Integration of Genomics into Nursing Practice

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National Cancer Institute
Top 10 Leading Causes of Death

- Heart Disease 24.8%
- Malignant Neoplasms 23.5%
- Chronic Respiratory Disease 5.7%
- Cerebrovascular 5.3%
- Unintentional Injury 4.8%
- Alzheimer's Disease 3.3%
- Diabetes Mellitus 2.9%
- Influenza & Pneumonia 2.2%
- Nephritis 2.0%
- Suicide
Emerging Science/Technology
The Race for the $1000 Genome
Are we There Yet?

• The ability to sequence someone’s entire genome for $1,000 or less
• Cost in the range of many diagnostic tests so considered realistic for routine clinical application
• Technology has outpaced our capacity for understanding this genomic information to inform and improve healthcare

Mardis, E. (2010). The $1000 genome, the $100,000 Analysis. Genome Medicine, 2: 84.
Precision Medicine

• Evolving taxonomy
• Personalized Healthcare
• Personalized Medicine
• Precision Medicine

• Approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person

Precision Medicine Initiative

• Aim: Accelerate the pace of moving precision medicine into every day clinical practice
• Expand research in cancer genomics
• Establish a research cohort of >1,000,000 Americans
  • Share data, bio-samples, diet/lifestyle information, link to EHR if they choose
  • Who are Americans (i.e. citizens?)
  • Issues of diversity
Genetic and Genomic Influences Across the Healthcare Continuum

Preconception/Prenatal

Newborn Screening

Risk Identification

Screening/ Diagnosis

Disease Characterization

Individualized Therapy

Management Of Symptoms

After End Of Life

Interdisciplinary Collaboration to Improve Patient Outcomes

## Genomics and the Nursing Workforce

<table>
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<td>National Nursing Workforce Study in collaboration with ANA (NNWF)</td>
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<td>ANA House of Delegates (HOD)</td>
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<td>National Coalition of Ethnic Minority Nurses (NCEMNA)</td>
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<td>Expanding RN Scope of Practice: A Method for Introducing a New Competency into Nursing Practice (MINC)</td>
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</table>

Calzone, K. et al. (2013). National Nursing Workforce Survey of Nursing Attitudes, Knowledge and Practice in Genomics. Personalized Medicine, 10, 719-728.
Preconception

- Testing for carrier status prior to pregnancy, often for autosomal recessive disorders
  - i.e. MYH associated polyposis (MAP)
- Predisposition cancer genetic testing using chorionic villus sampling and amniocentesis using preimplantation genetic diagnosis

Prenatal testing

- Performed during pregnancy
- Indications include
  - Advanced maternal age
- Non-invasive prenatal screening using cell free fetal DNA testing can identify evidence of malignancy in mother

Newborn Screening

Newborn screening consists of a public health approach to the identification and management of health conditions identifiable in the newborn:

- Approximately 4 million newborns screened annually
- About 12,500 new diagnoses as a result of testing
- Newborn screening constitutes the most extensive use of genetics for public health benefit
- All states provide newborn screening

US Secretary of Health and Human Services Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC) provides national guidance about which health conditions should be included.
Newborn Screening, cont

- Health conditions included in newborn screening panels vary by state
- States can opt to include screening for health conditions not recommended by the DAC HDNC
- Health conditions recommended for screening meet the following criteria:
  - Adequate evidence that early diagnosis can improve health outcomes
  - Screening benefits outweigh possibility of harm
Newborn Screening, cont

- Family members may derive benefit from newborn screening even if there is little to no benefit for the newborn
  - Facilitate diagnostic assessments.
  - Inform future reproduction decisions.
  - Prepare for care requirements of the child.

- Newborn screening tests can provide false positive, false negative, or ambiguous results

- Newborn screening is conducted using a dried blood spot from a heel prick.

- Residual dried blood spots can be stored for future uses.
Newborn Screening, cont

- Policies for the disposition of dried blood spots and research use vary
- Exploration of next generation genome technologies (i.e., whole genome sequencing) for newborn screening
  - Funding for research exploring this type of technology application is being conducted
  - Plans for management of potential findings, changing evidence base of genetic variations identified and management of incidental findings
Risk Assessment

- More than 55 hereditary cancer syndromes have been identified
- The most common cancer syndromes are those associated with breast, ovarian, and gastrointestinal cancers
  - Tumor features at diagnosis are now being used as an indication for genetic assessment
- Risk assessment also performed in other healthcare arenas such as cardiovascular diseases
- Germline susceptibility gene testing is available
  - Relevant to individuals whose disease management may be altered
  - At-risk family members
## Family History

<table>
<thead>
<tr>
<th></th>
<th>In the prior three months nurses seeing patients who RARELY OR NEVER assessed a family history</th>
<th>AGREED OR STRONGLY AGREED that family history taking should be a key component of nursing care</th>
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<tr>
<td>NNWFS</td>
<td>67%, (n=288/510)</td>
<td>84% (n=369/442)</td>
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<td>HO D</td>
<td>58% (n=59/102)</td>
<td>91% (n=219/242)</td>
</tr>
<tr>
<td>MINC</td>
<td>65% (n=3193/4923)</td>
<td>71% (n=4204/5942)</td>
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## Family History, MINC

<table>
<thead>
<tr>
<th>Question</th>
<th>% (N)</th>
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<tr>
<td>Not at all or only a little confident in deciding what family history information is needed to identify genetic susceptibility to common diseases.</td>
<td>52% (n=3313/6000)</td>
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<tr>
<td>Not at all or only a little confident in deciding which patients would benefit from a referral for genetic counseling and possible testing.</td>
<td>64% (n=3837/5962)</td>
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<td><strong>Always Collect:</strong></td>
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<tr>
<td>Relationship to the patient</td>
<td>72% (n=4010/5591)</td>
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<tr>
<td>Age of diagnosis</td>
<td>29% (n=1617/5566)</td>
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<td>Maternal and paternal lineages</td>
<td>53% (n=2953/5551)</td>
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<tr>
<td>Race or ethnic background</td>
<td>33% (n=1819/5533)</td>
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</table>
Family History in Nursing Practice

“It’s one of those times in your life that you are grateful you had the knowledge.”

Quote from: Barbara Ganster, RN, BSN
Breast Cancer Case Manager
National Naval Medical Center
Genetic and Genomic Influences Across the Healthcare Continuum

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Interdisciplinary Collaboration to Improve Health Outcomes

Screening

- Genetic information is being used to personalize health screening recommendations.
- SNP test results are being studied as a means to increase the specificity of risk calculation models (i.e. Gail model for breast cancer risk).
- Screening tests that include DNA analysis are being developed such as the multi-target stool DNA test, a less invasive means to screen for colon polyps or cancer.

Heigh et al. (2014). Detection of colorectal serrated polyps by stool DNA testing: comparison with fecal immunochemical testing for occult blood (FIT). PLoS One, 9, 9(1)e85659
Genetic and Genomic Influences Across the Healthcare Continuum

Preconception/Prenatal Screening
Newborn Screening
Risk Identification
Screening/Diagnosis
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Interdisciplinary Collaboration to Improve Health Outcomes
Diagnosis/Prognosis

- Establish an accurate diagnosis
- Tumor profiling is being used to identify recurrence risk to guide adjuvant therapy

Genetic and Genomic Influences Across the Healthcare Continuum

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Interdisciplinary Collaboration to Improve Health Outcomes
Targeting Treatment to a Specific Variant in the Melanoma Gene

Cancer Tumor Profiling and Precision Medicine Trials

- **Molecular Analysis for Therapy Choice (NCI-MATCH)**
  - Identify mutations/amplifications/translocations in patient tumor sample and assign patient to relevant agent/regimen

- **ClinOmics (NCI-Intramural)**
  - Molecular, genomic, proteomic, metabolomics and other high throughput (“Omics”) profiling on tumor and normal tissues for the identification of biomarkers and targets for therapy.

- **Basket trials hypotheses**
  - The presence of a molecular marker predicts response to a targeted therapy independent of tumor histology.

Pharmacogenomic Influences

- Efficacy
- Toxicity
  - inducers
  - inhibitors
- Pharmacodynamics
- Pharmacokinetics

PK = absorption, distribution, metabolism and excretion
PD = mechanism of action, drug concentration and effect
Polymorphisms and Phenotype

- **UM-Ultrarapid Metabolizer**
  - Unusually high activity of a drug metabolizing enzyme (DME) or drug transport protein (DTP)
  - Limited response to recommended doses

- **EM-Extensive Metabolizer**
  - Wild-type (normal activity) form of a DME or DTP
  - Expected efficacy at recommended doses

- **IM-Intermediate Metabolizer**
  - Reduced activity of a DME or DTP
  - Some decreased efficacy at recommended doses

- **PM-Poor Metabolizer**
  - Very low or no activity of a DME or DTP
  - Increased toxicity
  - Decreased efficacy at recommended doses

FDA Table of Pharmacogenomic Biomarkers in Drug Labeling

Drug labeling may contain information:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

163 drugs listed in this table

- Analgesia, cardiology, endocrinology, gastroenterology, hematology, in-bom errors of metabolism, neurology, oncology, infectious disease, psychiatry, rheumatology, toxicology, transplant

http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
Genetic and Genomic Influences Across the Healthcare Continuum

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Interdisciplinary Collaboration to Improve Health Outcomes
Symptom Management

- Priority area of nursing research is the study of the genetic influences of symptom clusters

Pharmacogenomics

- Inhibitors and/or Inducers
  - Implications for:
    - Medications used for other health conditions
    - Selecting medications to control
    - Use of over the counter medications like St. John’s Wort
    - Consumption of certain foods or supplements like grapefruit/grapefruit juice
Inhibitors and Inducers

- **Inhibitors**
  - Reduce the drug metabolizing enzyme or drug transport protein

- **Inducers**
  - Increase the drug metabolizing enzyme or drug transport protein
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<tr>
<th></th>
<th>1A2</th>
<th>2B6</th>
<th>2C8</th>
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http://medicine.iupui.edu/clinpharm/ddis/main-table/
Inhibitors compete with other drugs for a particular enzyme thus affecting the optimal level of metabolism of the substrate drug which in many cases affect the individual’s response to that particular medication, e.g., making it ineffective.

- **A Strong inhibitor** is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
- **A Moderate inhibitor** is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
- **A Weak inhibitor** is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

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*HIV Antivirals:
- indinavir
- nelfinavir
- ritonavir
- clarithromycin
- itraconazole
- ketoconazole
- nefazodone
- saquinavir
- suboxone
- telithromycin

*Grapefruit juice:
- verapamil
- diltiazem

*Others:
- cimetidine
- amiodarone
- NOT azithromycin
- chloramphenicol
- boceprevir
- ciprofloxacin
- dolavirdine
- diethyl-dithiocarbamate
- fluvoxamine
- gestodene
- induction
### P450 Drug Interaction Table

#### SUBSTRATES

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<td>saquinavir-boosted</td>
<td>meloxicam</td>
<td>pantoprazole</td>
<td>ketamine</td>
</tr>
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<td>pantoprazole</td>
<td>ketamine</td>
</tr>
</tbody>
</table>

**Notes:**
- N-acetylsalicylic acid can be a substrate or inhibitor depending on the dose.
- **PPIs:** propranolol, pimozide, and cimetidine can be inhibitors of CYP2C9.
- **Beta Blockers:** carvedilol, S-metoprolol, and propranolol can be substrates or inhibitors of CYP2D6.
- **Antidepressants:** amitriptyline, clomipramine, and desipramine can be substrates of CYP2C9.
- **Antipsychotics:** haloperidol, perphenazine, and risperidone can be substrates of CYP2D6.
- **Immune Modulators:** cyclosporine and tacrolimus can be substrates of CYP3A4.

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http://medicine.iupui.edu/clinpharm/ddis/main-table/
Genetic and Genomic Influences Across the Healthcare Continuum

- Preconception/Prenatal
- Newborn Screening
- Risk Identification
- Screening/Diagnosis
- Disease Characterization
- Individualized Therapy
- Management of Symptoms
- After End of Life

Interdisciplinary Collaboration to Improve Health Outcomes
Example of DNA Stability
Neanderthal Genome

Fig. 1 Samples and sites from which DNA was retrieved.

Genetic/Genomic Information

• Genetic and/or genomic tests can be performed on stored biospecimens
  ▪ Tissue blocks
  ▪ DNA banking
  ▪ Prior specimen collections
  ▪ Collections within 24 hours of death
## Genomic Knowledge

<table>
<thead>
<tr>
<th></th>
<th>NNWFS</th>
<th>HOD</th>
<th>NCEMNA</th>
<th>MINC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate their understanding of the genetics of common diseases as EXCELLENT or VERY GOOD</td>
<td>14% (n=73/510)</td>
<td>NA</td>
<td>15% (n=53/364)</td>
<td>7% (n=340/5091)</td>
</tr>
<tr>
<td>Have heard or read about the Genomic Nursing Competencies</td>
<td>33% (n=166/506)</td>
<td>NA</td>
<td>NA</td>
<td>9% (n=476/5250)</td>
</tr>
<tr>
<td>CORRECTLY answered question about whether genomic risk (as indicated by Fm Hx) has clinical relevance for coronary heart disease</td>
<td>99% (n=437/442)</td>
<td>98% (n=216/220)</td>
<td>98% (n=363/372)</td>
<td>99% (n=5108/5138)</td>
</tr>
<tr>
<td>INCORRECTLY stated that diabetes and heart disease are caused by a single gene variant</td>
<td>61% (n=268/442)</td>
<td>62% (n=137/220)</td>
<td>54% (n=105/193)</td>
<td>73% (n=3742/5138)</td>
</tr>
</tbody>
</table>
# MINC Genetic Education Impact

<table>
<thead>
<tr>
<th></th>
<th>Prior Genetics Education</th>
<th>No Prior Genetics Education</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported hearing or reading about the Competencies</td>
<td>24.9%</td>
<td>6.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Self described genetic/genomic knowledge and Good/Fair</td>
<td>44.6%</td>
<td>29.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean age of nurses reporting genetics in their curriculum</td>
<td>41.8 years</td>
<td>46.1 years</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Pharmacogenomic Knowledge Gaps

AMA office based MD (n=300) survey

Figure 2

<table>
<thead>
<tr>
<th>Percentage of respondents</th>
<th>Extremely or very familiar with pharmacogenomics</th>
<th>Strongly or somewhat agree that I am confident in my knowledge about influence of genetics on drug therapy</th>
<th>Have had formal training in pharmacogenomics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12.6%</td>
<td>37.0%</td>
<td>11.0%</td>
</tr>
</tbody>
</table>

Familiarity with, confidence in and knowledge of, and training in pharmacogenomics, as reported by physician respondents. “Formal training” was defined as medical school, residency, or continuing medical education.

Pharmacogenomic Knowledge Gaps

Figure 3

Reasons most commonly cited by physician respondents for not ordering a pharmacogenomic test in the past year, and for not anticipating ordering a pharmacogenomic test in the next year.

Notes: aSignificantly more primary care physicians than cardiologists reported that they did not know what test to order (75.0% versus 52.5%, $P<0.05$); bsignificantly more primary care physicians and psychiatrists than cardiologists reported that they would not know what test to order (84.6% and 83.9%, respectively, versus 44.8%; $P<0.05$).

Summary

- Recognize the relevancy and value of genomics to your role
- Evaluate your personal genomic competency and fill your competency gaps
- Utilize your leadership and skills to be a change agent/champion in your healthcare environment and within your professional organizations
- Recognize policy opportunities to ensure safe, effective and efficient translation of genomic clinical care
- Think creatively and be innovative about designing resources, education, infrastructures that facilitate appropriate adoption of genomics