment efforts, and new genetic research with implications for differential clinical outcomes for specific population groups.
- Conduct a review of current drug, biologic, and device approvals in collaboration with AHRQ and key national provider associations to identify available research that may identify population, age, or gender based differences in clinical outcomes and assemble a report to the field to inform providers and enhance quality.
- Establish a continuing education credits program in partnership with provider groups to encourage learning about genetic variation and clinical outcomes in different population groups.

III. Support Consumer Health Decision-Making. Launch an ongoing consumer support effort on using genetic information to inform health decision-making and ensure access to testing, counseling, and companion diagnostics.

While the past two decades saw a breathtaking advancement in genetic science, this decade is undoubtedly about translating advancements in science for use by the consumer. The effort requires supporting consumers in not only using genetic information to make the best decisions for their individual health, but also ensuring consumer access to the genetic clinical tools that are opening new options in personalized and quality health care. Overlaying the challenge is putting into place the policies including reimbursement policies that will make these clinical tools widely available. Steps in ensuring consumer information and access, include:

- Expand reach to underserved communities by key consumer groups to promote taking family health histories and encourage consumers to share them with their providers to inform their health decision-making.
- Establish an effort led by the FDA OTS, in collaboration with the NIH NCATS, to conduct a review of adequacy of gene-drug interactions labeling and establish a corollary effort to inform consumers of new genetic findings with clinical implications.
- Development of a collaborative monitoring effort by key consumer groups to ensure adequate coverage of drug choices based on current and emerging science on gene-drug interactions and access under health plans to genetic testing, counseling, and companion diagnostics.

The health community has a unique opportunity to increase health equity and ensure the promise of personalized medicine. Genetic research holds the promise of catalyzing the new era of personalized medicine and improved quality of health care for all. This promise will only be realized, however, when all population groups are adequately included in research and all consumers are provided the tools to use new genetic information to make the best health decisions for their well-being. It is an undertaking that holds the promise to transform health for this and future generations.



Supplement: Highlights of Hispanic Health

This supplement provides some information on selected topics related to the health of Hispanics that will benefit from recent research on genes and pharmacogenetics. The areas are listed in alphabetical order and include: Asthma, Cancer, Dementia and Alzheimer's Disease, Depression, Diabetes, Environmental Factors, Heart Disease, and Hepatitis C.

Asthma

Asthma is a complex, common disease that is strongly suspected of having a genetic component, but no single susceptibility or prevalence gene. "The striking racial and ethnic disparities in disease prevalence for common disorders, such as allergic asthma, cannot be explained entirely by environmental, social, cultural or economic factors, and genetic factors should not be ignored," wrote Kathleen Barnes in her 2005 article on genetic epidemiology of health disparities in allergy and clinical immunology.¹⁰⁷ Asthma affects 14 million people in the U.S.,¹⁰⁸ and increased in prevalence by 73.9% from 1980-1996.¹⁰⁹ Certain ethnic groups, including Puerto Ricans, are disproportionately represented in this trend of increasing asthma morbidity.^{110,111, 112}

U.S. Current Asthma Prevalence, 2011 and 2012

Adult (18+ years of age)

| | |
|-------------------------------|-------|
| Non-Hispanic White | 8.1% |
| Hispanic | 6.1% |
| Mexican American | 4.0% |
| Puerto Rican | 20.2% |
| Non-Hispanic Black | 10.4% |
| Asian American | 5.1% |
| American Indian/Alaska Native | 19.8% |

Children (Under 18 years of age)

| | |
|-------------------------------|-------|
| Non-Hispanic White | 7.9% |
| Hispanic | 8.8% |
| Mexican American | 7.6% |
| Puerto Rican | 15.6% |
| Non-Hispanic Black | 16.0% |
| Asian American | 7.1% |
| American Indian/Alaska Native | 14.8% |

Source: CDC. National Health Interview Survey (NHIS) Data. March 2014. Note: Data for A/A and AI/PI is from the 2011 NHIS and Summary Statistics for Children, 2013.

For example, Puerto Ricans have higher than expected asthma prevalence, morbidity, mortality and the poorest therapeutic response among several ethnic groups studied.^{113,114} Asthma prevalence is similarly “exceptionally high” among all Puerto Ricans regardless of where they reside, compared with other groups, including other Hispanics.¹¹⁵ Unfortunately, few studies of the genetics of asthma have included members of ethnic minority groups, a situation Scirica and Celedón, in their 2007 *Chest* article on the genetics of asthma describe as “unacceptable.”¹¹⁶

Researchers have noted that Puerto Ricans are more than twice as likely as Mexican Americans to have asthma and postulated that, “interethnic differences in disease severity might result from health care disparities but also might relate to genetic variations inherited from a specific ancestry that is associated with disease severity or therapeutic response to different therapies.”¹¹⁷

The interaction between unique genetic and environmental factors may explain marked differences in disease prevalence among subgroups of an ethnic group.¹¹⁸ For example, Puerto Rican children with abnormal variants of alpha1-antitrypsin, a protein involved in inflammatory reactions, are at increased risk for asthma.¹¹⁹ Furthermore, analysis of data from the Third National Health and Nutrition Examination Survey (NHANES)¹²⁰ revealed that Mexican Americans born in the U.S. had approximately twice the odds of having asthma as those born in Mexico.

Genetic variations may also contribute to observed differences among asthma patients in the effectiveness of albuterol, a beta-agonist drug widely prescribed to control asthma symptoms. Groups of genetic variations are called haplotypes, and different haplotypes are associated with patients’ varying response to this drug.¹²¹ Haplotype 2 is associated with high responsiveness to albuterol, and its frequency varies by ethnicity. It is the most frequent haplotype in Caucasians (48%) but occurs in only 27% of Hispanics, 10% of Asians, and 6% of African Americans.¹²² Thus, fewer Hispanics may respond well to albuterol. Further, polymorphisms in the gene for the β_2 -adrenergic receptor (ADRB2) may explain reduced bronchodilator responsiveness among Puerto Ricans.¹²³

Cancer

O’Brien and colleagues noted that, “Hispanics have lower incidence and mortality rates from all cancers combined and from the four most common cancers (breast, prostate, lung and bronchus, and colon and rectum) than non-Hispanic whites. However, Hispanics have higher incidence and mortality rates from cancers of the stomach, liver, uterine cervix, and gallbladder, reflecting in part greater exposure to specific infectious agents and lower rates of screening for cervical cancer, as well as dietary patterns and possible genetic factors.”¹²⁴ Vadaparampil and colleagues report that the difference in

U.S. Cancer Incidence Rates, 2006–2010 (per 100,000 persons)

| Incidence | Non-Hispanic White | African American | Asian American or Pacific Islander | American Indian or Alaska Native | Hispanic/Latino |
|--------------------------------|--------------------|------------------|------------------------------------|----------------------------------|-----------------|
| All Sites | | | | | |
| Male | 548.6 | 601.0 | 326.1 | 441.1 | 426.8 |
| Female | 436.2 | 395.9 | 282.6 | 372.0 | 330.8 |
| Breast (female) | 127.3 | 118.4 | 84.7 | 90.3 | 91.1 |
| Colon & rectum | | | | | |
| Male | 50.9 | 62.5 | 40.8 | 51.7 | 47.3 |
| Female | 38.6 | 46.7 | 31.0 | 42.7 | 32.6 |
| Kidney & pelvis | | | | | |
| Male | 21.6 | 23.0 | 10.6 | 30.6 | 20.5 |
| Female | 11.2 | 12.2 | 5.1 | 17.5 | 11.5 |
| Liver & intrahepatic bile duct | | | | | |
| Male | 8.7 | 14.9 | 21.3 | 17.8 | 18.8 |
| Female | 2.9 | 4.4 | 8.0 | 8.0 | 6.9 |
| Lung & bronchus | | | | | |
| Male | 82.9 | 94.7 | 48.8 | 70.2 | 45.9 |
| Female | 59.9 | 50.4 | 28.0 | 52.1 | 26.6 |
| Prostate | 138.6 | 220.0 | 75.0 | 104.1 | 124.2 |
| Stomach | | | | | |
| Male | 7.8 | 15.7 | 15.6 | 13.1 | 13.9 |
| Female | 3.5 | 8.1 | 9.0 | 6.9 | 8.2 |
| Uterine cervix | 7.2 | 10.3 | 6.7 | 9.7 | 10.9 |

Source: North American Association of Cancer Registries, 2013.

Note: Race and ethnic categories are not mutually exclusive; Hispanic/Latino origin may be of any race. Rates are age adjusted to 2000 U.S. population (≠AI/AN data based on Indian Health Service Delivery Areas).

early cancer diagnosis may be associated with less knowledge of, access to and utilization of preventive services such as cancer screening tests among Hispanics. Limited English proficiency was another factor suggested by the group's research. Patients who may have difficulty communicating with health care providers may be less aware of or have access to preventive health services or genetic testing and counseling.¹²⁵

In 2010, Patel and colleagues found that differences in breast cancer mortality rates also stemmed in part from differences in the genetics and biology of breast cancer in Latinas (e.g., a higher incidence of aggressive triple-negative breast cancers). "Genetics may significantly influence the disparities observed in breast cancer outcome in the Hispanic population," they note. Hispanics with breast cancer have a higher incidence of BRCA1 mutations than non-Hispanics.¹²⁶ Also, a 2013 study by Weitzel *et al* found a high degree of prevalence of BRCA mutations among Hispanics in the southwestern U.S. (25% of 746 familial clinic breast cancer patients), including the first documented Mexican founder mutation (BRCA1 ex9-12del).¹²⁷ This finding led the study authors to postulate that the mutation along with other recurrent mutations suggests the potential for a cost-effective approach to genetic cancer risk assessment that is ancestry-informed.

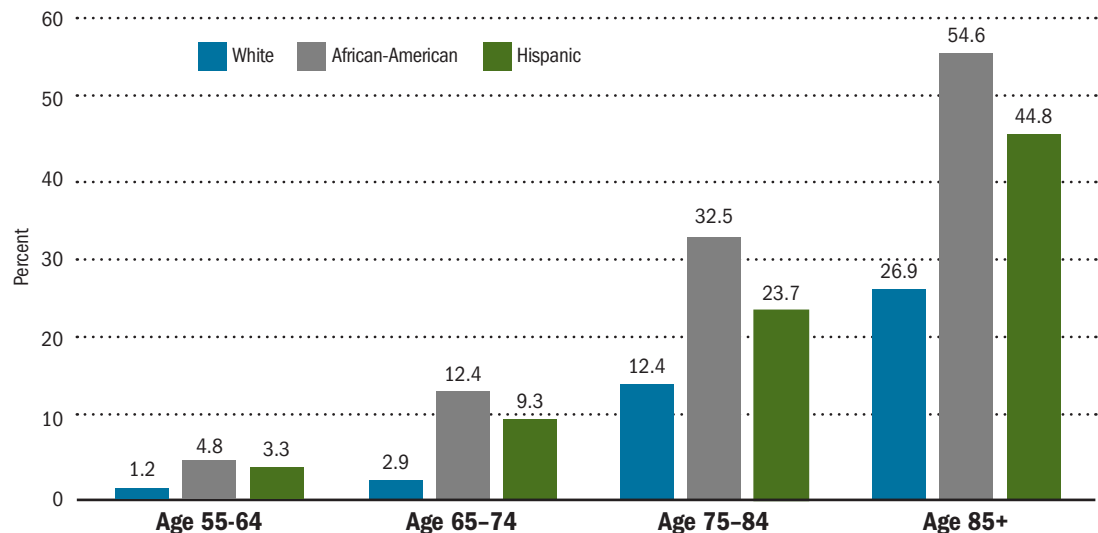
Dementias and Alzheimer's Disease

Genetic and environmental differences undoubtedly contribute to major differences between Hispanics and non-Hispanic whites in prevalence and presentation of neurodegenerative disorders. As Chin and colleagues noted in 2011, the prevalence of Alzheimer's disease and other dementias in Hispanics is approximately 1.5 times greater than in whites. Epidemiologic data suggest that certain risk factors for the development of Alzheimer's disease may be more prevalent in African Americans and Hispanics than in non-Hispanic whites,¹²⁸ including hypertension, diabetes, coronary artery disease and stroke.^{129,130,131,132}

Differences in clinical presentation of Alzheimer's disease among those groups remain poorly understood. "Recent evidence from the Penn Memory Center in Philadelphia suggests that Hispanics present with an earlier age of onset and that both African Americans and Hispanics exhibit a greater severity of symptoms at the time of onset. Hispanics presented with more cognitive impairment and greater severity of dementia, while both African Americans and Hispanics presented with more depression at the time of initial evaluation than non-Hispanic white patients."¹³³ Despite these severe clinical symptoms, evidence also suggests that Hispanics live longer with the disease than other racial/ethnic groups.^{134,135} Mehta *et al* in their 2008 report conclude that "neuropathology findings did not explain survival differences by race".¹³⁶

Alzheimer's disease is believed to have a genetic basis, with multiple genes likely to be involved.^{137,138} A variant of the apolipoprotein E (ApoE) gene has been identified as a genetic risk factor for late-onset Alzheimer's disease across most populations.^{139,140,141,142,143} Common variants of the ApoE protein, which are coded by variants of the ApoE gene, alter cholesterol profiles and correlate with diseases linked to cholesterol metabolism, particularly cardiovascular disease and Alzheimer's.¹⁴⁴ An association has been found

U.S. Incidence of Cognitive Impairment, 2006



Source: Health and Retirement Study, 2006; Special data run for the Alzheimer's Association by K. Langa, M. Kabaeto, and D. Weir, Jan, 8, 2010.

between Alzheimer’s disease and a common variant of the ApoE gene, called ApoE4.¹⁴⁵ However, the strength of the association varies across ethnic groups.¹⁴⁶ One study found a fivefold increase in the risk of Alzheimer’s among Hispanics having two copies of the ApoE4 gene variant.¹⁴⁷ However, an expert panel convened by the Alzheimer’s Association found the limited research available ambiguous about the relationship between inheritance of the ApoE4 gene variant and Alzheimer’s in Hispanic populations and called for more research to better understand the role of genetic mutations.¹⁴⁸

Depression

Although depression is a serious problem among Hispanics, they do not always receive the most advanced medications, including selective serotonin reuptake inhibitors (SSRIs), which have largely replaced tricyclic antidepressants.

Improving pharmaceutical care of Hispanics with mental illness may require custom dosing. Hispanics have been reported to be more sensitive to drugs used in treating mental illness and may require lower doses of these agents. Failure to give the proper dose may result in intolerable side effects and as a result, discontinuation of the medication. Both biological and cultural differences appear to underlie Hispanics’ heightened response o these medications.¹⁴⁹

Hispanic women were found to discontinue SSRI antidepressants at a higher rate than their non-Hispanic counterparts,¹⁵⁰ due perhaps to a perception that the side effects were intolerable. In another study, Hispanic women received less than half the daily dose of tricyclic antidepressants but reported more side effects than non-Hispanic white women.¹⁵¹ Pharmacokinetic factors, as well as the common interpretation of many Hispanic patients that the physical side effects produced by antidepressants are signs that their condition is worsening, may have led them to discontinue medication or comply with lower doses only.¹⁵²

Hispanics have been found to respond to lower doses and have lower effective concentrations of antidepressants than whites. However, increased sensitivity may in part be due to cultural differences in expectations about the effects of medication rather than pharmacokinetic differences. Current research is targeting the genetic underpinnings of the response of Mexican Americans to tricyclic and SSRI antidepressants.¹⁵³ Hispanics also tend to respond to lower doses of some antipsychotic medications.^{154, 155, 156, 157, 158} In one study, the average therapeutic dose of antipsychotic medication for Hispanics was half the dose of Caucasians and African Americans.¹⁵⁹

Diabetes

On average, Hispanics are almost twice as likely as non-Hispanic whites to have diabetes.¹⁶⁰ Risk factors for diabetes seem to be more common among Hispanics than non-Hispanic whites. These include obesity, physical inactivity, insulin resistance, higher

U.S. Percent of Population Reporting Symptom of Depression (Feeling Sad All or Most of the Time), 2012

| Adult (18+ years of age) | |
|-------------------------------|------|
| Non-Hispanic White | 2.3% |
| Hispanic | 3.6% |
| Non-Hispanic Black | 3.2% |
| Asian American | 1.5% |
| American Indian/Alaska Native | 4.0% |

Source: CDC. Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2012; Table 14; Feb. 2014. Note: Data age-adjusted.

U.S. Incidence of Diabetes, 2012

| Adult (18+ years of age) | |
|-------------------------------|-------|
| Non-Hispanic White | 7.3% |
| Hispanic | 12.2% |
| Non-Hispanic Black | 13.2% |
| Asian American | 8.9% |
| American Indian/Alaska Native | 17.9% |

Source: CDC. Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2012; Table 8; Feb. 2014. Note: Date age-adjusted.

than normal levels of fasting insulin, impaired glucose tolerance, and a family history of diabetes.¹⁶¹

Although environmental factors (e.g., diet and exercise) have a large impact on the manifestation of type 2 diabetes, genetic factors may also underlie the disturbances in insulin secretion and insulin resistance that characterize this disease.¹⁶² Several different regions of the human genome have been associated with susceptibility to type 2 diabetes and these may differ across populations. Mexican Americans appear to carry susceptibility genes for diabetes on certain chromosomes (chromosomes 2, 3, 4, 9, 10 and 15), while Pima Indians have genetic links to diabetes on other chromosomes (chromosomes 1 and 11).¹⁶³ This suggests that the genes and molecular mechanisms regulating insulin secretion and action may differ across populations¹⁶⁴ and raises the possibility of finding population specific molecular targets (enzymes, receptors, substrats) for new drug development.

A study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) found that both Hispanic and African American children were at higher risk than white children for insulin resistance, a stepping-stone to type 2 diabetes.¹⁶⁵ Hispanic children responded to resistance by producing more insulin, resulting in higher circulating insulin levels. Secreting too much insulin over time can eventually exhaust the pancreatic beta cells and lead to type 2 diabetes. By contrast, the elevated insulin levels in non-Hispanic black children were due to a reduced capacity of their livers to remove insulin from circulation.^{166,167} According to the study's lead researcher, Michael Goran of the University of Southern California, "This implies a potentially different disease mechanism [between these two groups] and ... has potential implications for treatment. The bottom line is that there is no 'one-size-fits-all' approach to prevention and treatment for everyone."¹⁶⁸

Heart Disease

Despite greater cardiovascular disease risk factors (e.g., diabetes, obesity, high cholesterol levels), Hispanics have a lower incidence rate for heart disease. Protective genetic or lifestyle factors may help explain why Hispanics have greater risk factors for heart disease, but have a lower incidence rate and mortality from heart disease.¹⁸⁴ Research is needed to clarify the role of risk factors in hear disease among Hispanic populations.

A major step forward is the National Heart, Lung, and Blood Institute (NHLBI) led SOL Study that has enrolled more than 16,000 Hispanics across four study centers across the country, the largest study ever fielded of Hispanic health.¹⁸⁵ In announcing the launch of the study in 2006, the NHLBI Director noted that the purpose of the study in part was to understand, "Why are Hispanics experiencing increased rates of obesity and diabetes and yet have fewer deaths from heart disease than non-Hispanics?"¹⁸⁶

Available data from other studies indicate that one factor could be that Hispanics may have a different lipid profile than other populations and, therefore, have different needs

regarding lipid-lowering therapy. Mexican Americans have higher blood concentrations of triglycerides and lower concentrations of “good” HDL cholesterol than non-Hispanic whites.^{187,188} Although genetic and environmental factors both play a role, one study found that genes account for 30% to 45% of differences in blood levels of lipids and lipoproteins between Mexican Americans and non-Hispanic whites.¹⁸⁹

Hepatitis C

The hepatitis C virus infection (HCV) is another chronic condition that exhibits racial/ethnic variability in both clinical presentation and response to therapy. HCV infection is the most common chronic blood-borne infection in the U.S., affecting approximately 3.2 million persons. Left untreated, chronic HCV can lead to liver cancer or liver cirrhosis requiring liver transplantation. The disease is the leading cause for liver transplantation in the U.S.¹⁹⁰ Mortality due to HCV infection appears to be increasing; in 2007, the CDC identified more than 15,000 deaths in the U.S., for the first time surpassing HIV mortality.¹⁹¹

A 2009 study by Wang *et al* showed that there are significant ethnic and geographical differences in the associations of human leukocyte antigen (HLA) genes with the outcome of HCV infection. Some HLA alleles conferred higher risk while others were protective, with certain associations found to be significant only in certain subpopulations of Caucasians. In some cases, certain HLA alleles conferred opposite associations in the Caucasian and non-Caucasian populations.¹⁹²

Also in 2009, Ge *et al* reported that a genetic polymorphism near the IL28B gene, encoding interferon- λ -3 (IFN- λ -3), is associated with an approximately twofold change in response to treatment, both among patients of European ancestry ($P = 1.06 \times 10^{-25}$) and African-Americans ($P = 2.06 \times 10^{-3}$). Because the genotype leading to better response is in substantially greater frequency in European than African populations, this genetic polymorphism also explains approximately half of the difference in response rates between African-Americans and patients of European ancestry.

In patients with HCV genotypes 2 or 3, the Sustained Virologic Response (SVR) rates reach 80%. SVR means that during the six months after you complete treatment, there is no detectable hepatitis C virus in your blood. In genotype 1 (the most common type) patients the SVR rate is substantially lower at 50%. Ultimately, the authors concluded, “In addition to viral and environmental behavioral factors, host genetic diversity is believed to play a role in each step of the different clinical outcomes in HCV infection (clearance of acute infection, progression of fibrosis, and treatment outcome).”¹⁹³

A 2009 article by the Latino Study Group investigated HCV treatment response in Hispanics and non-Hispanic whites. The study showed that with standard HCV therapy, rates of SVR among patients infected with HCV genotype 1 were lower among Hispanics than among non-Hispanic whites (34% vs. 49%), suggesting a need for strategies to improve SVR in Hispanics¹⁹⁴ particularly since Hispanics have a higher prevalence of

U.S. Incidence of Heart Disease, 2012

Adult (18+ years of age)

| | |
|-------------------------------|-------|
| Non-Hispanic White | 11.4% |
| Hispanic | 7.8% |
| Non-Hispanic Black | 11.0% |
| Asian American | 6.8% |
| American Indian/Alaska Native | 12.5% |

Source: CDC. Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2012; Table 2; Feb. 2014. Note: Data age adjusted. Heart disease includes coronary heart disease, hypertension, and stroke.

HCV¹⁹⁵ and more rapid fibrosis progression¹⁹⁶ than do non-Hispanic whites. They also noted, however, the limitation of findings due to the fact that Hispanics and other ethnic subpopulations are underrepresented in clinical trials.

Environmental Factors

Gene-environment interaction means that some people carry genetic factors that may make a person susceptible or resistant to a certain disease or disorder and these genetic factors can be switched on or off by a particular environment.¹⁶⁹ For example, the CYP3A4 gene mediates the metabolism of over 50% of commonly used drugs.¹⁷⁰ CYP3A4 enzyme activity is highly sensitive to environmental factors and varies substantially across ethnic groups with distinct diets. Foods such as corn, grapefruit juice, and charbroiled beef featured in the Hispanic diet, have been shown to alter the efficiency of the CYP3A4 gene.¹⁷¹ Certain aspects of the Hispanic diet, including lower intake of cruciferous vegetables (e.g., cabbage, broccoli, brussels sprouts), lower protein consumption, and higher intake of carbohydrates, may also alter the metabolic efficiency of certain drugs in connection with a range of genetic variations.¹⁷²

Other environmental influences on genetic-environment interaction having an impact on disease expression or drug efficiency may include lower levels of smoking and alcohol use, and higher medicinal herb use, all of which have been reported in Hispanic populations.^{173,174} A balanced understanding of the role of genetics in health cannot be reached without including diet and life-style environmental factors in understanding disease risk and clinical applications for prevention, treatment, and management of disease including cardiovascular disease, cancer, and other major causes of mortality.¹⁷⁵

Furthermore, a growing body of evidence is linking environmental contaminants to switching on and off genetic susceptibility to disease expression. A review of literature found that environmental contaminants shown to affect gene expression include air pollutants, arsenic, bisphenol A, dioxins, polychlorinated biphenyls (PCBs), phthalates, some heavy metals, and trichloroethylene.¹⁷⁶ At the same time, a majority (71.2%) of Hispanics live in counties with high ozone concentrations,¹⁷⁷ 40% of Hispanics live within 30 miles of a power plant which releases nitrogen oxides and sulfur dioxide forming particulate pollution,¹⁷⁸ and Hispanics are three times (18.5%) more likely than non-Hispanic whites (6.0%) to live in areas that have high levels of airborne lead pollution.¹⁷⁹ In addition, urban Hispanic communities are at risk from lead exposure in older buildings,¹⁸⁰ both industrial and biological contamination is a persistent problem along the U.S. Mexico border in colonias (unincorporated areas),¹⁸¹ and over 1.5 million Hispanics actively participate in fishing but rates of awareness about toxic chemical risks that may be in the water they fish or in the fish they eat is low.¹⁸² Furthermore, many Hispanics are employed in occupations in which the risk of exposure to a variety of chemicals, gases, and other toxic substances is present.¹⁸³ The impact of environmental contaminants in genetics and health is a growing area of research and one of particular concern to Hispanic communities given exposures to environmental pollutants in the air we breathe, food we eat, and water we drink.

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Notes



Who We Are and What We Do

We are a leading non-partisan health organization for research, service, and advocacy throughout the Americas. We impact the entire spectrum from the individual to policy makers. We identify important health issues that are at the cutting edge and address urgent unmet needs.

Our Mission: Best health outcomes for all. We work to insure that health incorporates the best of science, culture, and community. We achieve this by listening to the individual, investing in leading community based organizations, working with national partners, examining and improving the resources and systems available, and designing solutions to make health a part of each person's life. We continually work to improve the quality of care and its availability to all.

Our Goal: To close the gaps in three key areas:

1. research, services, and policy;
2. scientific discovery and benefit for the individual; and,
3. community services and medical practice.

Our Work: We believe that quality health means shared decision-making that focuses on the needs of the individual throughout their lives. This means that health includes the long-term services and care needs of individuals. Moreover, our efforts reflect that mental health and physical health are central to well-being. We particularly focus on:

- Decision-making that takes into account science, culture, and community.
- Health care providers being able to tailor care to the individual.
- Individuals having the tools and resources to manage their health.
- National efforts that are connected to global and international efforts.
- Capacities and competencies to respond to health emergencies.
- Services that integrate physical and mental health.

We collaborate with our members, a broad range of partners, and many others to do our work.

National Alliance for Hispanic Health
Board of Directors
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