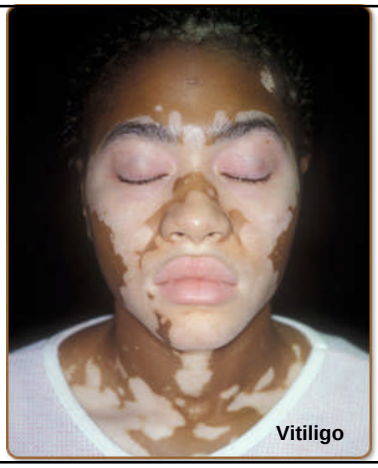
Benjamin Rush

- "Father of American Psychiatry"
  - Fascinated by the case of Henry Moss
    - Reputedly lost his dark skin color
  - Rush published a note in 1799
    - Moss's condition prompted Rush to propose leprosy as "the cause of the Black Color (as it is called) of the Negroes."
    - Suggested that the only way Moss could turn white was by being completely cured of leprosy



Vitiligo

Samuel A. Cartwright

- Prominent Louisiana physician
  - 1851 published "Report on the diseases and physical peculiarities of the Negro race"
    - Cartwright claimed to discover two mental diseases peculiar to blacks, which he believed justified their enslavement
      - **Drapetomania** from *drapetes,* a runaway slave, and mania, meaning mad or crazy
        - » This disease caused blacks to have an uncontrollable urge to run away from their masters
        - » The treatment for this illness was whipping the devil out of them
      - **Dysaesthesia Aethiopis** affected mind and body
        - » The signs included disobedience, answering disrespectfully and refusing to work
        - » The cure was to put the person to some kind of hard labor which apparently sent vitalized blood to the brain to give liberty to the mind
        - » If that didn't work, you whip the devil out of him

Dr. J. F. Miller

- Superintendent Eastern Hospital, Goldsboro, NC
  - Emancipation as the cause of health problems

"From close personal observation, embracing a professional life of nearly forty years among the Negroes and from data obtained from professional brethren in different sections of the South, I have no hesitancy in declaring that **insanity and tuberculosis were rare diseases among the Negroes of the South prior to emancipation**. Indeed, many intelligent people of observation and full acquaintance of the Negro have stated to me that they never saw a crazy or consumptive Negro of unmixed blood until these latter years."

(1896, The Effects of Emancipation upon the Mental and Physical Health of the Negro)

Frederick Hoffman

- Prudential Life Insurance statistician
  - 1896, Race Traits and Tendencies
    - The conditions of life therefore . . . would seem to be of ***less importance than race and heredity***.
    - It is not the conditions of life but in ***the race traits*** and tendencies that we find the causes of the excessive mortality.
    - For the root of the evil lies in the fact of an immense amount of ***immorality, which is a race trait***.
    - A combination of these traits and tendencies must in the end cause the ***extinction of the race***.

Frederick Hoffman

- The mixture of the African with the white race has been shown to have seriously affected the longevity of the former and left as a heritage to future generations the poison of scrofula, tuberculosis, and most of all, of syphilis
- The vitality of the Negro may well be considered the most important phase of the so-called race problem, for it is a fact which can and will be demonstrated by indisputable evidence that of all races for which statistics are obtainable and which enter at all into the consideration of economic problems as factors **the Negro shows the least power of resistance in the struggle for life**.

Sickle Cell Anemia

- 1910: James B. Herrick finds "peculiar, elongated and sickle-shaped red blood corpuscles" in the blood of a black patient with symptoms of severe anemia.
- 1917: Victor Emmel (anatomist, University of Washington) publishes his paper on an "experimental technique" to observe the sickling of red blood cells.
  - Technique used to diagnose a "potential disease", a latent disorder that – like tuberculosis – may or may not turn virulent.

Sickle Cell History

- 1922: Verne Mason uses Emmel's technique to undertake a survey among black and white Americans
  - Coins the term sickle cell anemia focusing on the shape of the red blood cells in his 1922 article in the Journal of the American Medical Association
  - Emphasizes the racial nature of the disease (only three cases had been identified, all in African Americans) in claiming it is congenital or hereditary

Sickle Cell History

- 1923: John Huck studies its inheritance patterns in one black family and concludes sickle cell is:
  - a hereditary condition
  - occurs only in blacks and
  - is passed on according to Mendelian laws
    - as a single, **DOMINANT**, Mendelian character
    - The assumption of dominance means an imminent threat not only to African Americans but also to white populations in cases of intermarriage
    - This seems to be supported by occasional observations of sickle cell trait in whites

Sickle Cell

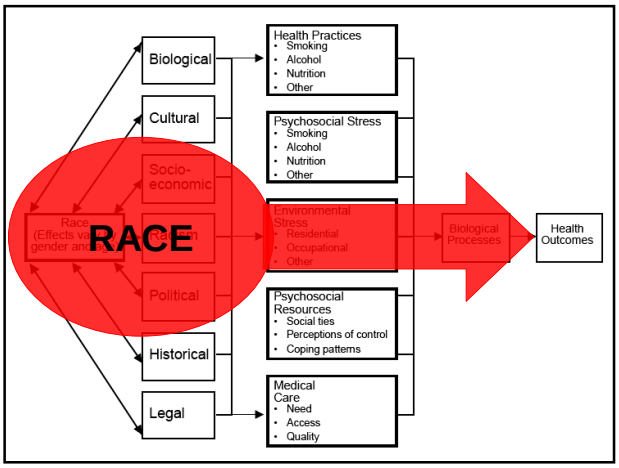
- 1947 editorial in JAMA declares race to be "a strong etiological factor" in sickle cell; "the role of other factors is not clear"
  - Black Americans are perceived as "disease vectors"
  - Sickle Cell disease is used to explain backwardness and perceived laziness in Blacks
- Set the scene for the early 1950s findings of relationship to malaria

Medical History

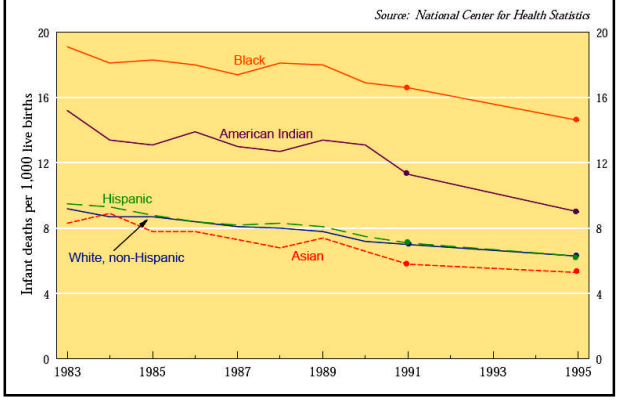
- Three key descriptors to start any patient record: "Patient is a 47 y.o. White female.
  - Age
  - Race
  - Sex
- These form the mind set of the doctor trying to diagnose the patient
  - By pigeon-holing, limits the universe of diagnoses
  - However, the race designator, in particular, can be dangerous

Biomedicine

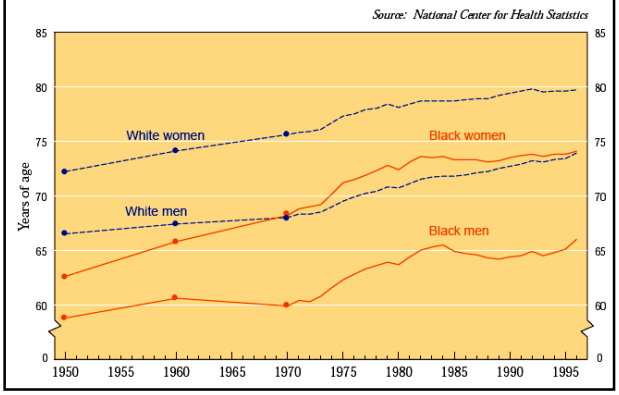
- Two General Approaches
  - Race is a good proxy for the **genetic makeup** of an individual
    - As such, it is a good predictor of genetic predisposition toward health and disease
    - **Biological fallacy as we have seen**
  - Race is a **social construct** that affects health primarily through social, not genetic, pathways
    - As such, it can be a good predictor of health when viewed in the context of other social aspects of the patients identity
    - **Not the whole picture—income, education, occupation, etc. do not capture cultural effects including racism!**



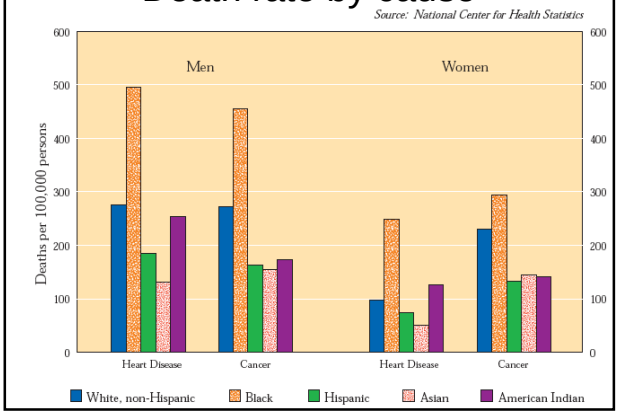
Infant Mortality

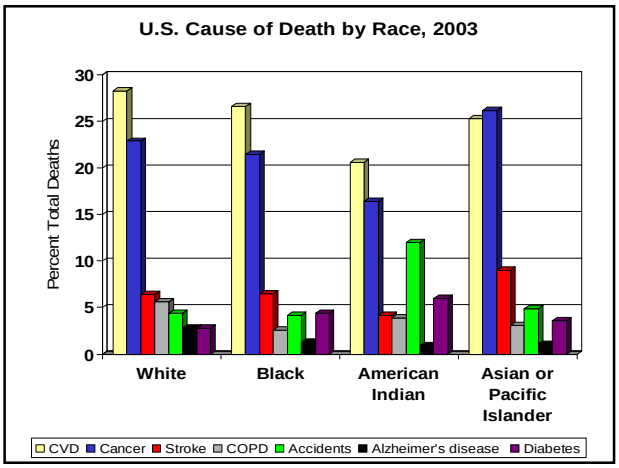


Life Expectancy



Death rate by cause





NEJM, March 2003

- Editorial comment:
  - It is because of the potential usefulness of gene variants in predicting risk and targeting therapies that the quest for genes that underlie complex traits continues. The goal of personalized medicine is the prediction of risk and the treatment of disease on the basis of a person's genetic profile - which would render biologic consideration of race obsolete. But **it seems unwise to abandon the practice of recording race** when we have barely begun to understand the architecture of the human genome and its implications for new strategies for the identification of gene variants that protect against, or confer susceptibility to, common diseases and modify the effects of drugs.

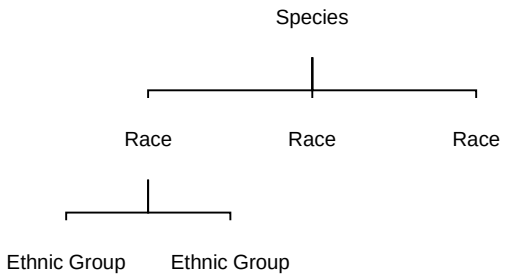
NEJM, March 2003

- Burchard et al.: Race--Yes
  - Definitions of race and ethnic background have often been applied inconsistently. The classification scheme used in the 2000 U.S. Census, which is often used in biomedical research, includes five major groups: ***black or African American, white, Asian, native Hawaiian or other Pacific Islander, and American Indian or Alaska native***
  - In general, this classification scheme emphasizes the geographic region of origin of a person's ancestry

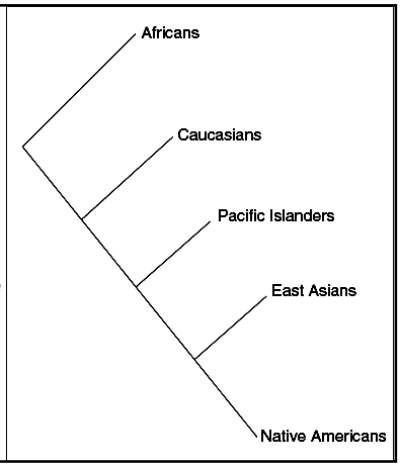
NEJM, March 2003

- Ethnic background is a broader construct that takes into consideration cultural tradition, common history, religion, and often a shared genetic heritage
- ***The past two decades of research in population genetics has also shown that the greatest genetic differentiation in the human population occurs between continentally separated groups***

Burchard's taxonomic use of race and ethnicity



Burchard et al.'s categorization of humans in biomedical research: genes, race, and disease



NEJM, March 2003

- There are ***racial and ethnic*** differences in the causes, expression, and prevalence of various diseases. The relative importance of bias, culture, socioeconomic status, access to care, and environmental and genetic influences on the development of disease is an empirical question that, in most cases, remains unanswered

NEJM, March 2003

- Although there are potential social costs associated with linking race or ethnic background with genetics, we believe that these potential costs are outweighed by the benefits in terms of diagnosis and research
- ***Ignoring racial and ethnic differences in medicine and biomedical research will not make them disappear***

Cooper et al.: Race--No

NEJM, March 2003

- Although we acknowledge the salience of these arguments, ***the value of continental race as a classification scheme must be questioned*** in this context much as it was in the context of genetics
- For example, persons who could be classified as having "African ancestry" have wide variation in rates of hypertension and diabetes, as do all large continental populations

Cooper et al.: Race--No

NEJM, March 2003

- Without the context provided by such variables as the level of education, occupation, type of diet, and place of residence, ***race as a social category is not a useful predictor of health outcomes***
- Just as most genetic heterogeneity occurs within populations, there is enormous variation in the patterns of culture-derived behavioral and risk factors
- ***An unintended result of categorizing people according to race can be to foreclose the question of why they have ill health, leaving us blind to the meaning of the more relevant local and individual context***

2004 Editorial in *Clinical Investigations in Medicine*

- ***Genetic information can be used to distinguish the ancestry of human groups, but such groupings do not correspond well with traditional descriptions of race***
- Dividing people according to genetic information rather than according to race may add information on the incidence of disease and the response to drugs within the groups
- ***In the end, race simply cannot be used as a surrogate for genetic constitution***
- ***If you need to know whether a patient has a particular genotype, you will have to do the test to find out***

So they tried

- Hinds et al., 2005. Science, 307:1072-1079.
  - They genotyped 1,586,383 single-nucleotide polymorphisms (SNPs) in 71 Americans of European, African, and Asian ancestry
  - Found that these SNPs capture most common genetic variation
  - The distributions of allele frequencies are very similar for the European-American and Chinese samples, with a higher frequency of rarer alleles in the African-American sample
  - The greatest genetic diversity was found in individuals of African descent
  - **Conclusion:** It is difficult to make more definitive statements regarding the precise distribution of SNP allele frequencies in different populations
  - **Results are that most functional human genetic variation is not race-specific**
    - That is, you can't just look at someone and tell what alleles they have

BiDil

Race Medicine

Or

Race Marketing?

"Do a double-blind test. Give the new drug to rich patients and a placebo to the poor. No sense getting their hopes up. They couldn't afford it even if it works."

A Race Specific Drug

- On June 23, 2005 the U.S. Food and Drug Administration (FDA) granted formal approval to BiDil as a race-specific drug to treat heart failure
  - BiDil is a heart medication supposedly developed for African Americans and the first drug to be based on a patent formulated in terms of its benefit to a specific racial or ethnic group
  - In announcing the approval, Robert Temple, FDA associate director of medical policy, declared that BiDil "is a striking example of how a treatment can benefit some patients even if it does not help others"

How did we get here?

- The 1980s saw the beginning of a revolution in the treatment of heart failure
  - Two cooperative studies administered through the Veterans Administration (VA) led to important breakthroughs in heart failure treatment
  - The first of these, the Vasodilator Heart Failure Trial (V-HeFT I) found that a combination of two generic vasodilators (hydralazine and isosorbide dinitrate [H/I]) seemed to have a beneficial effect in treating heart failure
    - H/I would later be combined into a single pill to form BiDil (Two Dilators)

How did we get here?

- A second VA study, found that an angiotensin-converting enzyme (ACE) inhibitor was even more effective in treating heart failure than H/I
  - Angiotensin is a powerful vasoconstrictor and ACE inhibitors work by blocking the enzymatic conversion of its precursor into its active form
- At this point, ACE inhibitors became the treatment of choice for heart failure for all patients

The BiDil Patent

- In 1987, Jay Cohn, the lead cardiologist on the V-HeFT studies, submitted a "methods" patent on using the H/I combination to treat heart failure
  - ***Cohn could not get a combination of matter patent because the combined form of these two generic drugs did not act differently than using each separately***
  - A methods patent gives the holder a monopoly on marketing the combination for a particular purpose, in this case treating heart failure
    - But the patent holder couldn't prevent generic manufacturers from producing and selling the individual drugs

Medco Gets Involved

- The 1987 methods patent, which expired in 2007, was not race-specific
  - It claimed that H/I was appropriate as a therapy to treat heart failure for anyone
    - ***No mention was made of race***
  - Cohn licensed the patent to Medco, a North Carolina pharmaceutical company
    - They proceeded to conduct studies on BiDil and prepared a new drug application (NDA) to the FDA to get approval for marketing BiDil as a method to treat heart failure
    - ***Again the NDA for BiDil was <u>not race-specific</u>***

Rejecting the NDA

- In 1997 the FDA rejected Medco's NDA for BiDil
  - The FDA advisory committee stated that BiDil was clinically efficacious, but…
    - Medco's drug trial statistics were too sloppy to meet the FDA's criteria for new drug approval
    - The V-HeFT trials were designed as test of theory trials, not as new drug trials
- After the FDA rejection, BiDil seemed dead in the water
  - Medco let the intellectual property rights revert to Cohn
    - At this point Cohn and a cardiologist with whom he collaborated, Carson, went back to the fifteen-year-old V-HeFT data and analyzed them by race
    - Cohn had mentioned to the FDA advisory committee that he had data available by race but he didn't think them relevant
    - ***Race apparently became relevant only when it offered a way to improve the viability of BiDil***

Race Becomes An Issue

- 1999 Carson and Cohn published a paper showing significant racial differences in response to H/I
  - Based on the forty-nine African American subjects placed on H/I in V-HeFT
    - The same month that this article appeared, Cohn relicensed the intellectual property rights for BiDil, this time to NitroMed, a Massachusetts biotechnology company specializing in nitric oxide-based therapies
    - The following year Cohn and Carson jointly applied for a race-specific methods patent to use H/I to treat heart failure in an African-American patient
  - In 2001 the FDA told NitroMed that BiDil could be approved as a race-specific drug
    - Required a confirmatory trial in African American subjects

Money is a Bigger Issue

- NitroMed was able to raise more than $34 million in private venture capital financing at a difficult financial time
  - This was shortly after the internet bubble burst and the stock market tanked
  - The bulk of the money was to be used to conduct a confirmatory trial
    - A-HeFT (African-American Heart Failure Trial)
    - In November 2003, with A-HeFT under way, NitroMed went public with an offering of six million shares and raised approximately $66 million

A-HeFT

- 1,000 African American subjects with heart failure
  - ***Subjects remained on their current heart medication*** and then were randomized to receive, in addition, either a placebo or BiDil
    - The outcome was a score that combined death ***from any cause***, a first hospitalization, and change in quality of life
  - A-HeFT was supposed to run until 2005 but was terminated in July 2004
    - The researchers declared its benefits were so substantial that continuing some subjects on placebo was unethical
    - Subjects taking BiDil experienced a 43% reduction in rate of death from any cause and a 33% reduction in first hospitalization resulting from heart failure

Mo' Money

- In the week following the announcement of the early suspension of A-HeFT, NitroMed stock more than tripled in value
- In November 2004, when details of the study were released, the stock once again soared
- A month later, after announcing an amended NDA to the FDA, NitroMed had a secondary public offering raising nearly $80 million to fund the BiDil launch
- While expecting FDA approval, ***NitroMed hired an advertising agency known for its work selling beer and cars***, to handle the PR effort

And Mo' Money

- The revised BiDil patent based on treating African Americans gives the company marketing rights until ***2020***
  - Well beyond the 2007 expiration of the methods patent
  - By testing BiDil in doses that are not available for its generic components (hydralazine and isosorbide dinitrate), NitroMed discouraged doctors from easily devising ways for patients to get the same benefits from the much cheaper generics
    - The components are available in both lower and higher doses, but not the exact same doses as in the trial
  - NitroMed's race-specific methods patent also ***prevents insurers from recommending to doctors that they use generic substitutes to save money***

The FDA changes its mind

- Between the FDA 1997 rejection of the first NDA and its 2001 response to the amended one
  - There were no new studies showing BiDil's efficacy
    - There were three reanalyses of the old V-HeFT data and of data from another large cardiac study (Studies of Left Ventricular Dysfunction, or SOLVD)
    - Each of these studies included Cohn or Carson as authors.
  - These reanalyses claimed to identify racial differences in heart failure rates and drug response
    - There were problems with the claims in the articles
      - As part of the background, an article on the SOLVD trials incorrectly stated that overall mortality from heart failure was approximately twice as high for Blacks as for Whites
    - ***This double mortality figure formed a large part of the rationale for looking into race-specific drugs***

Problems with the Race Claims

- ***The best available data show the mortality differential from HF between Blacks and Whites is approximately 1.08 to 1 (non-significant)***
  - The 2 to 1 claim is simply wrong and never should have gotten through peer-review
- The study that claimed Black/White differences in response to H/I was based on a post hoc retrospective analysis of fifteen year-old data on 49 African American subjects
  - The sample was not matched for age and socioeconomic factors to test race effects and it was not a drug trial that was designed to demonstrate such differences
- The study of differential response to ACE inhibitors found no "racial" difference in ***mortality***, only in rates of ***hospitalization***
  - ***Claims about racially tailoring drug therapy for heart failure was later repudiated by one of the coauthors***

How did it play in the Press?

- Lay press coverage of A-HeFT tended to obscure important information
  - Some suggested that A-HeFT proved the efficacy of a new drug combo (which it wasn't—remember H/I?)
  - Some implied that BiDil alone, rather than BiDil in conjunction with the standard therapies the patients remained on, produced the trial's dramatic results
  - Fuller accounts document that BiDil's efficacy was established twenty years before by the V-HeFT I trial
    - Not as a substitute for, but as a complement to, standard therapy
  - Some BiDil proponents dismiss the press misstatements as insignificant
    - Maintaining that A-HeFT's dramatic success was in proving that BiDil works better for Blacks than Whites
  - ***The problem is, A-HeFT established no such thing, as even its lead investigators admit***

Black vs. White

- ***A-HeFT did not compare Blacks to Whites***
  - It enrolled only Blacks
  - It demonstrated that (Black) subjects given BiDil, along with their standard heart medication, did better than (Black) subjects given a placebo along with their standard heart medication
  - A study of any group of heart patients (you think up the categories) might have come up with the same finding
- Whether H/I helps heart patients in conjunction with standard medical treatment was not a question
  - That was established 20 years earlier in V-HeFT I

So what did A-HeFT show?

- The goal of A-HeFT was not to prove that H/I was effective
  - It was to prove BiDil's efficacy in such a way that patent law could protect it and an NDA could succeed and the drug company could make big bucks
- A study could have been conducted in a racially diverse population using the generic drugs (H/I), which might have resulted in the broader availability of a good, lower-cost medication
  - It might even have shown that the drugs worked better in one group than in another—for whatever reasons
- In the absence of a potential for substantial profit, NitroMed wasn't interested in doing such a study
  - Such a study likely would have confirmed that BiDil worked
    - ***But it would have risked showing that BiDil worked for everyone, not just blacks***
      - ***Negating the basis for the NDA and of NitroMed's race-specific patent***

The Great Irony

- NitroMed admits that BiDil might work in people who aren't African American
  - Many A-HeFT investigators hope that the drug is prescribed to anyone who might benefit from it, ***regardless of race***
    - NitroMed is OK with this contradiction as long as the FDA approval is race-specific
  - With the FDA approval based on race, only NitroMed can publicly market it as a therapy for heart failure
    - Generic manufacturers can sell hydralazine and isosorbide dinitrate (H/I) separately
      - But they cannot advertise them as treatments for heart failure for 3 years (an FDA "market exclusivity" issue)
    - ***After 3 years, NitroMed's race-specific patent will still prevent anyone else from marketing the generic drugs as a "method" to treat heart failure in African Americans until 2020***

Summary of BiDil

- The claim that HF mortality is 2 times greater in Blacks is wrong
- The claim that ACE inhibitors don't work as well to prevent HF mortality in Blacks is not true
  - Hospitalization rates differed, mortality was never analyzed
- The reanalyses of V-HeFT to demonstrate racially differential response to H/I were not adequate or appropriate tests
- The only reason BiDil is being manufactured and marketed as a drug for Black Heart Failure is because that was the only way NitroMed thought it could make money

It was wrong!

- October 23, 2008: NitroMed Sells Off Its Only Product, a Controversial Heart Pill for African Americans
  - Nine months after slashing its staff and discontinuing marketing of its only marketed product—a heart-failure drug approved specifically for African Americans—Lexington, MA-based NitroMed is selling all the assets related to the pill.

Medical Genomics

- Attempt to identify genes that cause diseases
- Newborn screening for sickle cell, PKU, etc. very effective
- Gene by Environment interaction
  - Hemochromatosis: iron overload that damages liver
    - Mutations Cys282Tyr was thought to cause the disease
      - Alarms about high frequencies were sounded, but much less disease materialized in surveys
    - Found that alcohol consumption is critical to expression of disease

Pharmacogenomics

- Adverse drug reactions (ADR) cause ~100,000 deaths per year in the U.S.
- Drug side effects don't affect everyone
  - Some people are more susceptible to some families of drugs than others
  - A lot of this has to do with the individuals ability to metabolize the drug, affecting the amount of circulating pharmaceuticals and causing overdoses

Adverse Drug Reactions

- A family of enzymes is critical in the metabolism of drugs
  - Cytochrome P_{450} family, especially CYP_2D_6 and CYP_2C_{19} which affect the rate of drug metabolism for many common drugs
    - Medications used to treat clinical depression, psychoses, heart arrhythmias, high blood pressure, and cough
    - The most commonly used drugs metabolized by CYP_2D_6 accounted for $12.8 billion in the U.S. in 2004!

Adverse Drug Reactions

- Warfarin is an anticoagulant or blood thinner used to prevent blood clots
- Warfarin is metabolized by CYP_2C_9
  - 30+% of "Europeans" have alleles that reduce metabolism by 30 – 90%
  - Vastly increases risk of bleeding
  - A second gene was implicated in reduced Warfarin metabolism among "Chinese-American" patients (VKOR gene)
- FDA is currently recommending screening for CYP_2C_9 and VKOR genes when prescribing Warfarin

Genomics, Race and Health

- Many genes that affect the metabolism of drugs occur at different frequencies in different ***populations*** (***NO SURPRISE!***)
- Just like for athletics, those genes are not unique to one socially constructed ***race*** or another, so screening by race would be extremely ineffective and potentially life-threatening
  - Think about someone classified as "Black" but carrying the "European" CYP_2C_9 gene
    - The racial classification would promote lack of caution with Warfarin, potentially deadly