


Burhansstipanov-Bemis GENA® obj. 14 miRNA & excerpt from obj. 29

"Genetic Education for Native Americans" (GENA®) Objective 14 with excerpts from Objective 29
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Native Cancer Survivor's Support Network: 1-800-537-8295
Web Page: <http://NatAmCancer.org>


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In honor of our brother, friend, colleague



Frank C. Dukepoo, Ph.D.
Hopi and Laguna Pueblo Nations

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**Excerpt from GENA®
Obj. 29**

Native American Cultural and
Ethical Issues related to Genetic
Science and Research

Objective: By the end of this session, the participant will be able to:

1. Identify at least two Native American cultural issues that are likely to be related to microRNA research.

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Contemporary Topics Related to Genetic Research that are of Interest to AIANs

- Native health issues / priorities
 - ▷ Alcohol
 - ▷ Diabetes
 - ▷ Heart Disease
 - ▷ Cancer
 - ▷ Obesity
 - ▷ HIV / AIDS

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Contemporary Topics Related to Genetic Research that are of Interest to AIANs

- Native plant issues
 - ▷ Medicinal plants and herbs
 - ▷ Crops (e.g., corn, tobacco)
 - ▷ Environmental contamination of plant life
 - ▷ Protection of Mother Earth
 - ▷ Hybrids / cloning

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Bemis & Burhansstipanov, Native American Cancer Research 303-838-9359; <http://NatAmCancer.org>

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Storage of Specimens

☞ "Most AI/AN tribes, ... consider any body part, blood or buccal scrape, as part and parcel of their being that should not be separated from the body."

Malcolm B. Bowekaty. Perspectives on Research in American Indian Communities. *Jurimetrics* : 42: 2002, p. 147

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Storage of Specimens

☞ "They believe that the spirit may be damaged if parts are apart from the body for long periods of time or upon death. We also believe that one must be whole for the journeys in the afterlife. Hence, autopsies are to be avoided at all costs."

Malcolm B. Bowekaty. Perspectives on Research in American Indian Communities. *Jurimetrics* : 42: 2002, p. 148

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Storage of Specimens

☞ "Research specimen collection without limits on storage ... is not acceptable. Our people have taboos against storage and permanent usage of biological specimens."

Malcolm B. Bowekaty. Perspectives on Research in American Indian Communities. *Jurimetrics* : 42: 2002, p. 148

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Storage of Specimens: Consents

☞ Many researchers don't think they need a new informed consent for blood specimens collected a long time ago (10 years)

☞ The science that was agreed to 10 years ago has changed significantly to make the earlier consent invalid

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Partnerships / Community-Based Participatory Action Research (short excerpt)

Community-based Participatory Research (CBPR) - definition

☞ CBPR is a partnership approach to research that equitably involves community members, organization representatives and researchers in all aspects of the research process.

Israel BA, Eng E, Schulz AJ, and Parker EA. Eds. *Multiple Methods for Conducting Community-Based Participatory Research for Health*. 2005 Jossey-Bass

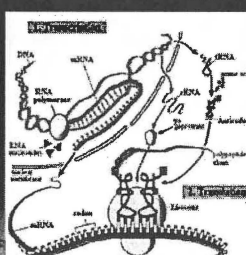
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Central Dogma of Biology

DNA → RNA → Protein



2%

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Human Beings are 99.9% Similar

- 3 billion base pairs total per genome
- 3 million base pairs differ through out the genome
- 2% of that or 60 thousand base pairs would be found in the coding regions.
- Differences in noncoding RNAs could be as much as 2.94 million.

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QUESTION: How do microarrays differ from microRNAs?

- Microarrays (also referred to as "biochips" earlier)
 - Act as a "catalog" of all of the genes
 - May catalog all of the genes in a particular organism
 - 30,000 genes or more can be in a microarray
- MicroRNAs can be included on a microarray
 - They may be cataloged within a microarray

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QUESTION: What are MicroRNAs?

abbreviated as "miRNAs"

- Small RNAs that can turn genes off
- miRNAs are 21-25 nucleotides long
- Found in all mammalian cells and in many other organisms including plant cells

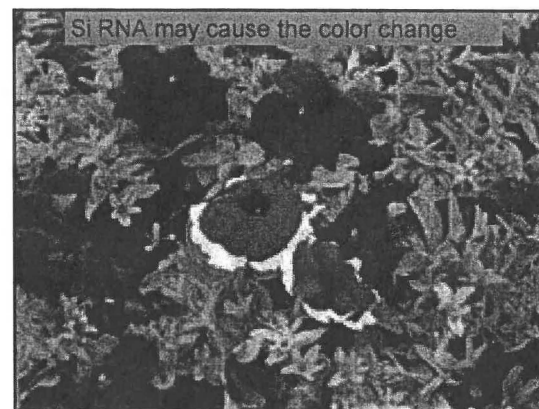
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What are MicroRNAs?

MicroRNAs are part of what has been referred to as "junk DNA"

- miRNAs function to silence cellular genes
- Function by binding to "messenger RNA" (mRNA) and blocking translation into a protein
- The petunia is an interesting example

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Where Have MicroRNAs Been All This Time?

- ☐ For 40 or more years we have been studying DNA and RNA.
- ☐ During that time the microRNAs were thrown out with the waste.
- ☐ Once the Human Genome Sequence was available MicroRNAs were discovered.
- ☐ Mostly Discovered by Bioinformatics.

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Where have MicroRNAs Been All This Time?

- ☐ Bioinformatics is not always correct.
- ☐ Each MicroRNA must be confirmed by laboratory experimentation.
- ☐ Bioinformatics experiments are called "in silico" experiments

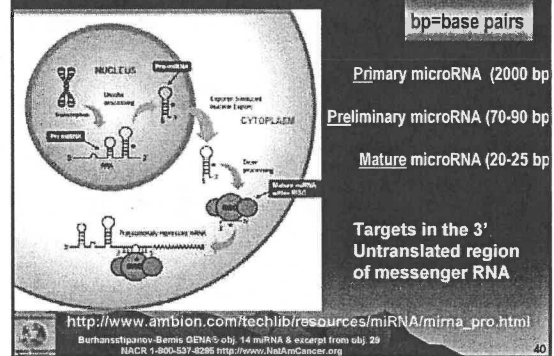
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miRNA Goes Through Changes To Become "Mature"

- ☐ MicroRNA starts out very large (1-2,000 nucleotides)
- ☐ As it matures, the miRNA becomes smaller
- ☐ "Mature" means it is 20-25 nucleotides
- ☐ miRNA must be mature to be active

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Processing and Activity of MicroRNAs



This Is How You Usually See Base Sequences

UGGGAUGAGGUAGUAGGUUGUAU
AGUUUUAGGGUCACACCCACCACU
GGGAGAUAAAUAUACAAUCUACU
GUCUUUCCUA

NOTE: Normally the DNA bases are AGTC, but in RNA the T becomes a U.

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How are MicroRNAs Made?

- ☐ Initially miRNAs are copied from the DNA
- ☐ They take on a unique shape
- ☐ You usually see *part* of the sequence in a straight line, but it has loops and stems

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How Are The Targets of miRNAs Identified / Found?

Bioinformatics approach

- Target Scan (software program) found 451 target messenger RNAs for one miRNA
- This represented 400 distinct genes
- Software estimates the likelihood of microRNA regulation with a percentile score

Lewis BP, Shih IH, Jones-Rhoades MW, Bartel DP, Burge CB (2003). Prediction of mammalian microRNA targets. *Cell* 115:787-98

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miRNA Web Resources

url to download TargetScan and TargetScanS results: <http://genes.mit.edu/targetscan>

url for miRBase
<http://microrna.sanger.ac.uk/sequences/index.shtml>

Searchable database of all known/predicted miRNAs and targets

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Interactive Activity

MicroRNA Group Activity and Relationship to Public Health

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MicroRNAs Background for Interactive Activity

- The mature MicroRNA can find its target and block gene expression.
- In cancer a miRNA could be shutting down a gene that prevents cancer (p53)
- Or if a microRNA is lost (e.g., through deletion), a gene that should not be present can not be turned off.

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Multiple Targets of MicroRNAs

- miRNA target multiple genes
- Since miRNAs can bind imperfectly more than one gene can be targeted in the same cell at the same time
- The Activity:

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Interactivity

- Each of you has a laminated "piece" of microRNA or a messenger RNA on your desk.
- These laminated pieces represent diseases like cancer, diabetes and heart disease. Remember than one miRNA regulates many different genes.
- Please walk around the room to find the "match" so that each disease-specific messenger RNA matches the respective microRNA.

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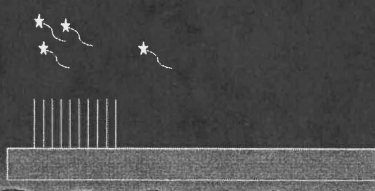
UCDHSC Student Projects

- Students selected Genes previously associated with melanoma
- WNT5A, BRAF, MITF, RB, p53
- Selected 20 microRNAs
- Bioinformatics approach

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Student Projects

- Experiment: Build a Microarray for MicroRNAs



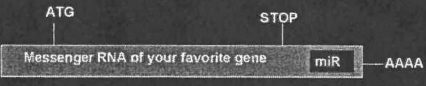
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Student Projects

- Experiment: Conducted a Microarray for MicroRNAs that was commercially available
- 11 miRNAs out of 20 were correctly identified (i.e., over-expressed in melanoma cell lines)

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MicroRNAs Activity



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MiRNAs Summary

- If a micro RNA is misregulated in disease, it may contribute to diabetes, heart disease, cancer
- We can expect to see new therapeutics targeting miRNA.

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MiRNAs

- "If ELSI is properly followed all people will have access to a customized drug for their disease....."
- "It is my hope that finances do not dictate who benefits and who does not."

Reggie Trevino
Medical School
class of 2010

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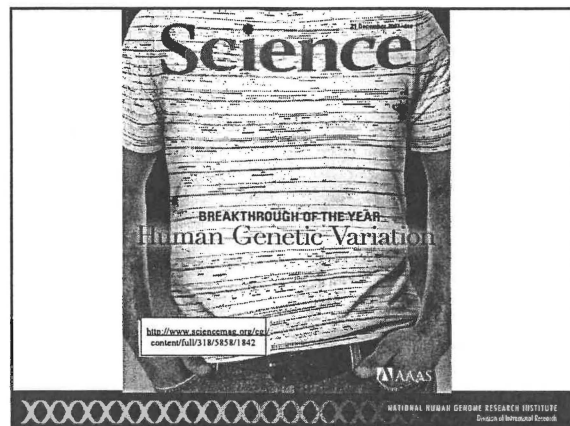
- Dilemma of Difference
- Physicians' Attitudes Towards Race, Genetics and Medicine
- Should We Study Genetics and Genomics to Understand and Reduce Health Disparities?
- Building Disciplinary Bridges



The Dilemma of Difference

"A finding that blacks and whites are different in some critical aspect need not inevitably lead to increased discrimination or stigma for blacks. ... But the Tuskegee experiment stands as a reminder that such favorable outcomes rarely if ever occur. More often, either racist assumptions and stereotypes creep into the study's design, or findings broken down by race become convenient tools to support policies and behavior that further disadvantage those already vulnerable."

Patricia A. King The Dangers of Difference, Hastings Report, 1992



Multiple regions within 8q24 independently affect risk for prostate cancer

Prostate Cancer

Christopher A. Haiman¹, Nick Patterson², Matthew L. Freedman^{2,3}, Simon R. Myers², Malcolm C. Pike¹, Aleksandra Waliszewski^{2,4,5}, Julie Neubauer^{2,4}, Arti Tandon^{2,4}, Christine Schirmer^{2,4}, Gavin J. McDonald^{2,4}, Steven C. Greenway¹, Daniel O. Stram¹, Loic Le Marchand⁶, Laurence N. Kolonel⁶, Melissa Frasca¹, David Wong¹, Lorelei C. Prober¹, Kristin Ardlie^{2,7}, Ingrid Oakley-Girvan^{8,9}, Alice S. Whittemore⁸, Kathleen A. Cooney^{10,11}, Esther M. Jahn^{8,9}, Sue A. Ingles¹, David Altshuler^{2,4,12,13}, Brian E. Henderson¹ & David Reich^{2,4}



Obesity

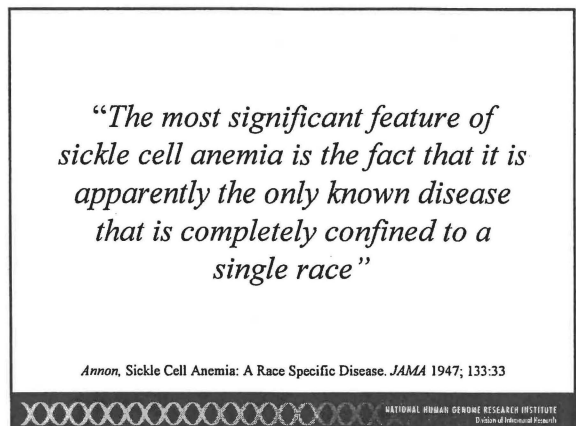
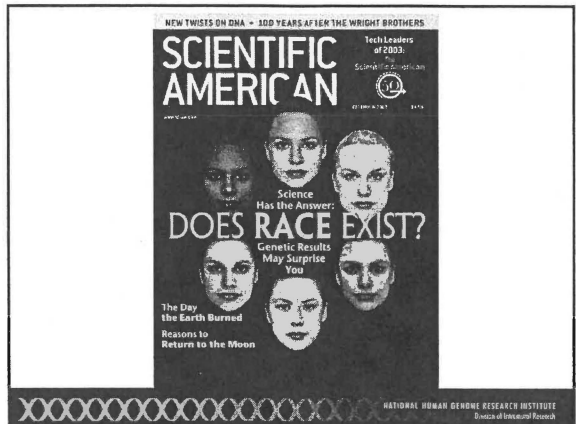
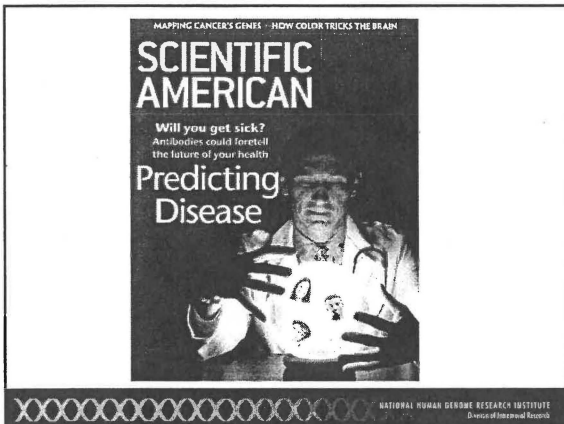


Question

If genomic medicine offers the next major breakthrough in diagnosis, prevention, and cure of disease: What role will it have in addressing racial and ethnic health disparities????



United States Physicians' Attitudes Towards Race, Genetics and Medicine



Relevance of Patient's Race in Clinical Decision Making

- *Physicians believed that race is a complex and poorly defined concept*

"Plus there's no certain line about what race is. I mean what percentage of a particular race do you have to be to be that race. Do you have a reflectometer to measure the skin color? What does it mean?"
(Baltimore, white)



Relevance of Patient's Race in Clinical Decision Making

- *Physicians believed that race is a complex and poorly defined concept*

"I think what 'Jack' mentioned -- trying to divide race and culture is a very hard thing because a lot of it is intertwined. A lot of the things that 'Peter' is mentioning are cultural things, are access to care, socioeconomics -- all those things maybe more prevalent in a certain race but it's not the race itself that's the problem." (Atlanta, white)



Relevance of Patient's Race in Clinical Decision Making

- *Physicians contended that patient's race is one of many factors in health care.*

"You know you're going to suspect certain diseases more commonly in women than in men and you're going to treat young maybe different than old. There are so many different factors. To me race is just one of the many of them." (Baltimore, white)



Relevance of Patient's Race in Clinical Decision Making

- *Differences between black and white physicians were found:*
 - White physicians more often described race as a sensitive issue.
 - Black physicians discussed socio-economic influences on health and their relationship with race for longer periods and in reference to their own practice experiences to a greater extent than did white physicians.



Race is a sensitive issue.

"But you still have to be careful. I mean if you tell somebody too many negatives about their 'race' or something like that, they might take it the wrong way."
(Philadelphia, white)



Socio-economic influences on health

When I think about resources and what we do know about health disparities, access to care, testing and being able to get the appropriate medication, education and support systems in place, that's something that we know, that's something that's in front of us.
(Baltimore, black)



Relationships Among Race, Genetics, and Disease

- *Physicians felt that genetics does not explain most racial disparities in disease.*

"I think there is a portion of it that's genetics but particularly with things like cancer, I'm going to say that I think most of it is probably environmental in access to care and treatment differences. I don't think the majority of the difference is accounted for by genetics. I think more of it can be accounted for in that people may not have access to a physician or wait to go to a physician or when they get there it takes them longer to be diagnosed and then longer to be treated." (Atlanta, black)

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Limitations

- Potential for selection bias.
- Social desirability in responses
- Not generalizable

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Health Professionals' Genetics Education Needs Exploration (HP GENE) Survey

National Human Genome Research Institute
National Institutes of Health

7. Random mutations cause all of the genetic variation in the human genome.

☐ true ☐ false ☐ scientific evidence inconclusive ☐ don't know

8. The variation in the human genome includes both disease causing gene variants and variants that have no effect on health and disease.

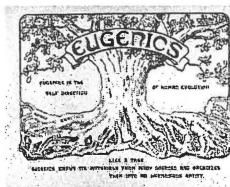
☐ true ☐ false ☐ scientific evidence inconclusive ☐ don't know

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Should We Study Genomics To Understand Health Disparities?

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U.S. Eugenics Movement



Eugenics is "the science of the improvement of the human race by better breeding"

--Charles B. Davenport, director of the Eugenics Record Office at Cold Spring Harbor (1911)

Image source: www.eugenicsarchive.org

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Buck v. Bell (1927)

US Supreme court upheld eugenic sterilization law

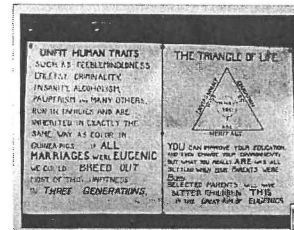


Image source: www.eugenicsarchive.org

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Points to consider: Genetics and health disparities

- Health disparities are real, and their understanding and resolution should be a major concern to all who care about medicine and public health
- Current OMB categories leave much to be desired, but eliminating all such categories would also eliminate the awareness of disparities
- For most disparities, the relative roles of genes and environmental factors remain undefined
- Research studies that only study genetics, or only study environmental factors, run the risk of becoming self-fulfilling prophecies



Points to consider: Genetics and health disparities (cont.)

- Research studies should seek to identify the most proximate environmental and genetic risk factors, rather than depending on the use of imperfect and potentially prejudicial surrogates (race/ethnicity)
- The most valuable studies will be those that have been done prospectively, collecting both Genetic and Environmental data with maximum sophistication
- A large scale national cross-sectional prospective cohort study of health would yield benefits for many years to come



Research Team

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