Genomics 101:

An Overview from Scientific Bench to NICU Bedside

National Association of Neonatal Nurses

CoCANN Annual Conference, California Endowment Center
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Disclosures

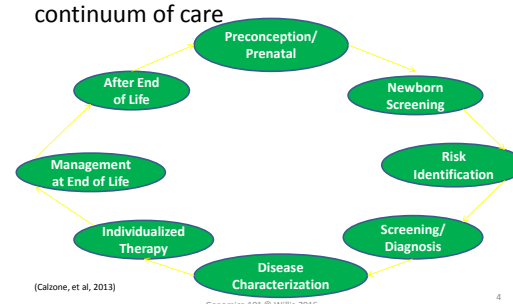
- I have no real or perceived financial relationships to disclose.
- No off-label use of pharmaceuticals will be discussed.
- Infant photographs used with parental consent.

Learning Objectives

- **Distinguish** genetics from genomics.
- **Demonstrate** family-centered neonatal care informed by genomics.
- **Identify and mitigate** two epigenetic influences in the NICU exposome.
- **Discuss** ethical, legal, and social implications of collaborative genomic medicine in the NICU.

Relevance to Healthcare

- Genetics & genomics throughout the continuum of care



(Calzone, et al, 2013)

Introduction to DNA

"It's a history book ~ a narrative of the journey of our species through time.

It's a shop manual, with an incredibly detailed blueprint for building every human cell.

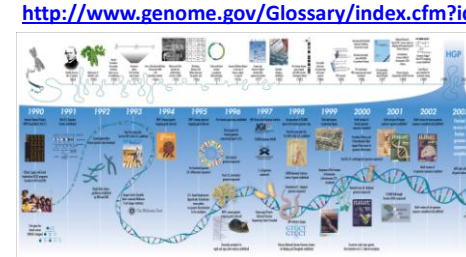
And it's a transformative textbook of medicine, with insights that will give health care providers immense new powers to treat, prevent and cure disease."

Francis Collins
American physician/geneticist
Former Director, Human Genome Project
Director, National Institutes of Health

DNA: A Fantastic Voyage

- **Genetic Code** (video)

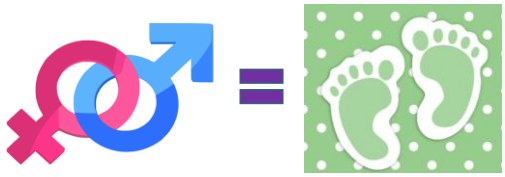
http://www.genome.gov/Glossary/index.cfm?id=78



www.genome.gov, NIH Genome.NHGRI-85325

Back to Basics

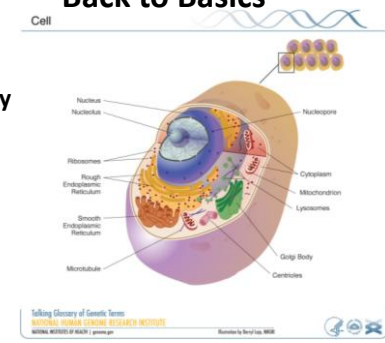
- **Where did we come from?**



https://pixabay.com/en/gender-sex-symbol-male-female-312411/ http://www.publicdomainpictures.net/view-image.php?image=37255&picture=black-footprints-clipart

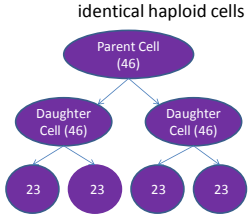
Back to Basics

- **Cell biology**

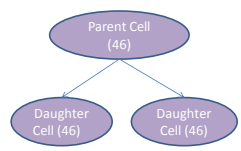


Cell Division

- **Meiosis**
  - Sex cells (Diploid germ cells: male or female)
  - Yield = 4 non-genetically identical haploid cells



- **Mitosis**
  - Body cells (Diploid: potential for any organ)
  - Yield = 2 genetically identical diploid cells



(GSLC, 2014; NHGRI, 2014; Rathnau-Minella, 2008)

Mendelian Inheritance

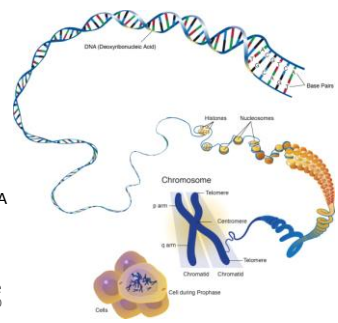
- **Basic concepts**
  - **Allele**
    - 1 of 2 or more different versions of a gene
  - **Dominant**
    - Only 1 allele of a gene necessary to express trait
  - **Recessive**
    - Both alleles of a gene must be identical to express trait
  - **Heterozygous**
    - Alleles of a particular gene are not identical
  - **Homozygous**
    - Alleles of a particular gene are identical

(GSLC, 2014; NHGRI Talking Glossary, 2014)

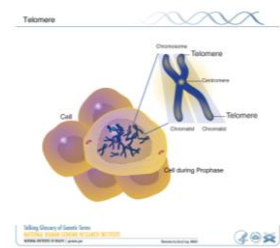
Genetics vs. Genomics

- **Genetics**
  - "Study of genes [the genome] & their role in inheritance."
    - Gene
      - Segment of DNA that tells cell how to make a certain protein
      - ~ 25,000 in human genome

(NHGRI, 2014; www.genome.gov)



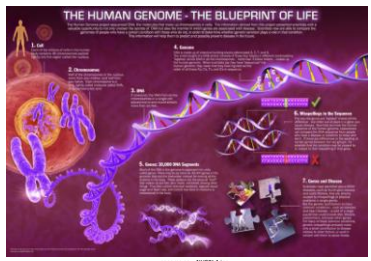
A Bit about Telomeres



- End of a chromosome
- Made of repetitive sequences of non-coding DNA (intron)
- Protect chromosome from damage
- Each time cell divides, telomeres shorten
- Eventually, telomeres so short, cell can no longer divide → Death

(Lyon, et al., 2014; NHGRI Talking Glossary, 2014)

Genetics vs. Genomics



www.genome.gov, NHGRI-1.jpg

- **Genomics**
  - "Study of all the genes in the human genome together, including their interactions with each other, the environment, & the influence of other psychosocial & cultural factors."

(Consensus Panel on Genetic/Genomic Nursing Competencies ,2009, p. 9)

ABCs of DNA

www.genome.gov, DNA Base Pair.NGHRI-85271.jpg

Genetic code ~ The alphabet

- 3 billion base pairs in human genome
- Combinations of base pairs specify amino acid sequence of proteins
- Rung of DNA ladder = 2 chemical bases
- Twisted ladder = Double-stranded helix
- Each strand = Backbone made of alternating sugar (deoxyribose) & phosphate groups
- Nucleotides (chemical building blocks) attached to each sugar
  - 1 of 4 nitrogenous bases, specifically paired & joined by hydrogen bonds
    - Adenine (A) with Thymine (T)
    - Cytosine (C) with Guanine (G)

(NHGRI Talking Glossary ,2016)

Grammar of DNA

- **Nouns**
  - What's currently known
  - DNA coding portions (*exons)*
    - 0.1% of total DNA
- **Other important parts of speech**
  - What's not known
  - Non-coding portions (*introns*), 99.9% of total DNA
    - Verbs: Action words
    - Adjectives: Modify noun (color, size, amount, speed)
    - Adverbs: Modify verbs or adjectives
    - Articles: Specificity
    - Punctuation: Regulates flow (start, stop, emphasis)

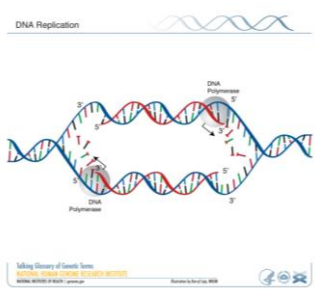
(Bob Blakesley, PhD, Director, National Automated Sequencing Center, 2014)

Fascinating Facts

- **In humans 99.9% of DNA bases/sequence are the same!** (i.e. genetic make-up/genotype)
  - 1 difference in every 1,000 nucleotides (0.1% or 3 million total nucleotide differences) determines unique:
    - Phenotype (observable expression)
      - Physical features
      - Behavior
    - Risk for disease
  - Variations in the 0.1%
    - Most due to SNPs
    - Harmless/Harmful
    - Imminent/Latent

(Jenkins & Calzone, 2014; Klug et al, 2007; NHGRI Talking Glossary, 2014)

Characteristics of DNA



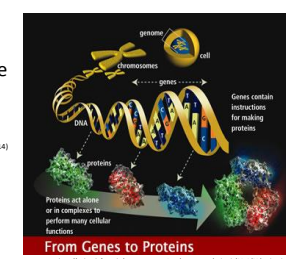
- **Replication**
- **Information**
  - Storage
  - Expression
- **Variation by mutation**

(NHGRI Talking Glossary, 2014)

Molecular Genetics

- **6-word synopsis:**
  DNA makes RNA which makes proteins!
  - Majority of proteins are enzymes (biologic catalysts essential to sustain life)

(Klug, et al, 2007; NHGRI Talking Glossary, 2014)

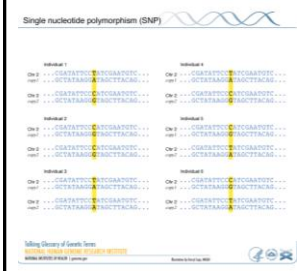


http://pubweb.fccc.edu/cancerconversations/wp-content/uploads/2013/02/Molecular Medicine.jpg

Variance in DNA Sequence

- **Polymorphisms**
- **Deletions**
- **Insertions**
- **Translocations**

Single Nucleotide Polymorphism



- **SNP**
  - Variation of a single base pair
  - > 1% of population
    - Common (10 million SNPs ID'd)
    - Usually in non-coding regions
  - Not harmful, weak or no effect (Ex. size, color, & shape of body parts)
  - However, NHGRI priority
    - How human genome correlates with disease, drug response, & other phenotypes

(Casellas, 2014; Jenkins & Calzone, 2014; NHGRI Talking Glossary, 2014)

Mutations

- **Incidence**
  - < 1% of population
- **Characteristics**
  - Change in DNA
  - Result from DNA copying mistakes
    - During cell division
    - Mutagenic events (Ionizing radiation; Chemicals; Infection by viruses; Cellular metabolites)
- **Types**
  - Germ line: Occur in eggs & sperm & CAN be passed on
  - Somatic: Occur in body cell & are NOT passed on to offspring

(Casalles, 2014; NHGRI Talking Glossary, 2014)

Effects of Mutations

- **(+)**
  - Most mutations are neutral
    - Most DNA does NOT code for proteins or RNA
    - Ancient change often adaptive for survival
  - Genomic medicine: Mutant genes serve as markers for location on chromosomes
- **(-)**
  - Recent change almost always harmful (disease, deformity, death)
  - Gain of function mutations often result in dominant disorders
  - Loss of function mutations result in recessive disease

(Casalles, 2014; Klug et al, 2007)

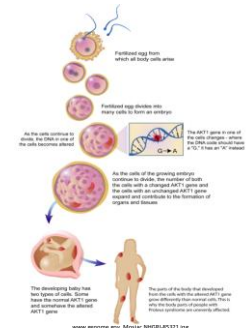
Products of Mutations

- **Single gene disorders**
  - **Dominant**
    - Huntington's Disease
  - **Recessive**
    - Sickle Cell Anemia
    - Cystic Fibrosis
  - **Sex linked**
    - Hemophilia
      - Son (+/- disease)
      - Daughter (+/- carrier)
- **Karyotype abnormalities**
  - **Translocation**: Movement of chromosomal segment to new location on genome → Change in chromosome number
    - Trisomies (13, 18, 21)
    - Kleinfelters Syndrome (XXY)
    - Turners Syndrome (X)
  - **Fragile sites** → susceptible to chromosomal breakage
    - Fragile X

(NHGRI, Talking Glossary, 2014)

Genetic Mosaicism

- **Definition**
  - *"an individual or cell culture having two or more cell lines that are karyotypically or genotypically distinct but are derived from a single zygote."* http://medical-dictionary.thefree dictionary.com/mosiac
  - *"…cells within the same person have a different genetic makeup."* http://www.nlm.nih.gov/medlineplus/ency/ article/001317.htm



www.genome.gov, Mosiac.NHGRI-85321.jpg

Genetic Mosaicism

- **Causes**
  - Error in cell division early in development of unborn baby
- **Symptoms**
  - Vary & difficult to predict
- **Diagnosis**
  - Genetic testing
- **Example**
  - Mosiac Down Syndrome
- **Treatment**
  - Depends on type and severity of disorder
- **Prevention**
  - None known
- **Prognosis**
  - Depends on which organs & tissues affected
  - ↑ Abnormal cells → similar to typical disease presentation
  - ↓ Abnormal cells → mild or no affect

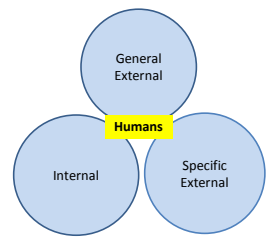
(Medicine Net, 2014; Medline Plus, 2014)

Epigenetics & Epigenomics

- ***Epi*: Greek "*above*"**
- **Interplay between genes & epi-genomic environment**
  - **Activation & deactivation** (turn on & turn off/silence) of genes WITHOUT any change in underlying DNA sequence
    - Reversible depending on exposome
  - **Exposome** (age, diet, stress, Rx, environment)
    - Chemical signature (Modifies or marks genome function)
    - Cell memory (Tells cell what to do & when to do it)
    - Not part of actual DNA
    - Can be passed along from cell to cell during division & from one generation to the next
  - **Methylation**
    - Marker for epigenetic change(s); possibly gene silencing
    - Transfer of methyl (CH3 group) to a DNA base
    - Involved in many cancers, auto immune disorders, mental illness, & diabetes

(NHGRI Talking Glossary, 2014; Jenkins & Calzone, 2014); Olden & White, 2005)

The Exposome



(Wild, 2012)

- **Internal**
  - Omes & omics

(Wild, 2012)

- **External**
  - Where we
    - Live
    - Work
    - Play
    - Pray

(Juarez, 2015)

Exposome & Epigenetics

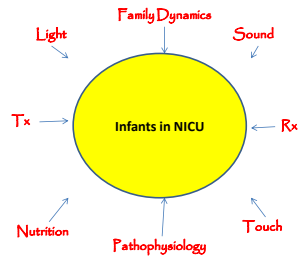
- **Sources in exposome that may cause epigenetic changes**
  - Developmental
    - In utero
    - Childhood
  - Environmental chemicals
  - Drugs
  - Aging
  - Diet
- **Potential sequelae of epigenetic changes**
  - Cancer
  - Diabetes
  - Autoimmune disease
  - Mental disorders

(Juarez, ,2015; Wild, 2012)

Epigenetics & NICU Exposome

- **Greatest vulnerability to epigenetic changes**
  - Beginning of life, at conception
    - Rapid cell division
  - Towards end of life
    - Aging system
    - Shortened telomeres
- **Impact of stress**
  - Some
    - **(+)** Gene expression → resilience
  - Too much
    - **(-)** Gene expression → toxic or lethal

(Coughlin, 2011; RWJF, 2014)



Role of the NICU-RN

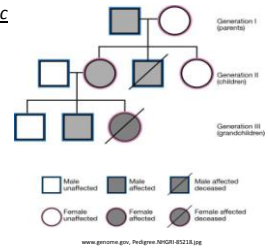
- **Care coordination & multidisciplinary team collaboration**
  - Genomic competence improves patient outcomes
    - Monitor & mitigate NICU exposome
  - Genetic risk assessment
  - Patient advocacy & ethical considerations
  - Personalized medicine

(GNCISP, 2014)

Genetic Risk Assessment

- **History**
  - Medical subspecialists, *genetic counselors*, & nursing
  - Family health hx (pedigree)
- **Recognize newborn risk**
  - Morbidity or mortality resulting from genetic errors of metabolism
- **Genetic Testing**
  - CLIA certified lab

(NHGRI, 2014)



www.genome.gov, Pedigree.NHGRI-85218.jpg

Genetic Risk Assessment

- **Antenatal/Pre-conception testing**
  - Single gene mutations carrier status
- **Prenatal testing**
  - Indications (risk factors)
    - Advanced maternal age
    - Family Hx
    - Ancestry/ethnicity
  - Types
    - Amniocentesis
    - Chorionic villus sampling
    - Peripheral maternal blood
- **Postnatal testing**

(Calif. DPH, 2014; NHGRI, 2014)

Postnatal Genetic Testing

- **Initial Newborn Screening**
  - Public health approach to early detection & management heritable conditions
    - ~12 million NBs screened/yr
    - ~12,500 new Dx
  - Federal mandate for several different genetic disorders
    - Specific conditions vary by state
      - Inborn errors of metabolism
      - Hemoglobinopathies
      - Single gene disorders
  - Storage for future use???

(California DPH, 2014)

Postnatal Genetic Testing

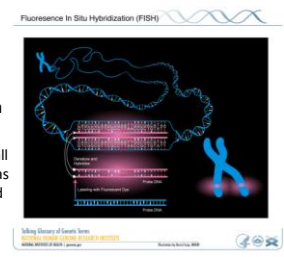
- **Karyotype**
  - Individual's collection of chromosomes
    - Chromosome analysis
    - Useful to determine
      - Sex
      - Presence of mono, tri, & tetrasomies

(NHGRI Talking Glossary, 2014)

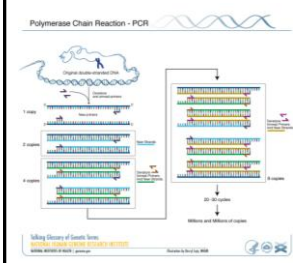
Postnatal Genetic Testing

- **Fluorescence in situ hybridization (FISH)**
  - Detects & locates a specific DNA sequence (small deletions or duplications) on a chromosome
    - Exposes chromosomes to small DNA sequence (probe) that has fluorescent molecule attached
    - Probe sequence binds to corresponding sequence on chromosome

(NHGRI Talking Glossary, 2014)



Postnatal Genetic Testing

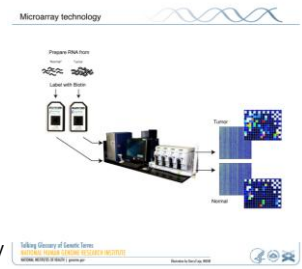


- **Polymerase Chain Reaction (PCR)**
  - Amplify DNA sequences
    - Short DNA sequences (primers) used to select portion of genome to be amplified
    - Temperature of sample repeatedly raised & lowered to help a DNA replication enzyme copy target DNA sequence
    - Can produce a billion copies of target sequence in just a few hours
  - Especially useful for crime scene investigation

(NHGRI Talking Glossary, 2014)

Postnatal Genetic Testing

- **Microarray**
  - **Types**
    - SNP
    - Mitochondrial DNA
    - RNA
    - Methylation
  - **Indications**
    - Study expression of many genes at once using chip technology

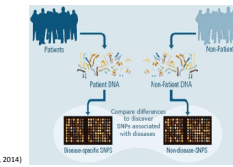


(NHGRI Talking Glossary, 2014)

Postnatal Genetic Testing

- **Genome-wide association study (GWAS)**
  - Associate specific genetic variations with particular diseases
  - Scanning genomes from many different people & looking for genetic markers that can be used to predict presence of a disease
  - Once genetic markers ID'd, can be used to understand how genes contribute to disease & develop better prevention & TX strategies
  - Types
    - Sequencing
      - Whole genome
      - Whole exome
      - RNA
      - mRNA
    - Analysis
      - Whole genome SNP

(NHGRI Talking Glossary, 2014)



Postnatal Genetic Testing

- **Nursing considerations**
  - **Informed consent**
  - **Quality specimen collection**
    - Personal protective equipment
    - Precision
      - Source
      - Quantity
    - Transport & storage
      - Prevent contamination & degradation

(GNCISP, 2014)

Patient Advocacy & Ethics

- **Nursing considerations in the NICU**
  - Patient Privacy
  - Incidental Findings
  - The Common Rule

Patient Privacy

- **HIPAA** (USHHS, 2014)
  - Health Insurance Portability & Accountability Act of 1996
    - Privacy rule for protected health information
- **GINA** (USHHS, 2014)
  - Genetic Information Nondiscrimination Act of 2008, Public Law 110-223
    - Debated in Congress for 13 years!
    - Baseline protection at federal level: Allows "people to take full advantage of the promise of personalized medicine without fear of discrimination." (genome.gov, 2012)
      - Title I: Health coverage
      - Title II: Employment
    - Part of informed consent for patient participation in research

Incidental Findings

- **Recommendations from American College of Medical Genetics & Genomics** (ACMG)
  - **Laboratory responsibilities**
    - Report constitutional mutations found regardless of original indication for clinical sequencing
      - Genes previously reported & recognized cause of the disorder or variants previously unreported, but are of the type which is expected to cause the disorder
    - Report regardless of age of patient
  - **Clinical team responsibilities**
    - Provide comprehensive pre & post-test parent counseling
    - Alert parents to possibility that clinical sequencing may generate incidental findings the could require further evaluation
    - Consult clinical geneticist prn for ordering, interpreting & communicating genomic testing

(Green, et al, 2013); McCullough, 2015) 42

The Common Rule

- Fundamental ethical principles to protect human participants in biomedical/behavioral research
- Ethical imperative
  - Application of Common Rule to care of high risk infants
    - **Respect**: for HRIs & their families: Acknowledge dignity & autonomy
    - **Beneficence**: Secure HRI/family well-being & refrain from harm
    - **Justice**: Fair distribution of benefits & burdens of care & care environment
    - **Vulnerable populations**
      - Neonates/infants require special protection due to diminished autonomy

(Belmont Report, 1979)

Personalized Medicine in the NICU

- **Definition**
  "…an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease." (NHGRI Talking Glossary, 2014)
  - **Dx specific: Omics & Omes**
    - Proteomics
    - Metabolomics
    - Nutriomics
    - Microbiome
    - Pharmacogenomics
    - Exposome
- **Challenge: BD2B**
  - **Volume:** Organizing big data
  - **Variety**: DNA, RNA, & Omics
  - **Velocity**: Timely analysis
  - **Veracity:** Truth

(IBM, 2014: Minich & Bland, 2013; Shonkoff & Phillips, 2000)

Nutrition: "etics" & "omics"

- **Nutrigenetics**
  - Effect of genetics on diet, nutrition, & health
    - Outcome of consuming different types of food
    - Influence on metabolism (especially fats)
    - Influence on food intake
      - Dopamine (food as reward)
      - Serotonin (↓appetite)
- **Nutrigenomics**
  - Impact of nutrients on function & stability of genes
- **Bench to bedside application**
  - Personalized nutrition plans to ↑health & ↓ disease

(Briere, 2015)

Human Microbiome

www.genome.gov.Human Microbiome.NHGRI-BS347.jpg

- **Flora**
  - Normal
  - Pathogens
- **Nursing implications**
  - Sepsis
  - MRSA
  - NEC
  - Tooth decay

(Cong, 2014; NHGRI Talking Glossary, 2014)

Neonatal Gut Microbiome

- NIH-Human Microbiome Project
  - Launched 2007
  - Pregnancy & preterm birth
- Microbes significantly outnumber human cells
- Initial acquisition at birth & infancy
  - Internal & external exposome
  - Impacts short & long-term health outcomes
  - Commensal vs. pathogenic microbes
- Brain-gut-microbiota axis ↔ Early life experience
- Ideal: healthy mother, NSVD, full-term, minimal mother-infant separation, breast milk feedings, no Abx or H2 blockers

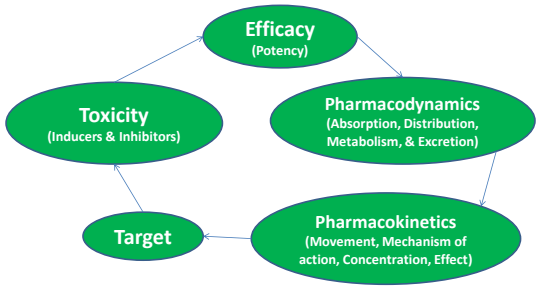
(Cong, et al., 2015; Cong, 2014; Gregory, 2015; Hartz, et al., 2015; NIH, 2015)

Pharmacogenomics

- **Branch of pharmacology**
  - Use of genetic & genomic information to inform drug development & testing
  - Correlate individual genetic variation w/drug responses
- **Goals**
  - I.D. biomarkers for drug labeling
  - Maximize effect
  - Minimize adverse reaction
    - 106,000 deaths/year in U.S.
    - 2 million suffer serious toxicities

(FDA, 2014; Jenkins & Calzone, 2014; NHGRI Talking Glossary, 2014)

Pharmacogenomic Influences



(Jenkins & Calzone, 2014)

Pharmacogenomics

- **Individualized response**
  - Anticipated response
  - No response
  - Toxic response
    - Adverse drug reaction at recommended dose
- **Polymorphisms & Phenotype**
  - Types of metabolizers
    - Ultrarapid
    - Extensive
    - Intermediate
    - Poor

(Katz, et al, 2008; Barkley, 2015)

Pharmacogenomics

- **Cytochrome P450**
  - System > 40 enzymes
  - Biosynthesis of steroids, fatty acids, & bile acids
  - Metabolism & biotransformation in liver of endogenous & a wide variety of exogenous substrates, such as toxins & drugs

(Budnitz, 2006; Wang, 2011)

- **Nursing implications**
  - 8-rights
  - Patient education
  - Monitor
    - Family Hx
    - Patient response
    - Drug levels prn

(GNCISP, 2014; USHHS, 2014)

Genomic-Informed FCC

- **NICU-Family Centered Care informed by genomics**
  - Dignity & respect
  - Information sharing
  - Participation
  - Collaboration

(AAP, 2003; Brazelton, 1992; Griffin, 2006; Inst. for FCC, 2008)

FCC-Dignity & Respect

- Honor & incorporate family perspectives, choices, knowledge, values, beliefs, & culture
- Parents respected as experts on their child
- Care, support, & education of patient in genomic era
  - Individual
  - Family
  - Community
  - Population

(AAP, 2003; Brazelton, 1992; Griffin, 2006; Consensus Panel, 2009; Jenkins & Calzone, 2014; Inst. for FCC, 2008)

FCC-Information Sharing

- Complete, accurate, timely, useful, affirming, & unbiased

(AAP, 2003; Brazelton, 1992; Griffin, 2006; Inst. for FCC, 2008)

- **In genomic era**
  - Recognize one's own attitudes & values
  - Assess client knowledge, perceptions, & responses
  - Advocate for patients & families
  - Professional development
  - Incorporate genomic technologies & information into practice
  - Tailoring genetic & genomic information & services based on family's culture, religion, knowledge level, literacy, & preferred language
  - Advocate for rights of all patients & families

(Consensus Panel, 2009)

FCC-Participation

- Encourage & support parent involvement regardless of the genetic driven prognosis
- Evidenced-based developmentally supportive care
  - Minimize NICU exposome

(AAP, 2003; Brazelton, 1992; Coughlin, 2011; Griffin, 2006; Inst. for FCC, 2008)

FCC-Collaboration

- **Apply & integrate genetic/genomic knowledge to family/NICU multidisciplinary team collaboration**
  - Ethical considerations unique to genomic issues
  - Policy, procedures, program development & evaluation
  - 3-generation family health hx (genetic, developmental, & environmental risks)
  - Prevention, screening, diagnostics, prognostics, TX selection & effectiveness
  - Plan of care, incorporating genetic & genomic assessments pre & post D/C
    - Referral Activities
    - Education, care, & support

(AAP, 2003; Brazelton, 1992; Consensus Panel, 2009; Griffin, 2006; Inst. for FCC, 2008)

Neonatal Case Study

- **Learning & growing together!**

Professional Development Exposome

- **Opportunities for Genomic Nursing Competence**
  - **National Human Genome Research Project:** www.genome.gov
  - **Genetics Science Learning Center:** learn.genetics.utah.edu/
  - **CDC Genomics & Family Health History**: www.cdc.gov/genomics
  - **DNA from the Beginning**: www.dnafth.org
  - **Global Genetics & Genomics Community (G3C):** http://g-3-c.org/en
  - **The ABCs of Genetics: Self-study course, 2nd Ed:** www.nann.org (Rathnau-Minnella; 2008)
  - **Coursera**: www.coursera.com
  - **International Society of Nurses in Genetics**-ISONG: www.isong.org
  - **Genomic Nursing Competency Implementation Strategic Plan, 2014-2020**
    - http://www.genome.gov/Pages/Health/HealthCareProvidersInfo/CompetencyImplementationStrategicPlan07-14-2014.pdf
  - **Genetics in Primary Care Institute Tool Kit:** www.geneticsinprimarycare.org
  - **"Genetic friendly" books**
    - Epi-Genetics: *The ultimate mystery of inheritance* (Francis, 2011)
    - From Neurons to Neighborhoods: The science of early childhood development (Shonkoff & Phillips, 2000)
    - *The Immortal Life of Henrietta Lacks* (Skloot, 2009)
  - **Field Trip: Human Genome Project Traveling Exhibit :** www.genome.gov

Summary

- **Genomics 101: An Overview from scientific bench to NICU Bedside**
  - Genetics = Genes
  - Genomics = Genes + Interactions among genes + Interactions w/environment, & the influence of other psychosocial & cultural factors
  - All NICU patients at risk for epigenetic changes
  - Prioritize minimization & mitigation of the NICU exposome
  - Incorporate Family Centered Care informed by genomics

THANK YOU!

- **Questions**
- **Comments**
- **Final thought**

"There are two ways to live your life, One is as though nothing is a miracle. The other is as if everything is."

~Albert Einstein, Preemie

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