Genes, Culture, and Medicines: Bridging Gaps in Treatment for Hispanic Americans

By
Carolina Reyes, MD
Leticia Van de Putte, RPh
Adolph P. Falcón, MPP
Richard A. Levy, PhD
ABOUT THE AUTHORS

Carolina Reyes, MD, currently serves as a faculty attending in obstetrics and gynecology at Cedars-Sinai Medical Center and as Assistant Clinical Professor at the UCLA School of Medicine. Dr. Reyes has dedicated her professional and personal activities to addressing disparities in health care. She served on the Institute of Medicine study committee “Understanding and Eliminating Racial and Ethnic Disparities in Health Care” that produced the landmark report Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. She was previously appointed as a Senior Scholar with the U.S. Agency for Healthcare Research and Quality (AHRQ), and co-edited the book Domestic Violence and Health Care: Policies and Prevention (Haworth Press, 2002). Dr. Reyes received her bachelor's degree in Human Biology from Stanford University and her medical degree from Harvard Medical School. She completed her residency in obstetrics and gynecology and a fellowship in maternal-fetal medicine at the Los Angeles County/USC Women's and Children's Hospital.

Leticia Van de Putte, RPh, a pharmacist for more than 20 years, is a member of the Texas State Senate representing a large portion of San Antonio and Bexar County. A former-five term state representative, she is now serving her second term as a Texas State Senator for District 26. In 2003 she became the Texas Senate Democratic Caucus Chair after having served as Chair of the Texas Senate Hispanic Caucus in 2001. Over the past two decades, Senator Van de Putte has been honored with numerous awards including the Texas Pharmacy Association “Pharmacist of the Year,” being recognized by Texas Monthly Magazine as one of “Texas’ Best Legislators,” the “Humphrey Award” from the American Pharmacists Association and numerous others. She is a leading advocate for children, health care, education, and economic development issues and has consistently authored and sponsored bills to assist families in securing opportunities. The Senator was a Kellogg Fellow at Harvard University’s John F. Kennedy School of Government in 1993 and received her Bachelor of Science from the University of Texas at Austin, College of Pharmacy.

Adolph P. Falcón, MPP, is Vice President for Science and Policy at the National Alliance for Hispanic Health (the Alliance). Mr. Falcón joined the Alliance in 1987. He oversees the organization's research and public policy portfolio, including serving as Principal Investigator for current research and policy initiatives funded by the Centers for Disease Control and Prevention, the Commonwealth Fund, the National Institutes of Health, and the Public Health Service Office of Minority Health. He currently serves on the Board of Directors of the Public Finance Project. Prior to joining the Alliance, Mr. Falcón was editor-in-chief of the Journal of Hispanic Policy. He received his Masters of Public Policy from the John F. Kennedy School of Government at Harvard University and a Bachelor of Arts from Yale University.

Richard A. Levy, PhD, is Vice President for Scientific Affairs at the National Pharmaceutical Council (NPC). Dr. Levy joined NPC in 1981. He is responsible for strategic planning of NPC’s research portfolio and development of information, programs, and studies on patient compliance, pharmaceutical innovation, value of pharmaceuticals, and the gap between medical theory and practice. Dr. Levy is the author of over 80 publications on pharmacology, the appropriate use of pharmaceuticals, health policy, and pharmacoeconomics. Prior to joining NPC, Dr. Levy was a member of the University of Illinois Medical School faculty where he taught and conducted research in pharmacology. He received his doctorate from the University of Delaware.

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ABOUT THE NATIONAL ALLIANCE FOR HISPANIC HEALTH (WWW.HISPANICHEALTH.ORG)

The mission of the Alliance is to improve the health and well-being of Hispanics. Founded in 1973, the Alliance is the nation's oldest and largest network of Hispanic health and human services providers. Alliance members deliver quality services to over 12 million persons annually. As the nation’s action forum for Hispanic health and well being, the programs of the Alliance strive to:

- Inform and mobilize consumers;
- Support providers in the delivery of quality care;
- Promote appropriate use of technology;
- Improve the science base for accurate decision making; and,
- Promote philanthropy.

The Alliance provides key leadership and advocacy to ensure accountability in these priority areas with the result of improving health for all throughout the Americas. The constituents of the Alliance are its members, Hispanic consumers, and the greater society that benefits from the health and well being of all its people.

ABOUT THE NATIONAL PHARMACEUTICAL COUNCIL (WWW.NPCNOW.ORG)

Since 1953, NPC has sponsored and conducted scientific, evidence-based analyses of the appropriate use of pharmaceuticals and the clinical and economic value of pharmaceutical innovations. NPC provides educational resources to a variety of health care stakeholders, including patients, clinicians, payers, and policy makers. More than 20 research-based pharmaceutical companies are members of NPC.


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OVERVIEW

His report brings together for the first time a growing body of scientific research demonstrating substantial disparities in pharmaceutical therapy for Hispanic Americans. Hispanics are less likely to receive or use medications for asthma, cardiovascular disease, HIV/AIDS, mental illness, or pain as well as prescription medications in general. These disparities in pharmaceutical treatment are substantial and often persist even after adjustment for differences in income, age, insurance coverage, and coexisting medical conditions.

Emerging research demonstrates that genetic variations affect Hispanic Americans and may require dosage adjustments to achieve an optimal therapeutic effect. Failure to recognize an individual who is a fast or slow metabolizer of a drug, and to adjust the dosage accordingly, can potentially result in therapeutic failure, increased side effects, or toxicity.

Eventually, advances in pharmacogenetics (the study of genetically determined variants in drug response) and genetic mapping will enable prescribing that is informed by the specific genetic make-up of individual patients. Until such information becomes generally available, ethnic background may offer some insight into the differences in drug response observed across populations.

“EMERGING RESEARCH DEMONSTRATES THAT GENETIC VARIATIONS AFFECT HISPANIC AMERICANS AND MAY REQUIRE DOSAGE ADJUSTMENTS TO ACHIEVE AN OPTIMAL THERAPEUTIC EFFECT.”

Medical errors can significantly compromise the quality of pharmaceutical therapy. Key areas for reducing medical errors among Hispanics have been identified in the literature, including the Institute of Medicine’s landmark report, To Err is Human: Building a Safer Health System. These include: better patient-provider communication, improved cultural and linguistic proficiency of the health system, increased awareness of coexisting conditions, and a better use of knowledge regarding patient response factors that impact the effectiveness and safety of drug therapy.

It is increasingly important for those involved in health care delivery and policy to better understand how all of these factors affect the delivery of quality medical care, and pharmaceutical care specifically, to Hispanic populations. Prescribing should be tailored to individual patient needs based on age, coexisting conditions, and responsiveness to medications. The choice of medications available must be broad enough to accommodate this range of factors and ensure access to advances in pharmaceutical therapy for all.

KEY FINDINGS

1. **Hispanics have less access to medications.** Hispanics are less likely than the majority population to receive or use needed medications, including drugs for asthma; cardiovascular disease; HIV/AIDS; mental illness; or pain due to fractures, surgery, and cancer (page 6).

2. **Advances in medications are less likely to reach Hispanics.** Research suggests that Hispanics may receive fewer state-of-the-art medications. For example:

   - Hispanics in a Medicaid population received fewer of the more effective second-generation antipsychotic agents compared with non-Hispanic whites (page 8).

   - Hispanic children in a variety of health care settings received fewer inhaled steroids and were less likely to be prescribed a nebulizer for home use than white children (page 7).

3. **Genetic and other factors influence medication effectiveness for Hispanics.** Hispanics can differ from other populations in their capacity to metabolize certain drugs. These differences may be due to variation in genes regulating drug metabolism, environmental factors, or their interaction. Such differences can result in higher or lower levels of drugs in the bloodstream (see box at right). If genetic or other factors suggest that a patient may be a slow or ultrarapid metabolizer of a given drug, appropriate adjustments to the patient’s therapy should be considered that may yield better outcomes.

4. **Optimal dosages vary for Hispanic populations.** Hispanics may require dosage adjustments to achieve optimal therapeutic levels. For example:

   - Some Hispanic subgroups may require lower doses of antidepressants and may be more prone to increased side effects at normal doses of these agents.

   - Hispanics tend to respond to lower doses of some antipsychotic medications. In one study, the average therapeutic dose for Hispanics was half the dose commonly given to Caucasians or African Americans.

   - Lower dosages of midazolam and nifedipine are commonly used in Mexico.
**GENES AND DRUG METABOLISM VARIATION IN HISPANIC POPULATIONS**

<table>
<thead>
<tr>
<th>GENE</th>
<th>HISPANIC VARIATION</th>
<th>MAJOR DRUGS REGULATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>Slower metabolism/higher blood levels in Mexicans</td>
<td>• nifedipine (cardiovascular)</td>
</tr>
<tr>
<td></td>
<td>(metabolism in U.S. Hispanics not yet studied)</td>
<td>• cyclosporine (immunosuppressive)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• midazolam (anesthetic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• sildenafil (erectile dysfunction)</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Faster metabolism in Mexican Americans</td>
<td>• many cardiovascular drugs</td>
</tr>
<tr>
<td></td>
<td>Slower metabolism in Dominicans and Puerto Ricans</td>
<td>• many psychotropic drugs</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Slower metabolism in Spaniards (metabolism in U.S. Hispanics not yet studied)</td>
<td>• warfarin (stroke prevention)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• phenytoin (epilepsy)</td>
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<tr>
<td></td>
<td></td>
<td>• diabetes medications</td>
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</tbody>
</table>

5. **Coexisting conditions can impact medication effects.** Conditions prevalent in the Hispanic population (diabetes, depression, asthma, cardiovascular disease) often coexist in the same individual, and are often undertreated. Choice of medications must take coexisting conditions into account.

6. **Cultural and communication issues impact quality of pharmaceutical care.** Inadequate patient-provider communication negatively influences medication compliance, self-management of chronic disease, and overall health outcomes. These issues include lack of compliance with culturally proficient standards of care, language barriers, and poor health literacy.

7. **Research addressing Hispanic populations is limited.** Current research suggests disparities in Hispanic access to pharmaceutical therapy overall, and specifically to the newest generations of medicines. Emerging research also suggests a genetic basis for variations in Hispanic drug response. However, the body of research is inadequate, only covering a few conditions and often drawn from research in Spain and Latin America, not including U.S. Hispanic populations.

**RECOMMENDATIONS**

1. **Improve access to pharmaceutical therapy.** Health care financing and reimbursement practices should be broad and flexible enough to enable rational choices of drugs, dosages and formulations for Hispanic patients based on their genetic, medical, and cultural needs. Choice of the best pharmaceutical therapy should be between patient and provider.

2. **Prescribe based on individual needs.** Prescribing for Hispanic populations must consider the biological, environmental, and cultural factors that can influence drug effectiveness and patient adherence to treatment regimens.

3. **Treat coexisting conditions.** Standards of quality for pharmaceutical treatment of Hispanics must account for coexisting conditions common in this population, including depression paired with asthma, diabetes or cardiovascular disease, or diabetes paired with depression.

4. **Meet quality standards of cultural proficiency and communication.** Communication barriers and cultural differences between health care providers and Hispanic patients can reduce treatment adherence and compromise overall disease management. Implementation of existing federal and professional accreditation standards for cultural and linguistic proficiency is a priority, including improved access to medical interpreters, cultural proficiency education for providers, and consumer information on securing culturally proficient care.

Individualized prescribing and access to the most appropriate medications will reduce medical errors, save costs associated with untreated illness, and secure the promise of advances in pharmaceutical therapy for all.
INTRODUCTION

Advances in genetic research have provided scientific insights at a new level of detail. Yet, we have been slow to translate knowledge into practice and apply new approaches to improve the quality of care that is delivered. The Institute of Medicine’s report To Err Is Human: Building a Safer Health System identifies the appropriate use of medicines as an area needing significant improvement. A key factor in ensuring appropriate medication use is a thorough understanding, not only of drug therapy, but also of patient response factors that may have an impact on the effectiveness and safety of drug therapy.

“PHARMACEUTICALS PLAY AN IMPORTANT ROLE IN THE TREATMENT AND MANAGEMENT OF CHRONIC CONDITIONS COMMON IN HISPANICS, INCLUDING DIABETES, DEPRESSION, ASTHMA, AND CARDIOVASCULAR DISEASE.”

Variations in response to medications exist between Hispanic and non-Hispanic populations and also among Hispanic subpopulations, and these variations may not be easily recognized. Hispanics share an increased risk for certain conditions and may have coexisting illnesses requiring treatment with multiple medications. As we undertake steps to address disparities and improve access and quality of care for Hispanic patients, it is important to recognize the increasing role that pharmaceuticals play in medical treatment today.

Modern medicines can extend life, enable a better quality of life, and reduce the use of health care services. Pharmaceuticals play an important role in the treatment and management of chronic conditions common in Hispanics, including diabetes, depression, asthma, and cardiovascular disease. The use of pharmaceuticals by employed persons with these and other chronic diseases has been shown to facilitate return to work and improve productivity on the job.

Pharmaceuticals have also contributed substantially to the large reduction in disability and institutionalization of elderly persons observed in recent years. This decline in disability is “consistent with the introduction of new biotechnologies [including better drug treatments for] osteoporosis, stroke, Parkinson’s disease and congestive heart failure.”

These findings underscore the value of medications in terms of quality of life to Hispanics suffering from these conditions. Unfortunately, compared with the majority population, Hispanics frequently have reduced access to pharmaceuticals, and even minimal use of medications is often not achieved.

Access to pharmaceutical care is more difficult without health insurance, and Hispanics are less likely to be insured compared with other population groups (Figure 1). Many of these individuals are the working-poor who have little

![Figure 1. People without Health Insurance Coverage for the Entire Year by Race and Ethnicity: 2002](image1)

![Figure 2. Proportion of Older Adults with Chronic Conditions without Prescription Coverage](image2)
access to employer-sponsored insurance. Less than one-third (31%) of older Hispanics with chronic conditions have coverage for prescription drugs, compared with 52% of their non-Hispanic white counterparts (Figure 2).

Even when Hispanics have access to pharmaceuticals, they may be less likely to receive or use prescriptions. For example, despite having more severe asthma than white children, Hispanic children with similar insurance and sociodemographic characteristics were found to be 42% less likely to be using inhaled anti-inflammatory medication (including inhaled steroids) to prevent the onset or worsening of an asthma episode.

As drug coverage policies evolve and expand to encompass more Hispanic patients, they must account for the specific pharmaceutical needs of these individuals. Disparities in health between Hispanic and other populations may be further exacerbated without access to individualized care with appropriate pharmaceuticals.

Improving patient-provider interaction is important in addressing disparities in pharmaceutical therapy for Hispanic communities. Adherence to medication regimens depends on an understanding of prescribed treatments. Hispanic Americans may have challenges in communicating with and understanding their health care provider because of language and cultural barriers.

Genetic and cultural factors may also vary considerably among Hispanic subgroups. Variations in the genetic mix, differences in cultural beliefs about disease and the treatment of disease, varying levels of language proficiency, and socioeconomic factors all have an impact on the effectiveness of treatment.

It is increasingly important for those involved in the delivery of health care and in health care policy to understand the implications of Hispanic heritage for medical care, and pharmaceutical care specifically. Currently, 38.8 million Hispanics reside in the mainland United States, with another 3.8 million in Puerto Rico. Persons of Mexican heritage comprise the majority of the U.S. Hispanic population (Figure 3).

The U.S. Hispanic population (42.6 million) is larger than the entire population of Canada (31.9 million) and more than twice that of Australia (19.5 million). At 14% of the U.S. population, Hispanics are the nation’s largest minority group. By the year 2050, 25% of the U.S. population will be Hispanic. Thus, improving access and quality of care for Hispanics will become increasingly important for the nation’s health.

The majority of the studies discussed in this report refer to Hispanic Americans living in the mainland United States or Puerto Rico. Hispanic is a term used to identify persons of any race of Mexican, Puerto Rican, Dominican, Cuban, and Central or South American heritage. The term Hispanic emphasizes the Spanish ancestry of these groups; however, within some U.S. Hispanic groups there is significant genetic and cultural influence from American Indians and Africans. Some prefer the alternative term, Latino, which recognizes the national heritage of many Hispanics in the Americas.

"AS DRUG COVERAGE POLICIES EVOLVE AND ENCOMPASS MORE HISPANIC PATIENTS, THEY MUST ACCOUNT FOR THE SPECIFIC PHARMACEUTICAL NEEDS OF THESE INDIVIDUALS. DISPARITIES IN HEALTH BETWEEN HISPANIC AND OTHER POPULATIONS MAY BE FURTHER EXACERBATED WITHOUT ACCESS TO INDIVIDUALIZED CARE WITH APPROPRIATE PHARMACEUTICALS."
Disparities in the quality of medical care provided to patients representing different racial and ethnic groups have been extensively documented. The recent landmark report of the Institute of Medicine (IOM), Unequal Treatment: Confronting Racial and Ethnic Disparities in Healthcare, discusses large disparities in the treatment of illness and in the delivery of health care services to racial and ethnic groups in the United States. Hispanics are the group least likely to have regular access to health care services. Nearly one-third (32%) of Hispanics are uninsured compared to 11% of non-Hispanic whites. Among uninsured persons, 38% report having no usual source of health care; 39% report skipping a recommended medical test or treatment; and, 30% report not filling a prescription.

Minorities in general receive less intensive pharmaceutical treatment than the nation as a whole, including fewer adolescent and adult vaccinations, less drug therapy for pain, fewer antiretroviral drugs for HIV/AIDS, and fewer antidepressants.

Specific disparities in pharmaceutical treatment of Hispanics versus non-Hispanics have been reported:

- Hispanics were undertreated for pain from fractures and received inadequate management of postoperative pain. Hispanic patients with cancer were less likely to have adequate analgesia and reported less pain relief than African American or non-Hispanic white patients.

- Hispanics were less likely than non-Hispanics to receive antipsychotic medication.

- Mexican Americans received fewer cardiovascular drugs following a heart attack than non-Hispanic whites, especially antiarrhythmics, anticoagulants, and lipid-lowering therapies. Furthermore, even when controlling for insurance, income, or adverse health practices, research has found that Hispanics with high blood pressure use medications less frequently compared to whites or blacks, and, despite awareness of hypertension, have poorer blood pressure control (Figure 4).

- Hispanic children were less likely to receive a prescribed medication compared with white children, even after adjusting for socioeconomic factors, health conditions, and number of physician visits.

Hispanics are also less likely to receive adequate pharmacy services. Older Hispanic patients have been reported to receive fewer ancillary pharmacy services compared with non-Hispanics, including delivery of medications, medication counseling, and written medication information. These disparities can stem from a variety of causes and lead to errors in use of medications and other prescribed treatments and ineffective management of disease.

**Figure 4. Lower Awareness of Hypertension, Medication Taking, and Blood Pressure Control in Hispanics**

![Figure 4](image)

*Among those aware of their hypertension

Sources: Sudano et al.; Havas et al.
ASTHMA AND HISPANIC CHILDREN

Hispanic children with asthma receive or use relatively fewer medications, and this is particularly problematic since Hispanic children—Puerto Ricans in particular—are at higher risk for asthma-related morbidity and mortality compared with non-Hispanic whites.

Puerto Rican children experience a greater prevalence of asthma than children of other Hispanic subgroups and non-Hispanic white populations. An estimated 500,000 Hispanic children in the United States have asthma, two-thirds of whom are Puerto Rican.32 The Hispanic Health and Nutrition Examination Survey (1982–1984) found that asthma affects 11% of U.S. children of Puerto Rican descent, more than triple the rate in Mexican Americans and non-Hispanic whites, more than double the rate in Cuban Americans, and nearly double the rate in African Americans.33 Among children with Medicaid-paid hospitalizations for asthma, Hispanics had a much higher risk for multiple asthma hospitalizations than whites.34

Appropriate treatment, particularly pharmaceutical therapy, can prevent asthma morbidity and mortality and reduce emergency department visits and hospitalizations.35-37 Despite their higher asthma prevalence and greater asthma-related morbidity and mortality, Puerto Rican children are less likely to receive or use treatment that can help control and manage the disease.

Hispanic ethnicity has been associated with lower use of inhaled steroids and with higher rates of emergency department visits and hospital admissions for asthma.40 In a study of Medicaid-insured children with asthma, Hispanic ethnicity was associated with underuse of controller medications.41 In private practices, Hispanic children received fewer inhaled steroids than white children even after adjusting for such factors as insurance status, severity, and maternal education.42 Upon hospital discharge, Hispanic preschoolers with asthma were 17 times less likely than their white counterparts to be prescribed a nebulizer for home use.43

A Harvard Medical School study suggests that improving medication use may be the key to reducing ethnic disparities in treatment of asthma in children.8 The study showed that Hispanic children had worse asthma status and less use of preventive asthma medications than white children within the same Medicaid managed care populations. Despite having more severe asthma than white children, Hispanic children with similar insurance and sociodemographic characteristics were 42% less likely to be using inhaled anti-inflammatory medication (including inhaled steroids) to prevent the onset or worsening of an asthma episode. Similar racial and ethnic differences in asthma medication use were found across the five health plans studied (Figure 5). In each of the plans, Hispanic children had the lowest use of anti-inflammatory drugs. The researchers concluded that “increasing the use of preventive medications would be a natural focus for reducing racial disparities in asthma.”8

The disparities in the use of asthma preventive medications in Hispanic children reported above8,42,43 persisted after adjusting for asthma severity, financial barriers, and sociodemographic variables, suggesting that “differences in health beliefs and concepts of disease, fears about steroids, or communication barriers (including language) between doctors and patients may play an important role in suboptimal medication use.”8

Figure 5. Racial/Ethnic Variation in Anti-Inflammatory Drug Use in Children with Asthma

Adapted from Lieu et al.8
MENTAL ILLNESS
Although Hispanics may receive pharmaceuticals for mental illnesses, in some cases the best available therapy may not always be prescribed. One study found that Hispanic patients in a Medicaid population did not receive newer, more effective second-generation antipsychotic agents as frequently as their non-Hispanic white counterparts. Not receiving such second-generation antipsychotic pharmaceuticals increases the risk for tardive dyskinesia, a potential side effect of older antipsychotic drugs characterized by repetitive, involuntary, purposeless movements that can persist long after discontinuing the drug.

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. An analysis of 1992–1995 data from the National Ambulatory Medical Care Survey found that Hispanics with depression were less likely than whites to receive SSRI medications. One state study found that for New Mexico residents, this gap in access had been closed.

Eliminating disparities in 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 to these medications.

Hispanic women were found to discontinue SSRI antidepressants at a higher rate than their non-Hispanic counterparts, 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 white women. 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.

A cross-cultural study comparing the efficacy of the antidepressants trazodone and imipramine in Colombian and U.S. (predominantly white) depressed patients also highlights differences between Hispanics and whites. Although the Colombians received only slightly higher doses, they experienced more side effects, and improvements were greater with both the antidepressants and placebo. While these results may suggest heightened biological and cultural sensitivity, a study with the tricyclic antidepressant nortriptyline in non-depressed patients found that Hispanics were not more sensitive than whites to drug effects.

In summary, Hispanics generally have been found to respond to lower doses and have lower effective concentrations of antidepressants than whites. However, this 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. Hispanics also tend to respond to lower doses of some
antipsychotic medications. In one study, the average therapeutic dose of antipsychotic medication for Hispanics was half the dose given to Caucasians and African Americans.

A study of Hispanics and non-Hispanics given the same dose of antipsychotic medication found that Hispanics had a faster response and also showed a higher rate of adverse effects, suggesting slower metabolism of the drug.

The increased sensitivity of Hispanics to antidepressant and antipsychotic agents may result partly from environmental influences. These influences may include lower levels of smoking and alcohol use, and higher medicinal herb use, all of which have been reported in Hispanic populations. These factors can suppress drug metabolism and thereby elevate blood levels of drugs. 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 suppress metabolism of psychiatric agents.

“**A STUDY OF HISPANICS AND NON-HISPANICS GIVEN THE SAME DOSE OF ANTIPSYCHOTIC MEDICATION FOUND THAT HISPANICS HAD A FASTER RESPONSE AND ALSO SHOWED A HIGHER RATE OF ADVERSE EFFECTS, SUGGESTING SLOWER METABOLISM OF THE DRUG.**”

**STATUS OF RESEARCH**

Response to medications and disease prevalence can vary considerably among individuals and population groups owing to a variety of complex and interdependent factors. These include environmental factors (e.g., climate, diet, smoking, alcohol consumption), biologic factors such as genetic polymorphisms (naturally occurring variations in the structures of genes, drug metabolism enzymes, receptor proteins, and other proteins involved in drug response or disease progression), age, and gender (Figure 6). As a result of this complex set of variables, patients from different population groups may require alternate drugs or dosages.

**Figure 6. Factors Affecting Drug Response**

Source: Lin and Smith
Significant differences have been reported among ethnic populations in the metabolism, clinical effectiveness, and side effect profiles of therapeutically important drugs. Most of these studies have concentrated on different responses to cardiovascular agents (beta-blockers, diuretics, calcium-channel blockers, and angiotensin converting-enzyme inhibitors) or central nervous system agents (antidepressants and antipsychotics). Pain relievers (acetaminophen, codeine), antihistamines, and alcohol are other pharmacologic substances with varying effects among different population groups.

While these studies present an emerging picture of ethnic variation in response to pharmaceutical therapy, much of the research applies to African Americans, Asians, and Caucasians. Very few studies have specifically targeted the response of Hispanics to these (or other) medications, although they are frequently prescribed in this population.

Only six studies exploring undermedication of Hispanic patients (Table 1) were found in the IOM’s comprehensive review of 103 studies on disparities in the treatment of ethnic minorities. The vast majority of the report’s studies focused on African Americans, indicating the need for additional research in Hispanic populations.

The Food and Drug Administration (FDA) has long requested race and ethnicity data on subjects in certain clinical trials. A recent FDA draft guidance for industry notes that some differences in response to pharmaceuticals have been observed in racially and ethnically distinct subgroups within the U.S. population. The guidance recommends the use of standard race and ethnicity categories for data collection. Uniform categories will be helpful in evaluating potential differences among ethnic and racial subgroups in the safety and efficacy of pharmaceuticals and will help to further ensure ethnic and racial diversity in clinical trials of new drugs.

**Table 1. Disparities in Pharmaceutical Treatment of Hispanic Patients**

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Disparity</th>
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</thead>
<tbody>
<tr>
<td>Pain (cancer)</td>
<td>Cancer patients treated in settings serving primarily Hispanic and African American patients were more likely to receive inadequate analgesia (77%) than patients in settings serving primarily white patients (52%).</td>
</tr>
<tr>
<td>Pain (postoperative)</td>
<td>Hispanic patients were prescribed less postoperative narcotic pain medications compared with whites and African Americans.</td>
</tr>
<tr>
<td>Pain (fractures)</td>
<td>55% of Hispanic bone fracture patients received no pain medication in the emergency room, vs. 26% of white patients. Hispanic ethnicity was the strongest predictor of no analgesia.</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>On discharge from hospital after myocardial infarction, Mexican Americans received fewer medications than whites, even after adjusting for clinical, socioeconomic, and demographic characteristics. Mexican Americans were less likely to receive all major medications, especially antiarrhythmics, anticoagulants, and lipid-lowering therapy.</td>
</tr>
<tr>
<td>Diseases in children</td>
<td>Hispanic children were less likely than white children to receive any prescription.</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Hispanic patients were less likely than whites to receive AIDS medications.</td>
</tr>
</tbody>
</table>

**“Significant differences have been reported among ethnic populations in the metabolism, clinical effectiveness, and side effect profiles of therapeutically important drugs.”**
GENETICS AND INDIVIDUALIZED RESPONSE TO DRUGS IN HISPANICS

Pharmacogenetics is the study of genetically determined variations in drug response. Such studies have shown that genetic differences can affect the probability that a person will respond as expected to a given drug. Response to medications may differ among U.S. Hispanic subgroups and this may reflect differences in genetic admixture. The contemporary U.S. Hispanic gene pool consists of American Indian, Spanish, and African ancestral populations (Figure 7). African heritage in Puerto Ricans living in the United States is much higher than that for Mexican Americans (37% vs. 8%); and DNA studies from several Caribbean and South American countries (Jamaica, Columbia, Belize) demonstrate high levels of West African inheritance.

Over time, different populations that come together become genetically homogeneous. However, contact between Europeans and the native population of the Americas was initiated only five centuries ago, a relatively short time span in the history of human cultures. Such recently defined populations can be highly heterogeneous in their genetic make-up, depending on the degree of mixing in the subgroup. Knowing the genetic composition of persons with Hispanic ancestry may be helpful in anticipating differences in drug response, because variations in drug metabolism can be greater in populations whose genetic pools have come together recently.

“According to Urs Meyer, a pioneer in the field of pharmacogenetics, ‘All pharmacogenetic variations studied to date occur at different frequencies among subpopulations of different ethnic or racial origin…this ethnic diversity…implies that ethnic origin has to be considered…in pharmacotherapy.’”

Pharmacogenetic variations can influence the magnitude of response to medications, frequency of adverse effects, and interactions with other drugs. Membership in a population group may be a marker for genetic variations in individuals. This knowledge can alert physicians to the possibility of an unexpected result. An understanding of genetic variation may help to avoid overdoses on the one hand, or reduced therapeutic effect on the other. Adverse reactions in particular may be avoided, since over half of the top 27 drugs cited in reports of adverse reactions are metabolized by an enzyme that has a poor-metabolizing genetic variant.

Emerging pharmacogenetic research is demonstrating that some of these enzyme variants may be more prevalent in Hispanic population groups. Eventually, advances in pharmacogenetics and genetic “fingerprinting” will enable prescribing informed by the specific genetic make-up of individual patients rather than imprecise ethnic population markers.

Knowledge relating particular genetic variations to disease progression and response to specific medications is beginning to emerge. Genetic factors are believed to influence susceptibility to asthma, diabetes, cardiovascular disease, and other chronic conditions common in Hispanics. Ongoing research to identify the genetic basis of these diseases and of patients’ responses to medications may lead to new insights into pharmaceutical management or prevention of these conditions.

“Eventually, advances in pharmacogenetics and genetic ‘fingerprinting’ will enable prescribing informed by the specific genetic make-up of individual patients rather than imprecise ethnic population markers.”

ASTHMA

While environmental and socioeconomic factors contribute to disparities in asthma prevalence and severity between Puerto Ricans and other Hispanic subgroups, differences in genetic predisposition to asthma or to greater asthma severity also play a role. The striking differences between Puerto Rican and Mexican Americans may be due in part to differences in the make-up of their respective gene pools.
The increased asthma risk among Puerto Rican children may also be related in part to genetic differences in the inflammatory response. Puerto Rican children with abnormal variants of alpha1-antitrypsin, a protein involved in inflammatory reactions, are at increased risk.47 Another reason why asthma prevalence may differ among Hispanics is that Mexican American children are thought to have better lung function and larger airways than their white and African American counterparts.47

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.79 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.79 Thus, fewer Hispanics (and other minorities) may respond well to albuterol compared to Caucasians.

DIABETES
On average, Hispanics are almost twice as likely to have diabetes than non-Hispanic whites.80 However, the prevalence of diabetes varies considerably among Hispanic subgroups. Diabetes is two to three times more common in Mexican Americans and Puerto Ricans than in non-Hispanic whites. In Cuban Americans, however, diabetes prevalence is similar to that for non-Hispanic whites.81 Risk factors for diabetes seem to be more common among Hispanics than non-Hispanic whites. These include obesity, physical inactivity, insulin resistance, higher than normal levels of fasting insulin, impaired glucose tolerance, and a family history of diabetes.82

Although environmental factors (e.g., diet and exercise) have a large impact on the manifestation of type 2 diabetes, genetic factors are also believed to underlie the disturbances in insulin secretion and insulin resistance that characterize this disease.83 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 one chromosome, while Pima Indians have genetic links to diabetes on other chromosomes.84 This suggests that the genes and molecular mechanisms regulating insulin secretion and action may differ across populations85 and raises the possibility of finding population-specific molecular targets (enzymes, receptors, substrates) for new drug development.

The variation in diabetes prevalence among Hispanic subgroups may also reflect different genetic contributions. Among the three groups of Hispanic ancestors (Spaniards, Africans, and American Indians) both Africans and American Indians have high rates of diabetes (13% for African Americans,86 21% for Pima Indians,85 and 23% for Navajos86 vs. 8% for whites85)

“ALTHOUGH ENVIRONMENTAL FACTORS (E.G., DIET AND EXERCISE) HAVE A LARGE IMPACT ON THE MANIFESTATION OF TYPE 2 DIABETES, GENETIC FACTORS ARE ALSO BELIEVED TO UNDERLIE THE DISTURBANCES IN INSULIN SECRETION AND INSULIN RESISTANCE THAT CHARACTERIZE THIS DISEASE.”

The high diabetes prevalence in Mexican Americans and Puerto Ricans may in part reflect a high proportion of American Indian and African genetic influence. Mexican Americans have more than 30% of their genetic heritage from American Indians and Puerto Ricans have almost 40% from Africans.78

Given their higher prevalence of diabetes and lack of access to care, Hispanics may be at greater risk for diabetes-related complications, such as heart, eye, and kidney disease than the general population.85 In addition, among diabetics, some (but not all) studies have shown higher rates of kidney and eye disease in Mexican Americans.82

A study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases 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.77 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 African American children were due to a reduced capacity of their livers to remove insulin from circulation.87,88 According to the study's lead researcher, Michael Goran of the University of Southern California Institute for Prevention Research, “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.”

HEART ATTACK

The fact that Mexican Americans are hospitalized for heart attack more frequently than non-Hispanic whites appears to reflect greater cardiovascular disease risk factors (e.g., diabetes, obesity, high cholesterol levels). Despite this relatively greater incidence, some (but not all) studies report that Hispanics have a lower mortality rate from heart disease compared with non-Hispanic whites. Protective genetic or lifestyle factors may help explain why Hispanics have greater risk factors for heart disease, but have less mortality. Research is needed to clarify the role of risk factors in heart disease among Hispanic populations. Available data indicate that Hispanics may have a different lipid profile than other populations and may 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. Although genetic and environmental factors both play a role, genes account for 30% to 45% of differences in blood levels of lipids and lipoproteins between Mexican Americans and non-Hispanic whites.

Heart attack is of particular concern since Hispanics, especially Caribbean Hispanics, have an increased prevalence and incidence of Alzheimer’s compared with white populations.

Alzheimer’s disease is believed to have a genetic basis, with multiple genes likely to be involved. A variant of the apolipoprotein E (ApoE) gene has been identified as a major genetic risk factor for late-onset Alzheimer’s disease across most populations. Common variants of the ApoE protein, which are coded by corresponding variants of the ApoE gene, alter cholesterol profiles and correlate with diseases linked to cholesterol metabolism, particularly cardiovascular disease and Alzheimer’s.

An association has been found between Alzheimer’s and a common variant of the ApoE gene, called ApoE4. However, the strength of the association varies across ethnic groups. One study found a fivefold increase in the risk of Alzheimer’s among Hispanics having two copies of the ApoE4 gene variant.

Although reports of an association have been inconsistent in Caribbean Hispanics in New York City having African heritage (Dominicans and Puerto Ricans), a clear association has been reported in Cubans living in Miami. These ethnic variations are potentially important in understanding the cause of Alzheimer’s and in targeting effective treatments for individual patients.

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Many patients do not receive an appropriate cholesterol-lowering “statin” drug in a dosage adequate to reach target LDL cholesterol levels. Since the potency of these agents varies considerably, access to a variety of statins, including high-strength agents, may be particularly important for Mexican Americans with very high cholesterol.

ALZHEIMER’S DISEASE

Effective treatment of the Hispanic elderly will become an increasing public health priority. The proportion of elderly who are Hispanic will increase from 4% today to 14.1% in the year 2020. The treatment of Alzheimer’s in the Hispanic elderly is of particular concern since Hispanics, especially Caribbean Hispanics, have an increased prevalence and incidence of Alzheimer’s compared with white populations.

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ApoE4 carriers may show a weaker response to some but not all Alzheimer’s drugs. Fewer patients with the ApoE4 variant appear to respond to treatment with tacrine compared with patients lacking this variant. By contrast, response to donepezil and several other Alzheimer’s agents (galantamine, metrifonate) did not predict treatment response in ApoE4 carriers. The response to various Alzheimer’s drugs in Hispanics carriers of the ApoE4 gene has not yet been studied.
CLINICAL IMPLICATIONS OF VARIATION IN GENES REGULATING DRUG METABOLISM

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. Persons with reduced ability to metabolize a specific drug are termed poor (or slow) metabolizers of that drug; those with enhanced metabolic activity are termed ultrarapid 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.

Drug metabolism and deactivation proceed via a process of chemical modification (e.g., oxidation, dealkylation, reduction, acetylation, sulfation). Cytochrome P450 is a super-family of iron-containing enzymes that are named after the genes that encode them (e.g., CYP3A4, CYP2D6, CYP2C9). Over 90% of drugs in common clinical use are converted (oxidized) in the liver by metabolic enzymes of the cytochrome P450 group. This conversion makes the drugs more soluble in water, which facilitates their elimination from the body. About 50 different forms of CYP450 have been characterized in humans, each encoded by a different gene.

Genetic variations in drug-metabolizing enzymes differ in frequency among ethnic groups. 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.”

In addition, environmental factors influence the activity of these metabolic enzymes. The activity of drug metabolizing enzymes can be increased or decreased by numerous substances, including foods, alcohol, tobacco, herbal medicines, as well as medications (Figure 6). As immigrant groups change their lifestyles and their exposure to these substances, their metabolic profiles can also change. 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.

“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.”

Relatively few studies have compared frequencies of genetic variations affecting metabolism in Hispanics compared with other population groups. However, studies of the CYP2D6 and CYP2C9 forms of the CYP450 enzyme series have reported different frequencies of variants of these genes in Hispanic groups, both within and outside the United States, compared with other populations. In addition, 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.

THE CYP3A4 GENE

The CYP3A4 gene mediates the metabolism of over 50% of commonly used drugs including the cardiovascular drug nifedipine, the anesthetic midazolam, the immunosuppressant cyclosporine, and sildenafil. Nifedipine metabolism appears to be slower, and blood levels are higher in Mexicans compared with individuals in the United States, the United Kingdom, or Germany (Figure 8). One study found 58% of Mexicans to be slow metabolizers of nifedipine, in contrast to reports of 17% of Europeans (Dutch). Diet may influence metabolism, as evident in a study showing that quercitin, the main flavonoid ingredient in corn, substantially increases the frequency and severity of side effects from nifedipine. These results indicate that Mexicans may require lower doses.

The metabolism of the anesthetic midazolam is also slower and blood levels are higher in mestizos (the main ethnic group in Mexico, having combined heritage from Spaniards and Indians) compared with Caucasian Americans and Europeans (Figure 9). Nifedipine and midazolam are commonly studied...
prescribed in lower dosages in Mexico compared with other countries\textsuperscript{133,134} in order to avoid untoward effects that may result from slower metabolism.\textsuperscript{133}

Cyclosporine is metabolized by CYP3A4 and is widely used in organ transplantation and in the treatment of autoimmune diseases. Cyclosporine blood levels are higher in Mexicans than in whites,\textsuperscript{135} possibly due to genetic variants or inhibition of the CYP3A4 enzyme by flavonoids in foods, especially some citrus fruits and corn, which are common in the Mexican diet.\textsuperscript{124,130,135} Lastly, one study found that concentrations of sildenafil, also influenced by CYP3A4, in Mexican men were about twice those reported in other studies for white men.\textsuperscript{136}

These reports of slow metabolism of several CYP3A4-metabolized medications in Mexicans outside the U.S. suggest that Mexican Americans may also be slow metabolizers of these drugs. Direct studies in Mexican Americans would be useful, especially since one study found no difference in midazolam concentrations between white Americans living in Tennessee and recent Mexican immigrants in Los Angeles who still adhered to a traditional diet.\textsuperscript{137}

Unlike CYP2D6 and CYP2D9, variations in CYP3A4 metabolic activity do not appear to be under genetic control.\textsuperscript{124,128} Variant forms of the CYP2D6 and CYP2D9 genes exist and are more or less prevalent in particular ethnic groups. In contrast, observed ethnic differences in CYP3A4 activity are believed to be due to the existence of natural substrates in the environment that serve as inhibitors or inducers of the enzyme encoded by this gene.\textsuperscript{124,128} CYP3A4 appears to be highly sensitive to environmental influences such as diet, pollutants, and smoking.\textsuperscript{124,128}

\textbf{Figure 9. Blood Levels of the Anesthetic Drug Midazolam in Mestizos from Mexico and Caucasians from the U.S. and Europe}

\textit{Source: Adapted from Chavez-Teyes et al.\textsuperscript{133}}

\textbf{The CYP2D6 Gene}

The enzyme encoded by this gene mediates the metabolism of 25\% to 30\% of all therapeutically important medications\textsuperscript{138} including cardiovascular agents and almost all psychotropic drugs.\textsuperscript{133,139} Individuals deficient in this enzyme are slow metabolizers, while others may range from intermediate to ultrarapid metabolizers. The CYP2D6 gene has many variations that may result in an enzyme with absent, reduced, or enhanced metabolic activity. These differences affect how rapidly a drug is metabolized, leading to unexpected drug effects, or altered frequency of side effects.\textsuperscript{75,123,140}

Differences in the frequency and expression of variations in the CYP2D6 gene have been widely reported within and across racial and ethnic groups.\textsuperscript{121,123,124,140}

\textbf{"THE ABILITY TO IDENTIFY POOR OR RAPID METABOLIZERS OF A DRUG WOULD HELP CLINICIANS PREDETERMINE THE CORRECT DOSAGE, THEREBY AVOIDING ADVERSE OR SUBOPTIMAL EFFECTS."}

Metabolism of drugs governed by CYP2D6 has been reported to be faster in Mexican American populations compared with Caucasians.\textsuperscript{141} This faster metabolism, which may result in the need for higher dosages to achieve therapeutic effects, is believed to result from the overall lower frequency in the Mexican American population of several variants of this gene (CYP2D6*4, CYP2D6*10, and CYP2D6*17) that are associated with poor or slow metabolizer status. This faster metabolism in Mexican Americans contrasts with the slower metabolism observed mostly in Caribbean Hispanic populations (Dominicans and Puerto Ricans).\textsuperscript{137} One explanation for this difference (in addition to diet and lifestyle factors) may be that Caribbean Hispanics have a large African genetic influence and thus also have a high frequency of CYP2D6*17, a variant associated with slow metabolism that is common in Africans.\textsuperscript{127,128,140,141}

\textbf{"IDENTIFICATION OF INDIVIDUALS WITH CYP2D6 VARIANTS IS NOW POSSIBLE USING COMMERCIAL AVAILABLE GENETIC TESTS."}
The ability to identify poor or rapid metabolizers of a drug would help clinicians predetermine the correct dosage, thereby avoiding adverse or suboptimal effects. Patients deficient in CYP2D6 activity treated with psychiatric medications primarily metabolized by this enzyme have more adverse effects, stay longer in the hospital, and are more costly to treat than patients with efficient CYP2D6 activity. The annual cost of treating patients with severe mental illness with extremes in CYP2D6 activity (either poor or ultrarapid metabolizers) was $4,000 to $6000 greater than treatment costs for those with normal metabolism.142 Identification of individuals with CYP2D6 variants is now possible using commercially available genetic tests.143

"DOSAGE MUST BE ADJUSTED FOR BOTH AN INDIVIDUAL’S METABOLIC CAPACITY AND THE SPECIFIC ANTIDEPRESSANT PRESCRIBED."

Substantial dosage adjustments in poor- and rapid-metabolizer individuals are recommended for many antidepressants metabolized by CYP2D6 (Figure 10).144 It is important to note that the recommendations for individual antidepressants differ widely based on the importance of CYP2D6 in metabolizing the drug and the ability of small changes in drug dosage level to cause toxic or subtherapeutic effects. Thus, dosage must be adjusted for both an individual’s metabolic capacity and the specific antidepressant prescribed. Switching antidepressants in individuals with CYP2D6 variants who are already stabilized on an agent may require dosage readjustment based on both these factors.

**The CYP2C9 Gene**

The enzyme encoded by this gene governs the metabolism of several clinically important drugs for diseases common in Hispanics, including warfarin (used to prevent blood coagulation, clotting, and stroke in patients with various cardiovascular conditions), the antiepilepsy agent phenytoin, medications for diabetes, and various anti-inflammatory agents. Variant forms of the gene encoding the CYP2C9 enzyme occur with different frequencies across various ethnicities and may predict response to therapy or risk of adverse events.127 The frequency of variants is reported to be higher among Spaniards than that reported for other Caucasians; nearly 10% of Spaniards may be poor metabolizers of drugs handled by the CYP2C9 enzyme.145 Since the contemporary U.S. Hispanic population has a high frequency of Spanish-derived genes, understanding the metabolic variations in Spaniards may provide clinically relevant insights for Hispanic Americans. This may be especially true if Hispanic Americans also exhibit a significant proportion of poor metabolizers of CYP2C9-mediated drugs in their population.
Ethnic differences in the frequency of gene variations place some individuals at greater risk for adverse effects, especially for drugs with a “narrow therapeutic index.”

Individualized dosing in slow-metabolizer individuals is essential for narrow-therapeutic-index drugs such as warfarin and phenytoin, since small increases in circulating blood levels of these agents can cause life-threatening side effects. For example, even modest overdosing with the anticoagulant warfarin may result in increased incidence of major bleeding events and prolonged hospitalization during the initiation of therapy.127

It is useful to determine whether a patient is likely to be a poor metabolizer, especially when prescribing from a drug class that contains agents metabolized by different enzymes. For example, the statin drug class (used to reduce cholesterol) contains agents metabolized by CYP3A4, CYP2C9, and CYP2C19146 (Table 2). If genetic or other factors suggest a high probability that a patient will be a slow metabolizer of a given drug, other choices from within the class may potentially yield better outcomes.

Research findings on genetic differences in drug metabolism provide some understanding of the pharmacogenetics of Hispanic populations. Additional studies would be useful in fully elucidating the role of genetic factors in drug response differences. However, knowledge of ethnic differences in the frequency of gene variants may offer some general insight into the differences in drug response observed across populations.127 “The patient’s ethnicity...could probably help guide clinicians to prospectively evaluate those patients with the greatest probability of expressing a variant genotype.”127

**Table 2. Statin Agents Associated with Metabolic Pathways Subject to Genetic Variation**146

<table>
<thead>
<tr>
<th>CYP450 Pathway</th>
<th>Statin</th>
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<tbody>
<tr>
<td>CYP2C9</td>
<td>cerivastatin</td>
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<tr>
<td></td>
<td>fluvastatin</td>
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<td>rosuvastatin</td>
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<tr>
<td>CYP2C19</td>
<td>rosuvastatin</td>
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<tr>
<td>CYP3A4</td>
<td>atorvastatin</td>
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<td></td>
<td>lovastatin</td>
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<tr>
<td></td>
<td>simvastatin</td>
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<tr>
<td>Little metabolism</td>
<td>pravastatin</td>
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“**Individualized dosing in slow-metabolizer individuals is essential for narrow-therapeutic-index drugs such as warfarin and phenytoin, since small increases in circulating blood levels of these agents can cause life-threatening side effects.”**
Choice of medications for a given condition must take coexisting conditions into account. As mentioned previously, Hispanic children with asthma are often undertreated with medications. However, treating asthmatic children with coexisting conditions may pose an even greater challenge. Recent findings suggest that children from Puerto Rico with severe asthma may also suffer from anxiety disorders. Thus, it is important to treat both conditions.

Cardiovascular disease often coexists with diabetes and is a leading cause of death and disability in patients with diabetes. Aggressive management of high blood sugar, high blood pressure, or high cholesterol reduces cardiovascular complications in patients with diabetes. Optimal care requires treatment of all three coexisting conditions. But even when diabetes is aggressively managed, coexisting high blood pressure and high cholesterol may not be.

The presence of heart disease should also be taken into account in the choice of drugs for the treatment of diabetes. For example, the diabetes drug metformin is contraindicated for patients with chronic heart failure. Similarly, the thiazolidinedione class of diabetes agents should be avoided in cases of severe heart failure and used with caution in less severe cases.

Coexisting conditions may also complicate treatment of psychosis. Choice of an antipsychotic agent must consider coexisting obesity, diabetes, or an individual’s potential for developing these conditions. Newer agents, termed atypical antipsychotics, have demonstrated greater efficacy than previously used drugs in treating schizophrenia, bipolar disorder, and other mental illnesses, and are generally favored for their reduced risk of side effects. However, this drug class has also been associated with a higher risk for hyperglycemia and diabetes. According to the FDA, the comparative risk for diabetes among users of atypical antipsychotic agents needs further research. Caution should be used in prescribing these agents for patients in Hispanic and other ethnic groups at risk for diabetes. It may be particularly important when such at-risk patients are in need of antipsychotic therapy that their physician consider the diabetogenic potential of the antipsychotic when choosing among these vital medicines.

Depression frequently coexists with other chronic illnesses such as diabetes and chronic obstructive pulmonary disease that are common in Hispanics and are frequently undertreated. Depressive symptoms can begin in childhood for individuals with diabetes or asthma. One study found that 39% of Mexican children and adolescents with asthma had depressive symptoms.

Death rates in older Mexican Americans were substantially higher when a high level of depressive symptoms coexisted with diabetes, cardiovascular disease, hypertension, stroke, or cancer. Coexistence of depression and diabetes is particularly common in older Mexican Americans. Depression was present in 31% of older Mexican Americans with diabetes, which is higher than the rate found in Hispanics without diabetes. The health risks associated with the presence of both diseases may be greater than the effects of either single condition, since depression has been associated with poor blood glucose control and inadequate treatment adherence. A synergistic effect has been found for coexisting depression and diabetes in older Mexican Americans; the odds of dying in those with high levels of depressive symptoms were threefold that of those without high levels of depressive symptoms. Recognition of diabetes in depressed individuals is essential for effective management of depression, and better control of glucose can improve mood and well being.

Depression is especially problematic in patients with serious cardiovascular disease. Depression affects at least 30% of hospitalized patients with coronary artery disease, is associated with increased mortality, and is underrecognized and undertreated in many cardiac patients. This lack of diagnosis and treatment for depression is of primary importance because depression is a major risk factor in the development of coronary artery disease and in death after heart attack. Patients with depression are more likely to develop ischemic heart disease and suffer cardiac-related death than those who are not depressed.

The use of older antidepressants such as monoamine oxidase inhibitors or tricyclics in these patients is not advisable because these agents have been associated with cardiovascular disorders due to their arrhythmogenic effects and their tendency to reduce blood pressure. The newer SSRI antidepressant medications have fewer cardiovascular side effects and appear to be safer in the treatment of depression in cardiac patients.
Improving patient-provider communication is central to addressing disparities in pharmaceutical therapy for Hispanic communities. A Commonwealth Fund survey found that regardless of language ability, insurance status, educational level, and economic status, Hispanics were substantially more likely than whites and African Americans to have difficulty fully understanding prescription instructions (Figure 11). When language barriers exist, interpreters can help persons with low English-proficiency understand prescription instructions. Twenty-seven percent of hospital patients who stated that they needed but were not provided an interpreter reported leaving the hospital without understanding how to take their medications, compared with 2% of those with an interpreter. Although Title VI federal civil rights requirements mandate access to translation services for limited English-proficient persons, only half of persons who need an interpreter during health visits report receiving such services. Reduced access to medication counseling and written information at the pharmacy by older Hispanic patients with poor English language skills has been reported. Such patients may not understand instructions about how often to take medication, whether it should be taken with food, how long it should be continued, what to do if a dose is missed, or the nature of side effects. Lack of explanation of side effects decreases compliance with medication and satisfaction with care. Among Spanish-speaking patients, those with good English skills reported more frequently that the side effects of medications were explained to them compared with those with limited English proficiency. Among adult Hispanics with asthma who spoke only Spanish, there was a greater likelihood of missed follow-up appointments and nonadherence to medications among those whose physicians spoke only English compared to those with bilingual physicians. This is of particular concern since, according to the 2000 U.S. Census, an estimated 8 million Hispanics speak English “not well” or “not at all.”

Self-management/health literacy was identified in the IOM report Priority Areas for National Action: Transforming Health Care Quality as one of 20 important areas to focus on to improve health care quality and delivery. The IOM recommends that public and private entities provide educational programs and interventions that increase patients’ skills and confidence in managing and assessing their health problems. With a higher level of health literacy, more patients would have the skills to read, understand, and act on health care information.
The Commonwealth Fund survey\textsuperscript{174} found that 33\% of all Hispanics and 43\% of those Hispanics speaking primarily Spanish at home reported having a problem understanding or communicating with their doctor versus 16\% of non-Hispanic whites (Figure 12). The Commonwealth Fund survey\textsuperscript{174} also found that compared with non-Hispanic whites, Hispanics reported less confidence in their doctor and were less satisfied overall with their health care. One way to boost patients’ confidence in their physicians is to improve cultural proficiency among doctors. A key factor in improving the quality of care is to inform providers who care for Hispanic patients so that they become familiar with sociocultural beliefs that may affect prescribed treatment regimens. Increased cultural proficiency among practitioners may help to reduce patient dissatisfaction with treatment and increase compliance.\textsuperscript{175}

Additionally, health educational materials intended to answer questions about medications and side effects are frequently written at an inappropriate reading level, especially for patients for whom English is a second language. Problems may also be complicated by the fact that patients often conceal their inability to understand a physician.\textsuperscript{176}

Inadequate patient-provider communication compounds the overall threat to health from chronic diseases like diabetes and asthma that are common in Hispanics because treatment relies on a high level of self-management. Access to understandable printed instructions is important to a successful self-management program, but such materials often are poorly written because of a lack of cultural proficiency among providers and the health care delivery system.

Such communication challenges have also been documented to have a negative impact on patients’ ability to take medications properly.\textsuperscript{177,178} One example is that, compared with those with sufficient health literacy, diabetes patients with inadequate health literacy had poorer control of their blood sugar levels and higher rates of retina damage, which may progress to blindness if left untreated.\textsuperscript{177} Another example is the relatively poor technique exhibited by asthma patients with low health literacy when using a metered-dose inhaler.\textsuperscript{180} The importance of communication and cultural barriers is also suggested by the finding of inadequate pharmaceutical therapy in Spanish-speaking children with asthma.\textsuperscript{181}

In moving toward better patient-provider communication, cultural proficiency of the health care system, and improved pharmaceutical therapy, it is important to understand the role of normative cultural values in health and health communication. Normative cultural values are the beliefs, ideas, and behaviors that a particular cultural group finds important and expects in interpersonal interactions. Such values, as well as beliefs regarding the properties and effects of medications, may influence a patient’s adherence to a particular drug therapy, and thus the effectiveness of treatment.

While today’s health care professionals work within the structures of conventional medicine to provide separate physical and mental health care, Hispanic culture tends to view health from a more synergistic point of view. This view is expressed as the continuum of body, mind, and espíritu (spirit). Combining respect for the benefits of mainstream medicine, tradition, and traditional healing, along with a strong religious component from their daily lives, Hispanic patients may bring a broad definition of health to the clinical or diagnostic setting. Respecting and understanding this view can prove beneficial for all health care professionals in treating and communicating with patients.

\textit{“Increased cultural proficiency among practitioners may help to reduce patient dissatisfaction with treatment and increase compliance.”}

Patients’ beliefs regarding the properties and effects of medications are of central importance in determining compliance with treatment regimens. Variations in attitudes toward medicines may be driven by culture and philosophy.\textsuperscript{182} For example, although Hispanic patients are generally disinclined to receive intramuscular injections, Haitians regard injections as powerful weapons against external threats to the mind or body.\textsuperscript{183}

Hispanics have been reported to differ from other ethnic groups in their presentation of symptoms of psychiatric illness and in their preferences and attitudes toward medications for these conditions. Hispanics with mental illness tend to describe their emotional problems in language that emphasizes body complaints.\textsuperscript{184,185} Hispanics with depression were less likely to find antidepressant medications acceptable and more likely to find counseling acceptable than whites.\textsuperscript{186} Also, Hispanic patients are relatively more sensitive to the physical effects of psychiatric drugs\textsuperscript{55,120,128,187} and may therefore require lower doses to prevent discontinuation of therapy as a result of side effects.\textsuperscript{54,55}
Indigenous health beliefs and practices may continue, even after exposure to modern Western medicine. Hispanics often expect rapid relief from symptoms and are cautious about the side effects of modern medicines. In addition, concerns about addictive and toxic effects of drugs have often been seen in Mexican and Puerto Rican patients. These beliefs may interfere with the acceptance of drugs with a delayed onset of action (e.g., antidepressants, anti-inflammatory medications for asthma) or compliance with medications that must be taken over a long period of time. While it is important that health care professionals respect patients’ cultural beliefs, it is equally important to be alert for misinformation or gaps in information tied to these beliefs. Such gaps in information are part of all cultural beliefs and practices. For instance, while a patient may assume that seeing an alternative medicine practitioner or using an herbal remedy is independent of other medical treatment, it is crucial that the patient tell the physician in order to prevent treatment interactions, unpredictable effects, and treatment duplication.

It is important to note that, according to the National Center for Complementary and Alternative Medicine, the use of alternative therapies is as common among Hispanics as in the general population. However, according to a Commonwealth Fund survey, it is less common for Hispanics to notify their doctor that they are using alternative therapies than it is for non-Hispanic whites (50% vs. 70%). For all groups, awareness of interaction between prescribed and alternative therapies is vital to quality care.

The following examples illustrate the complex influence of Hispanic health beliefs and practices on the use of medicines:

- Working class immigrants often place importance on folk religion and healing rituals. Patients who perceive a negative response to these rituals from the physician may view it as a direct assault on their beliefs or religion. For example, a study of newly arrived Caribbean immigrants in East Harlem reported they may favor folk medicine—the type of health care familiar to them in the rural areas of their homeland—because they believe that medicine prescribed by a U.S. health care provider is made of harmful chemicals and is therefore toxic.

- A study examining the use of folk healing and healers by Hispanics from Colombia, the Dominican Republic, and Guatemala living in New England noted they limited their use of conventional health care providers because of a perceived lack of holistic care and use of medicines that are not natural. Family nurse practitioners working with Mexican Americans report that some of their clients use folk healing in conjunction with modern medicine.

- Recent immigrants may have access to controlled substances and other medications not generally available in the United States. For example, antibiotic, neuroleptic, anti-emetic, and most other prescription drugs are easily obtained over the counter in Brazilian pharmacies, and many pain-relieving medicines are available without a prescription.

- An evaluation of the use of alternative preparations in the El Paso, Texas, region identified 599 instances of use of such remedies that could counteract prescribed pharmaceuticals, based on interviews with 547 survey participants.

- A survey of Spanish-speaking Hispanic families visiting a pediatric clinic in Salt Lake City found that 35% reported using a nonsteroidal anti-inflammatory drug (metamizole) associated with a blood disorder side effect. The drug is available over the counter in Latin American countries and in markets serving immigrant communities in the United States.
A lack of understanding about the nature of chronic disease and how it differs from acute illness also represents a barrier for effective management of chronic illness among Hispanics. One study of older individuals found Hispanics saw their role in managing illness as taking medication, and the word “chronic” was not well understood. They acknowledged that they must take medication, but believed they were cured when symptoms disappeared. The recurrence or worsening of symptoms, especially in diseases with multiple symptoms, was seen as a new illness rather than the re-emergence of the same underlying disease. The reluctance reported in some studies of Mexican and Puerto Rican patients to take medicine indefinitely due to concerns about toxicity and addiction may also impede effective management of chronic disease.

Helping people to fully understand prescribed treatment regimens and to participate as informed partners in their health are hallmarks of the good practices health care professionals strive to achieve. Unfortunately, practitioners face many obstacles to delivering this level of care. Some of these obstacles involve cultural misunderstandings and miscommunications with patients whose languages, experiences, and backgrounds are different from those of providers. Since low health literacy also prevents ethnic minority patients from receiving quality care, patient education materials designed for Hispanics should match their health literacy levels.

Greater diversity in the health professions will strengthen the patient-provider relationship and improve cross-cultural communication. Perhaps nowhere are cultural differences more apparent than in approaches to and definitions of health. By deepening understanding of culture and implementing systematic changes, the promise of high-quality health care that is accessible, effective, and cost-efficient for all can be strengthened.

Minority patients may forge stronger bonds with providers who are able to bridge cultural and linguistic gaps. Patients and providers belonging to the same ethnic group are more likely to share similar cultural beliefs and values, allowing them to communicate effectively. As a result, patients may feel they are more involved in decisions affecting their care and are more likely to be satisfied with the technical and interpersonal aspects of their care.

In order to improve health care delivery for diverse populations, the Institute of Medicine has recommended increasing the proportion of underrepresented ethnic minorities among health professionals and increasing professional education in issues of culture and quality health care delivery. Consequently, hospitals, managed care groups, and other providers of health care services for Hispanic populations should endeavor to employ Hispanic practitioners and provide adequate cultural proficiency training for all providers.

"Greater diversity in the health professions will strengthen the patient-provider relationship and improve cross-cultural communication."

Disease management programs strive to integrate care for patients with chronic illnesses so that better outcomes may be achieved while overall costs are managed. These programs have been growing in popularity, and some academic medical centers are incorporating disease management into their graduate medical training. Many state Medicaid agencies are implementing comprehensive disease management programs covering multiple chronic diseases as well as developing programs for elderly patients with comorbidities. Since Medicaid covers 16% of non-elderly Hispanics and 30% of elderly Hispanics, medical training in disease management must continue to be emphasized, and should incorporate an understanding of differences in pharmaceutical response by Hispanic individuals due to genetic, cultural, or environmental factors, or to coexisting diseases common in Hispanics.
CONCLUSIONS AND RECOMMENDATIONS

The emerging findings described in this report indicate complex relationships among culture, environment, population genetics, drug metabolism, and drug response. Hispanics differ among themselves and from other ethnic groups in clinical response to drugs, rates of drug metabolism, and drug side effects. These findings underscore the need for individualized prescribing for Hispanic populations that accounts for environmental, biologic, and cultural factors that may impact a drug’s effectiveness and patient compliance with prescribed treatment regimens.

The Hispanic population represents one in seven persons in the U.S. Yet, little systematic research examining the pharmacological response of Hispanics currently exists. The Hispanic response to specific drugs used to treat common chronic conditions (asthma, diabetes, and cardiovascular disease) is not well understood. For example, although the differences between African Americans and Caucasians in the effect of drugs used to lower blood pressure are well studied, little is known about the response of Hispanics to these agents compared with other ethnic groups. Moreover, genetic and cultural variation in drug response exists not only between Hispanics and other ethnic groups, but also within Hispanic subgroups. As a result, it is often difficult to characterize a uniform “Hispanic” response.

Cost containment trends may exacerbate existing pharmaceutical disparities faced by Hispanics. These trends in both the public and private health care sectors have led to the development of pharmacy benefit packages that limit selection of pharmaceutical agents. In their review, The Hispanic Response to Psychotropic Medications, Mendoza and Smith urge physicians to resist this trend and support prescribing practices that serve the clinical needs of Hispanic patients:

“More traditional and older-generation antipsychotics and antidepressants may be preferred because of their reduced per-pill costs. Such clinically irrational influences can adversely affect prescribing practices and may have long-term consequences in the form of suboptimal or negative outcomes. Physicians must remain staunch advocates for their patients and secure approval…for a drug selection that is guided by clinical indicators and not by a one-size-fits-all formulary.”

The design of pharmaceutical benefit management policies must be broad enough to allow appropriate care that considers the specific needs of Hispanic populations. Such policies must also consider any possible discriminatory effects and not contribute to existing disparities in pharmaceutical treatment.

Additionally, patients with low health literacy or language barriers may be ill-equipped to understand the limitations of restrictive policies and the appeals processes necessary to obtain a more appropriate drug. Even enrolling in public insurance programs that include drug coverage may be difficult for many Hispanics. For example, one survey found that 46% of Spanish-speaking parents were unsuccessful at enrolling their children in Medicaid because the forms were unavailable in Spanish.

While this report demonstrates Hispanic biological and cultural variation in drug response, it is important that these findings not be over-interpreted. Stereotypical interpretations may be misleading, as substantial variability often exists within individuals of any group. Ethnicity is an imprecise marker for genetic differences among populations and should only be used to alert providers to alternate medications or dosages that may be warranted for a patient or an increased likelihood of side effects. Eventually, it will be possible to determine the genetic profile of individuals and base prescribing on this information.
The success of any pharmacotherapy is dependent on the quality of the interaction between patients and providers. Both parties bring their own expectations, beliefs, and values to the clinical encounter that affect the choice of therapeutic intervention and compliance. A greater understanding of the cultural, genetic, and environmental factors that may contribute to the disparity in treatment of disease in Hispanic populations is consistent with the national goal set by the federal Healthy People 2010 initiative to reduce health disparities among different population groups.

The following recommendations address the goal of eliminating health disparities and would improve the quality of pharmaceutical care for Hispanic Americans:

1. **Improve access to pharmaceutical therapy.** Health care financing and reimbursement practices should be broad and flexible enough to enable rational choices of drugs, dosages and formulations for Hispanic patients based on their genetic, medical, and cultural needs. Choice of the best pharmaceutical therapy should be between patient and provider.

2. **Prescribe based on individual needs.** Hispanic populations require prescribing that considers the many biological, environmental and cultural factors that can influence drug effectiveness and patient adherence to treatment regimens.

3. **Treat coexisting conditions.** Standards of quality for pharmaceutical treatment of Hispanics must account for coexisting conditions common in this population, including depression paired with asthma, diabetes or cardiovascular disease, or diabetes paired with cardiovascular disease.

4. **Meet quality standards of cultural proficiency and communication.** Communication barriers and cultural differences between health care providers and Hispanic patients can reduce treatment adherence and compromise overall disease management. Implementation of existing federal and professional accreditation standards for cultural and linguistic proficiency is a priority, including improved access to medical interpreters, cultural proficiency education for providers, and consumer information on securing culturally proficient care.

For the Hispanic community, the promise of pharmaceutical therapy is compromised by a lack of access to advances in medicines. While Hispanic individuals are more likely than the population in general to suffer from a number of chronic illnesses, they are less likely to receive the very medications that can help manage these conditions.

A quality health system must understand and account for how access, genetics, and culture affect the delivery of medical care, and pharmaceutical care specifically, to Hispanic populations. Prescribing should be tailored to individual patient needs based on age, coexisting conditions, responsiveness to medications, and cultural perceptions of disease and treatment. The choice of medications available must accommodate this range of factors. Individualized prescribing and access to the most appropriate medications will reduce medical errors, save costs associated with untreated illness, and secure the promise of advances in pharmaceutical therapy for all.
REFERENCES


