Genomics and Health Disparities
Exploring the Role of Genomics in Achieving Health Equity

Genomics: Will it help us address health disparities?

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Genomics: Will it Help Us Address Health Disparities?

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Mark R. Cullen M.D.
Stanford Center for Population Health Sciences
Reasons we shouldn’t go there
1. First things first
Survival to Age 70 ($S_{70}$) for White Male Pop. in 2000, by county

Legend

Counties $s_{70m}$

- 5416 - 6422
- 6422 - 7119
- 7119 - 7485
- 7485 - 8288
<table>
<thead>
<tr>
<th>Construct</th>
<th>Variable</th>
<th>Data Source</th>
<th>Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low educational attainment</td>
<td>Education &lt;12 years</td>
<td>Census</td>
<td>% of subgroup *10^-2</td>
</tr>
<tr>
<td>High educational attainment</td>
<td>Education &gt;12 years</td>
<td>Census</td>
<td>% of subgroup *10^-2</td>
</tr>
<tr>
<td>High occupational attainment</td>
<td>Managerial or professional job</td>
<td>Census</td>
<td>% of subgroup *10^-2</td>
</tr>
<tr>
<td>Income</td>
<td>Household income per adult equivalent</td>
<td>Census</td>
<td>Mean (Household income in$/adult equivalents) *10^-3</td>
</tr>
<tr>
<td>Poverty</td>
<td>Under the poverty line</td>
<td>Census</td>
<td>% of subgroup *10^-2</td>
</tr>
<tr>
<td>Wealth (property)</td>
<td>Log of property value</td>
<td>Census</td>
<td>Mean log (property value/5X10^4) among homeowners</td>
</tr>
<tr>
<td>Homeownership</td>
<td>Homeowner</td>
<td>Census</td>
<td>% of subgroup *10^-2</td>
</tr>
<tr>
<td>Wealth (property) distribution</td>
<td>Gini coefficient on property values</td>
<td>Census</td>
<td>Coefficient between 0 and 1</td>
</tr>
<tr>
<td>Immigrant status</td>
<td>Not a US citizen</td>
<td>Census</td>
<td>% of subgroup *10^-2</td>
</tr>
<tr>
<td>Living without a partner</td>
<td>Divorced, separated or never married</td>
<td>Census</td>
<td>% of subgroup *10^-2</td>
</tr>
<tr>
<td>Construct</td>
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<tr>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Between race disparity in (property) wealth</td>
<td>Mean Black/Mean White property value</td>
<td>Census</td>
<td>Sex-specific quotient</td>
</tr>
<tr>
<td>Urban county</td>
<td>Metro by census definition</td>
<td>Dummy (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Part urban</td>
<td>Part metro by census definition</td>
<td>Dummy</td>
<td></td>
</tr>
<tr>
<td>In the south</td>
<td>Southern by census definition</td>
<td>Dummy</td>
<td></td>
</tr>
<tr>
<td>Proportion of county population that is black</td>
<td>Proportion of adults self-reported as black</td>
<td>Economic census</td>
<td>% *10^-2</td>
</tr>
<tr>
<td>Black population in surrounding area</td>
<td>Proportion of adults in the State, excluding county, that is black</td>
<td>Economic census</td>
<td>% *10^-2</td>
</tr>
<tr>
<td>Availability of fast food</td>
<td>Proportion of food sales classified as from limited service establishments</td>
<td>Economic census</td>
<td>% sales *10^-2</td>
</tr>
<tr>
<td>Quality of acute care</td>
<td>Proportion of acute MI patients getting beta-blockers</td>
<td>Ref</td>
<td>% hospitals* 10^-2</td>
</tr>
<tr>
<td>Cold climate</td>
<td>Mean January temperature</td>
<td>Ref</td>
<td>Degrees F*10^-2</td>
</tr>
<tr>
<td>Warm climate</td>
<td>Mean July temperature</td>
<td>Ref</td>
<td>Degrees F*10^-2</td>
</tr>
<tr>
<td>Air pollution</td>
<td>County mean conc. of fine particulate PM$_{2.5}$</td>
<td>EPA website</td>
<td>PM$_{2.5}$ in mg/M$^3$</td>
</tr>
</tbody>
</table>
T-statistics for each significant predictor variable

Size and magnitude
Actual and predicted $S_{70}$
Frequency distribution (kernel plot) for $S_{70}$
Percent of counties with actual & predicted race differences in $S_{70}$
Percent counties with actual & predicted race differences in $S_{70}$
Risk distribution based on genetic and environmental factors
Risk association with genetic & environmental factors for:

- Stroke
- Diabetes
- CHD
Evidence that healthcare disparities contribute

- Differential access
- Differential quality
- Differential adherence
- Differential efficacy of those interventions adhered to
1. First things first

2. Genome-Wide Association Studies (GWAS) are not too informative for racial minorities.
Diversity in Biomedical Research: Then and Now

PERSISTENT BIAS

Over the past seven years, the proportion of participants in genome-wide association studies (GWAS) that are of Asian ancestry has increased. Groups of other ancestries continue to be very poorly represented.

2009
373 studies
1.7 million samples

96% European ancestry

2016
2,511 studies
35 million samples

81% European ancestry

Bustamante, Burchard, De La Vega, *Nature* 2011
Populations Vary by “Variation”

4.1 - 5.3 million variants per sample
1. First things first

2. Genome-Wide Association Studies (GWAS) are not very informative, except for Caucasians

3. Differential access and insurance coverage could result in widening of disparities.
Differential cost and access

- Benefits of many advances—including those in gene-directed cancer meds—may be inaccessible to many due to cost of care and insurance differences

- There is evidence that many ethnic groups are less willing to accept genetic testing or guidance it confers
Should We Reconsider?
1. Environmental influences driving disparities might be “gene-modulated”.

Should We Reconsider?
Male, Female, and Total $s_{70}$ versus % Poverty (Black Americans)

2005-2010 CDC condensed mortality tables and US Census for 2005-2010 (American Community Survey) for US counties where black population is at least 5% ($N=833$ out of 3,140)
Male, Female, and $M/F_{S70}$ vs % Poverty (Black Americans)

2005-2010 CDC condensed mortality tables and US Census for 2005-2010 (American Community Survey) for US counties where black population is at least 5% (N=833 out of 3,140) and linear fit is weighted by square root of county population.
Male, Female, and Total $S_{70}$ versus % Poverty, with Linear Fit (Black Americans)

2005-10 CDC condensed mortality tables and US Census for 2005-10 (American Community Survey) for US counties where black population is at least 5% (N=833 out of 3,140) and linear fit is weighted by square root of county population. Removing county population wts has almost no impact on slopes (<3%).
Male, Female, and $M/F_{S70}$ versus Poverty, Log Income, Education, and Occupation

(A1) (A2) (B1) (B2) (C1) (C2) (D1) (D2)
Asthma Health Disparity in the United States

Prevalence of Asthma

- Mexican American: 8%
- Caucasian: 12%
- African American: 13%
- Puerto Rican: 37%

Mortality

- Mexican American: 0.8
- Caucasian: 1.2
- African American: 3.2
- Puerto Rican: 4.4

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL), NHLBI 2014
Barr et al., AJRCCM 2016
Akinbami L. CDC/NCHS
Asthma is the most disparate common disease.
1. Environmental influences driving disparities might be “gene-modulated”.

2. Pharmaco-genomic evidence suggests treatments should be tailored to race/gene interactions.
Variation in drug response may contribute to disparities

![Graph showing drug response (Delta FEV%) for Puerto Ricans, African Americans, and Mexicans. Good drug response is indicated by a dotted line.](image)

Naqvi et al. (2007) J. of Asthma
1. Environmental influences driving disparities might be “gene-modulated”.

2. Pharmaco-genomic evidence suggests treatments should be tailored to race/gene interactions.

3. “Omics” studies may reveal pathways of therapeutic opportunity.
Social signal transduction

Simple questions

1. Which gene modules are sensitive to social processes?
2. Which transcription control pathways mediate those effects?
Social signal transduction

Simple questions
1. Which gene modules are sensitive to social processes?
2. Which transcription control pathways mediate those effects?

Not-so-simple questions
1. Recursive persistence
2. Environmental embedding
Example: Impact of Social Isolation

Cole et al. Social regulation of gene expression in human leukocytes, Genome Biology 2007
Instability/sensitivity:
1.2 vs. 3.2 critical points ($d'$), $p < 10^{-10}$
1.9 vs. 3.7 inflection points ($d''$), $p < 10^{-10}$
Projects Exploring Opportunity in Omics Profiles

Mark Cullen, MD
Yvonne Maldonado, MD
Bio-Repository for American Indian Capacity, Education, Law, Economics and Technology (BRAICELET)
1. Establish an **American Indian Biobank** with BRAICELET (Bio-Repository for American Indian Capacity, Education, Law, Economics and Technology).
   - Create a Lakota Health Community Advisory Group that will optimize educational methods and promote cultural exchange
   - Establish Lakota Biobank infrastructure and engage, educate and train tribal community members as biobank personnel
   - Endorse longterm sustainability through strategic and business management and early pursuit of diverse funding approaches.

2. Establish a **pilot for first set of biobank material** through the collection of 200 additional participants for SAIL (Studies of AutoImmune Illnesses with the Lakota).

3. Develop, implement and evaluate **Science Health Education and Literacy** among Lakota as part of BRAICELET.
Project 2: Why do Some Obese Latino Adolescents Respond?

**Primary outcome:** BMI trajectory over 3 years.

**Baseline:**
- N = 268
- 7-11yo (241 families)
- 98% Latino
- BMI ≥85th %ile
- Low-income, EPA & RWC

**Intervention:** Home (Diet, Screen Time, PA), After School Team Sports, Primary Care Reports

**Control:** Health/Nutrition Education
Omens Measurements

- Genome
- Epigenome
- Transcriptome
- Proteome
- Cytokines
- Metabolome
- Lipidomics
- Autoantibody-ome
- Microbiome (Gut, Urine, Nasal, Tongue, Skin)
- Medical Tests and Questionnaires

Biosensors

Billions of Measurements!

Viral infection

Year 1

Year 2

Personal Omics Profiling
### Project 2: Why do Some Obese Latino Adolescents Respond?

**BASELINE**
- N = 268
- 7-11yo (241 families)
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**INTERVENTION:** Home (Diet, Screen Time, PA), After School Team Sports, Primary Care Reports

**CONTROL:** Health/Nutrition Education

### Measurements

<table>
<thead>
<tr>
<th>Anthropometrics/Physical</th>
<th>Accelerometry</th>
<th>Self-Reported Behavioral</th>
<th>Self-Reported Demographic &amp; Psychosocial</th>
<th>Biological Measures</th>
<th>Multi-Omics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, Weight, BMI</td>
<td>Actigraph GT3X+ (triaxial) Waist 24h/d x 4-7+ days (min. 3 week days + 1 weekend day) Recorded @ 40Hz</td>
<td>3 x 24-hour dietary recalls Screen time; other sedentary behaviors Sleep times &amp; symptoms Parent behaviors</td>
<td>Demographics, Household income, Parental Education, Acculturation, etc. Sexual maturation Weight concerns Depressive Sxs</td>
<td>Fasting Total Cholesterol, HDL-C, TG, LDL-C Fasting Glucose, Insulin, HgA1c hsCRP ALT</td>
<td>Genomics Transcriptomics Epigenomics Metabolomics Lipidomics Oral Microbiomics</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>Triceps skinfold BP Resting HR Parent Ht, Wt, WC</td>
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</table>

### Primary outcome
- BMI trajectory over 3 years.
1. Assess associations of iPOP markers with measures of adiposity and diabetes risk at baseline.

2. Assess the associations of baseline and 3-year longitudinal iPOP markers with changes in measures of adiposity and diabetes risk.

3. Test the additional predictive value of iPOP signatures for changes in adiposity and diabetes risk over 3-years when combined with cognitive, behavioral, socio-demographic and environmental measures, across all participants and as possible moderators and mediators of intervention effects.
1. Assess confidence of clinicians communicating genetic test results and genetic risk information on breast cancer to diverse patients.

2. Audiotape the information that clinicians communicate during the clinical encounter in delivering genetic test results and assess whether the information provided to patients differs by patient ethnicity, health literacy, and study site.

3. Assess the correspondence between the recommendations of doctors and the subsequent actions of patients over and whether this correspondence differs by ethnicity, health literacy, and study sites.

4. Identify if/when patients share their personal genetic risk information with family member(s) and to what extent this process is influenced by ethnicity, health literacy, and study sites.
Thank you!