HESSP Project 1

Title: Correlation between childhood trauma, gene expression, and health outcomes in adults

Mentor: Professor Laurens Holmes, Jr.

Project Description:

Background:
Adverse childhood events such as physical and psychological trauma characterized by violence, child abuse and neglect have been observed in clinical and translational research to predispose to poor health outcomes in adult life, with mechanisms not fully understood. However, proven data exist to encourage environmental stimuli with less violence and child maltreatment in normal growth and development of children. Children exposed adverse environment are more likely to present with poor health, behavioral dysfunction, lack of opportunity, low education and disadvantaged neighborhood factors, all which reflect health inequity and social determinants of health. We postulate that adverse childhood event is associated with unhealthy gene expression that plays a proliferative role in disease development as well as progression and poor prognosis; and that children exposed to traumatic environment are more likely to present with chronic disease and behavioral dysfunction later in life due to gene-environment interaction (gene expression).

Hypothesis:
(H_o: I) There is no association between childhood traumatic event; and gene expression via DNA microarray studies. **(H_o:II)** Gene expression via DNA microarray is not associated with health outcomes. (**(H_o:III))** Childhood traumatic event is not associated with gene expression via DNA microarray as well as poor health outcome.

Specific Aim:
(I) To obtain and review published literature on "gene expression and childhood trauma";" gene expression and health outcomes"; "childhood trauma and health outcomes" (II) To perform a systematic review of the eligible published literature to address the research question: Does adverse childhood experience predispose to poor health outcomes through gene expression in adulthood. (III) To assess the association between childhood traumatic event and health outcomes via gene expression (DNA microarray studies), as well as the association between gene expression via DNA microarray studies and health outcomes.

Methodology:
(1) **STUDY DESIGN:** A systematic review and applied meta-analysis termed Quantitative Evidence Synthesis (QES) (2) **PATIENT SAMPLE, SAMPLING TECHNIQUE & DATA SOURCE:** Published literature will be retrieved from PubMed based on eligibility criteria; the PRISMA checklist for minimum set of items for evidence-based review reporting (meta-analysis and QES –www.prisma.statement.org). (3) **STATISTICAL ANALYSIS:** *Summary statistics:* Frequency, percentage, proportion, and mean, SD (normally distributed data) of the studies in the systematic review and QES. *Inferential Statistics:* This will involve estimation, confidence interval method and hypothesis testing with p value method. (1) Random effect method of DeSimonian-Laird that adjusts for between studies heterogeneity will be used for the summary or pool estimate of effect or association; (2) Heterogeneity test after random effect procedure; and (3) Meta-regression with graph of the regression will be performed.

HESSP Project 2

Title: Survival by race of children with acute lymphocytic leukemia

Mentor: Professor Laurens Holmes, Jr.

Project Description:

Background:
Childhood cancer is the leading cause of disease-related death among children, 0-14 years in the US. Despite the improvement in the overall survival due in part to advancement in therapeutics, difference in survival continues by health disparities indicators mainly race/ethnicity, income, sex, race, education, and geography, and persist after adjustment for known confounding factors. Whereas available clinical and epidemiologic data associate survival disadvantage of blacks/AA in ALL to social determinants of health, adjustment for such confounding variables fails to remove the excess mortality observed in blacks/AA relative to whites. The persisting racial disparities in childhood ALL is explained in part by unmeasured confounding such as tumor subtypes, biomarkers, gene expression (epidenomic), and genomic variability by race in pediatric ALL. We aimed to examine the implication of T Cell leukemia subtype in overall ALL survival, determine the distribution of T cell ALL among blacks/AA as well as the risk of ALL mortality associated with ALL. Additionally, we sought to determine the contributory effect of T cell subtype in ALL mortality among blacks/AA. The **overall objective** is to utilize the Surveillance Epidemiology End Result (SEER) dataset; 1973-2014 to contributory effect of subtype T cell ALL in overall childhood ALL mortality.

Hypothesis:
(Ho:I) There is no differences in overall childhood ALL survival comparing T to B cell subtype (HR_1=HR_2). (Ho:II) Survival disadvantage of blacks/AA is not affected by T cell ALL subtype (HR_1=HR_2). (Ho:III). T cell subtype, tumor progression biomarker and social determinants of tumor survival interaction do not explain the survival disadvantage of childhood ALL among black/AA.

Specific Aim:
(1) To characterize childhood ALL demographics, clinical features and ALL prognostic factors.(2) To examine the risk of overall ALL mortality associated with T cell subtype (3) To the determine the effect of T cell type in excess overall ALL mortality in blacks/AA relative to whites .

Methodology:
(1) **STUDY DESIGN:** A retrospective cohort non-experimental design (2) **PATIENT SAMPLE & SAMPLING TECHNIQUE:** Pre-existing data using from the SEER registry, 1973-2014 (3) **STATISTICAL MODELING**: *Summary statistics*: Frequency, percentage proportion, annual percent change will be used for temporal trends. *Inferential Statistics*: This will involve estimation, confidence interval method and hypothesis testing with *p* value method. (1) Stratification analysis: C-M-H for effect measure modifier and confounding assessment. (2) Cox Proportional Hazard model (univariable and multivariable) for overall and subpopulation survival experience.

HESSP Project 3

Title: Health inequity exposure effect in asthma severity and cerebral palsy co-occurrence

Mentor: Professor Laurens Holmes, Jr./ Kirk Dabney, MD,MHCDS

Project Description:

Background:
Asthma remains one of the leading chronic diseases among children in the US, and while the cumulative incidence varies by health disparities indicators, the predisposing factors are not fully understood and neither the underlying cause (pathophysiologic mechanism). Cerebral palsy is a cognitive and motor dysfunction diagnosed early in life as asthma, and is most prevalent in some subpopulations. Similar to asthma, the underlying cause of CP remains unknown. However, clinical, epidemiologic and population-based data indicate subpopulation differences in the prevalence of CP and asthma, with the cumulative incidence of asthma highest among Blacks and Hispanics, intermediate among whites and lowest among Asians, while CP is most prevalent among AA/blacks. However, the risk factors are multifactorial including social determinants as health inequity, environmental and disadvantaged neighborhood factors. With the similar prevalence distribution by subpopulation characteristics, the investigative team proposes to examine the co-occurrence of CP and asthma in children, given the motor involvement in CP that may predispose early to bronchospasm and vasoconstriction in the bronchial tree. Additionally to assess the subpopulation variability in the co-occurrence and determine the predisposing and risk factors in the variabilities.

Hypothesis:
(H_o): (H_o: **I**) There is no racial and ethnic differences in the prevalence of asthma and CP co-occurrence ($p_1=p_2=p_3=p_4$). (H_o: **II**) There is no association between asthma/CP co-occurrence and health inequity factors (Odds Ratio (OR) = 1.0). (H_o: **III**) There is no racial and ethnic heterogeneity in the association between asthma/CP co-occurrence and health inequity factors ($OR_1=OR_2=OR_3=OR_4$).

Specific Aim:
(1) To characterize the demographics, BMI and health inequity factors such as poverty, insurance coverage, in a representative sample of United States children using the most recent National Survey of Children's Health (NSCH), 2016. (2) To examine the prevalence of asthma and CP co-occurrence in the sample stratified by states namely DE, PA, NJ (mid-Atlantic), and by subpopulations (race, ethnicity, education, language, disability, poverty). (3) To determine the factual and non-confoundable association between asthma/CP co-occurrence and health inequity, as well as the effect measure modification by race and ethnicity.

Methodology:
(1) **STUDY DESIGN:** A cross-sectional non-experimental design variant, termed atypical Case non-Case hybrid design (2) **PATIENT SAMPLE & SAMPLING TECHNIQUE:** Data from the NSCH, 2016 will be used as a representative sample of US children. Atypical case-noncase design utilizes data reduction sampling from legacy or "big data" for study efficiency. The power of the study (1-β) will be estimated prior to the data assessment. (3) **STATISTICAL MODELING**: *Summary statistics*: Frequency, percentage, proportion, proportion interval. *Inferential Statistics*: This will involve estimation, confidence interval method and hypothesis testing with *p* value method. (1) Stratification analysis: C-H-M for effect measure modifier and confounding assessment. (2) Binomial regression model (univariable and multivariable) will be used in examining the association between diabetes and CDD and the racial heterogeneity. (3) A structural equation model (**SEM**) will be used to examine CP and asthma as two response variables in the model for exposure effect of race, ethnicity and health inequity factors.

HESSP Project 4

Title: Health inequity in mortality from pediatric trauma

Mentor: Professor Laurens Holmes, Jr. / Alfred Atanda, MD / Kirk Dabney, MD, MHCDS

Project Description:

Background:
Motor vehicular trauma has been reported to be associated with substantial cumulative incidence and period prevalence of mortality in the state of Delaware. A preliminary data from the Delaware Trauma Registry (DTR), 2004-2010 indicate racial variability in pediatric mortality (Holmes & Atanda, 2011). However what is not fully understood are the factors that predispose to such racial variances in order to develop and implement risk-adapted intervention in reducing the excess mortality in some subpopulations namely blacks/African Americans. The observed mortality variability in the preliminary data may be due to health inequity, since heath disparities or subpopulations differences in health outcomes remain the function of health inequity and social determinants of health. We aim to examine the cumulative incidence of pediatric trauma mortality, age-adjusted racial and sex differences, as well as percent change and annual percent change, 2004-2016. Additionally, we aim to assess the predisposing factors, implying potential confounding in the relationship between race/ethnicity and overall pediatric trauma mortality. The **overall objective** of the proposed research project is to examine the temporal trends in pediatric trauma mortality, subpopulations variability mainly race and the role of health inequity mainly access and utilization of care in racial/ethnic difference in mortality.

Hypothesis:
(**H_o: I**) There is no temporal trends by race in DE pediatric trauma mortality. (**H_o: II**) Pediatric trauma mortality does not vary by race and ethnicity.(**H_o: III**) Racial/ethnic variances in pediatric trauma mortality is not associated with health inequity factors, namely insurance.

Specific Aim:
(1) To characterize the demographics and clinical features such as injury severity scores in children with trauma in DE .(2) To examine the age-adjusted temporal trends in overall pediatric trauma cumulative incidence by race and sex (3) To assess exposure effect of health inequity in the association between race/ethnicity and pediatric trauma mortality.

Methodology:
(1) **STUDY DESIGN:** A cross-sectional non-experimental design (2) **PATIENT SAMPLE & SAMPLING TECHNIQUE:** De-identified data from the DTR, 2004-2016. (3) **STATISTICAL MODELING**: *Summary statistics*: Frequency, percentage, proportion, and mean, SD (normally distributed data). *Inferential Statistics*: This will involve estimation, confidence interval method and hypothesis testing with *p* value method. (1) Stratification analysis: C-H-M for effect measure modifier and confounding assessment. (2) Binomial regression model (univariable and multivariable models) will be used in examining the association between trauma and race, as well as the exposure effect of insurance (health inequity) in the association. (3) Poisson regression will be used for health graphic description (cumulative incidence) with DE as the reference group.

HESSP Project 5

Title: Variances in diabetes and dental disorders among children

Mentor: Professor Laurens Holmes, Jr./Kirk Dabney, MD

Project Description:

Background:
Dental disorders mainly toothache, tooth decay (dental caries) and cavities remain the leading cause of chronic disease among children in the United States , and is associated with school absenteeism, poor overall health, and several comorbidities. Epidemiologic ad population-based data indicate subpopulation differences in the prevalence of childhood dental disorders (CDD), with the cumulative incidence highest among Blacks and Hispanics, intermediate among whites and lowest among Asians. **However, the risk factors are multifactorial including social determinants as health inequity, environmental and disadvantaged neighborhood factors**. With the implication of excessive high glycemic index carbohydrates in microvascular compromise, which may explain caries and cavities, the investigative team proposes to **examine diabetes as exposure effect of CDD, and to access race as an effect measure modifier or/and confounding in the nexus, given the observed racial disparities in CDD.**

Hypothesis:
(H_o: **I**) There is no racial and ethnic differences in the prevalence of CDD ($p_1=p_2=p_3=p_4$). (H_o: **II**) There is no association between diabetes and CDD (Odds Ratio (OR) = 1.0). (H_o: **III**) There is no racial and ethnic heterogeneity in the association diabetes and CDD ($OR_1=OR_2=OR_3=OR_4$).

Specific Aim:
(1) To characterize the demographics, BMI and comorbidities in a representative sample of United States children using the most recent National Survey of Children's Health (NSCH), 2016. (2) To examine the prevalence of CDD in the sample stratified by states namely DE, PA, NJ (mid-Atlantic), and by subpopulations (race, ethnicity, education, language, disability, poverty). (3) To determine the factual and non-confoundable association between diabetes and CDD, as well as the effect measure modification by race and ethnicity.

Methodology:
(1) **STUDY DESIGN:** A cross-sectional non-experimental design variant, termed atypical Case non-Case hybrid design (2) **PATIENT SAMPLE & SAMPLING TECHNIQUE:** Data from the NSCH, 2016 will be used as a representative sample of US children. Atypical case-noncase design utilizes data reduction sampling from legacy or "big data" for study efficiency. The power of the study (1-β) will be estimated prior to the data assessment. (3) **STATISTICAL MODELING**: *Summary statistics*: Frequency, percentage, proportion, proportion interval. *Inferential Statistics*: This will involve estimation, confidence interval method and hypothesis testing with *p* value method. (1) Stratification analysis: C-H-M for effect measure modifier and confounding assessment. (2) Binomial regression model (univariable and multivariable) will be used in examining the association between diabetes and CDD and the racial heterogeneity.

HESSP Project 6

Title: Subpopulation differences in pediatric health, quality of life, and health literacy

Mentor: Professor Laurens Holmes, Jr. / Kathleen Cronan, MD / Kirk Dabney, MD, MHCDS/Patricia Oceanic, MS

Project Description:

Background:
Health literacy which is the degree to which individuals have the **capacity to obtain , process, and understand basic health information and services needed to make appropriate health decisions** (for their child), has been implicated in health disparities. **National data indicate that 10% of American adults have proficient health literacy**, which might explain in part adverse health outcomes (worse overall health and higher mortality rates) in subpopulations with low health literacy; **and is associated with more medical errors, more ED visits and hospitalization, more missed appointments and less preventive care, and higher healthcare cost.** The **overall objective** of the proposed research is to examine the prevalence of health literacy in Nemours Healthcare System and determine whether or not health literacy predicts health outcomes in children and the subpopulation variances therein.

Hypothesis:
(1) There is no association between health literacy and health outcomes (2) Health literacy (HL) is not associated with subpopulation differences in global health (GH) and quality of life (QOL).

Specific Aim:
(1) To characterize the demographics and health conditions of sample of pediatric patients in A.I.duPont Children Hospital (AIDCH) .(2) To examine the prevalence of health literacy among children and families in Nemours (AIDCH) (3) To assess exposure effect of health literacy on health outcomes (Global health and Quality of life) by health disparities indicators.

Methodology:
(1) **STUDY DESIGN:** A cross-sectional non-experimental design (2) **PATIENT SAMPLE & SAMPLING TECHNIQUE:** De-identified survey using adapted and replicated *Newest Vital Sign* instrument (Weiss BD, DeWalt DA, et al. *Quick Assessment of Literacy in Primary Care*: ***The Newest Vital Sign***). Data will be collected on 264 participants on health literacy assessment and global health and QOL survey. (3) **STATISTICAL MODELING**: *Summary statistics*: Frequency, percentage, proportion, and mean, SD (normally distributed data). *Inferential Statistics*: This will involve estimation, confidence interval method and hypothesis testing with *p* value method. (1) Stratification analysis: C-H-M for effect measure modifier and confounding assessment. (2) Logistic regression model (univariable and multivariable models) will be used in examining the association between HL and GH,QOL.

HESSP Project 7

Title: Epidemiologic characterization of childhood opium overdose and mortality

Mentor: Professor Laurens Holmes, Jr.

Project Description:

Background:
Opium overdose and mortality epidemic requires a scientific based approach to addressing the risks/predisposing factors, economic burden and potential life loss due to this epidemic in the nation. Addiction to opium and its current epidemic has been associated with mismanagement of chronic pain with opium derivatives such as "oxycodone" as well as "fentanyl". While excessive prescription of opium derivatives might account in part for the epidemic, medicine is substantially limited in the management of pain associated with failed back surgery and comparable clinical conditions. With the current exponential nature of epidemic, we need to address opium epidemic through etiologic studies (epigenetic, genomics and socio-epigenomics), as well to assess how best to manage chronic pain in medicine. Clinical and population-based data have observed subpopulation variability in opium overdose and mortality as well as addiction and dependence. However, what is not fully understood is the predisposition to opium dependence, overdose and mortality following pain management for chronic pain in adult and children settings. The investigative team aims to characterize childhood opium overdose and mortality in the State of Delaware, and to identify the risk and predisposing factors, especially among subjects with chronic pain managed with opium-derived analgesics using translational epidemiologic approach. Additionally, we aimed to examine subpopulation variances in predisposing factors for data dissemination of risk-adapted intervention mapping.

Hypothesis:
(1) Opium overdose and mortality in children is not associated with socio-demographics and chronic pain (2) Chronic pain management with opium derivative is not associated with opium dependence, overdose and mortality. (3) There is no association between childhood opium overdose and mortality; and social determinants of health.

Specific Aim:
(1) To characterize the demographics and clinical features of opium overdose and deceased pediatric patients in DE Valley.(2) To perform descriptive epidemiology of overdose and mortality in the State of Delaware based on Nemours ED and inpatient data (3) To assess exposure effect of health inequity on racial, sex, ethnic and age disparities in opium overdose and mortality.

Methodology:
(1) **STUDY DESIGN:** A cross-sectional non-experimental design based on electronic medical records (retrospective) (2) **PATIENT SAMPLE,SAMPLING TECHNIQUE & DATA SOURCE**. The ER records on overdose opium cases from 2010 to 2017, as well as EMR on all deceased patients from opium overdose or opium related condition during the study period (3) **STATISTICAL MODELING**: *Summary statistics*: Frequency, percentage, proportion, and mean, SD (normally distributed data). *Inferential Statistics*: This will involve estimation, confidence interval method and hypothesis testing with *p* value method. (1) Stratification analysis: C-H-M for effect measure modifier and confounding assessment. (2) Logistic regression model (univariable and multivariable models) will be used in examining the association between opium overdose, mortality and social determinants of health. (3) Poisson regression will be used to examine the risk associated with geographic locale, with DE as the reference group fir the zip codes associate with opium overdose and mortality.

HESSP Project 8

Title: Gene expression, physical activity, and nutrition in chronic disease predisposition

Mentor: Professor Laurens Holmes, Jr.

Project Description:

Background:
Physical activities and healthy or balanced diet have been observed in clinical and translational research to predispose to ultimate health outcomes, with mechanisms not fully understood. However, proven data exist to encourage exercise and balanced diet enriched with vegetables and fruits in health promotion practices and disease control. The observed differences in health outcomes among those with healthy lifestyle may reflect the gene product such regulatory proteins due to gene expression that result in mRNA translation to protein synthesis. We postulate that healthy lifestyle results in healthy gene expression that plays a protective role in disease development; and that individual with healthy lifestyle mainly physical activities and healthy diets (fruits and vegetables) are less likely to develop chronic diseases (HTN, diabetes, CAD, stroke, asthma) due to gene-environment interaction (DNA microarray).

Hypothesis:
(H_o: I) There is no association between physical activities and diet; and gene expression via DNA microarray studies. **(H_o:II)** Gene expression via DNA microarray is not associated with chronic diseases. (**(H_o:III)**) Physical activities and diets are not associated with gene expression via DNA microarray as well as chronic diseases.

Specific Aim:
(I) To obtain and review published literature on "gene expression and diet"; "gene expression and chronic disease"; "diet and chronic disease"; "physical activities and chronic disease"; "gene expression and physical activities".(II) To perform a systematic review of the eligible published literature to address the research questions. (III) To assess the association between diet and physical activity and gene expression via DNA microarray studies, as well as the association between gene expression via DNA microarray studies and chronic diseases.

Methodology:
(1) **STUDY DESIGN:** A systematic review and applied meta-analysis termed Quantitative Evidence Synthesis (QES) (2) **PATIENT SAMPLE, SAMPLING TECHNIQUE & DATA SOURCE**. Published literature will be retrieved from PubMed based on eligibility criteria; the PRISMA checklist for minimum set of items for evidence-based review reporting (meta-analysis and QES –www.prisma.statement.org). (3) **STATISTICAL ANALYSIS**: *Summary statistics*: Frequency, percentage, proportion, and mean, SD (normally distributed data) of the studies in the systematic review and QES. *Inferential Statistics*: This will involve estimation, confidence interval method and hypothesis testing with *p* value method. (1) Random effect method of DeSimonian-Laird that adjusts for between studies heterogeneity will be used for the summary or pool estimate of effect or association; (2) Heterogeneity test after random effect procedure; and (3) Meta-regression with graph of the regression will be performed.

HESSP Project 9

Title: Subpopulation variability in pediatric renal cancer

Mentor: Professor Laurens Holmes, Jr.

Project Description:

Background:
Childhood cancer is the leading cause of disease-related death among children, 0-14 years in the US. While cancer cumulative incidence continues to increase and varies by health disparities indicators mainly race/ethnicity, income, sex, race, education, and geography, survival has improved due to therapeutic advances but not without subpopulation differences. Whereas available clinical and epidemiologic data associate higher incidence of childhood cancer among whites and survival disadvantage among blacks, this observation may not apply to renal carcinoma incidence and survival. We postulate that the renal physiologic subpopulation variation may predispose some population relative to others to renal cancer (abnormal cellular proliferation) and the likelihood of survival disadvantage as well. The **overall objective** is to utilize the Surveillance Epidemiology End Result (SEER) dataset, 1973-2014 to assess childhood renal cancer cumulative incidence and survival, as well as to examine sub-population variances.

Hypothesis:
(1) There are no subpopulation differences in childhood renal cancer cumulative incidence ($p_1=p_2=p_3$). (2) Survival in childhood renal cancer does not differ by race ($HR_1=HR_2=HR_3$) and sex ($HR_1=HR_2$).

Specific Aim:
(1) To characterize childhood renal carcinoma by demographics and clinical features.(2) To examine the temporal trends as age-adjusted incidence and annual percent change (3) To assess event free survival and survival differences by race and sex.

Methodology:
(1) **STUDY DESIGN:** A retrospective cohort non-experimental design (2) **PATIENT SAMPLE & SAMPLING TECHNIQUE:** Pre-existing data using from the SEER registry, 1973-2014 (3) **STATISTICAL MODELING**: *Summary statistics*: Frequency, percentage proportion, annual percent change will be used for temporal trends. *Inferential Statistics*: This will involve estimation, confidence interval method and hypothesis testing with *p* value method. (1) Stratification analysis: C-H-M for effect measure modifier and confounding assessment. (2) Cox Proportional Hazard model for overall and subpopulation survival experience.