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PERSONALIZED GENOMICS IN THE 21ST CENTURY: IMPLICATIONS FOR NURSING RESEARCH WITH CHILDREN AND FAMILIES

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Abstract

The purpose of this paper is to present an overview of advances in genome research and personalized genomics, and the implications for nursing research and practice relevant to children and families. Personalized genomics carries significant promise to improve health care. Current significant advances in genome research have been centered on cancer. As the cost of genome data are decreased significantly, it has been projected that genome data will become part of health care data, beginning with newborn populations in next 10 years. Genome related nursing research for children and families can involve aspects of bio-behavioral susceptibility, gene expression profile analyses, as well as epigenetics in developing children and families. Research on nursing

interventions can target environmental influences on children and families, to design early interventions for vulnerable populations to reduce genome related disease risks and to improve health care outcomes. True collaborations among multi-disciplinary teams are required to improve the health care delivery for the best interests of the children, families, and future generations.

Keywords: personalized genomics; Genome; genetics; bio-behavioral susceptibility; gene-environment interaction; epigenetics in developing children, families, and future generations

PERSONALIZED GENOMICS IN THE 21ST CENTURY: IMPLICATIONS FOR NURSING RESEARCH WITH CHILDREN AND FAMILIES

Personalized Health Care in the 21st Century

The practice of personalized genomics is broadly defined as the study of entire deoxyribonucleic acid (DNA) sequences of an individual's complete human genome sequencing (CHGS), which may have indications for personal health and disease. It carries significant promise to improve treatment precision and the care by which treatments can be customized to individual patients by delivering the right treatment at the right time.[1-3] With the completion of the human genome project in 2003, about 25,000 genes and the sequencing of over 3 billion base pairs of human DNA have been determined.[4-6] [7] [7(cont.)] In 2007, the United States Department of Health and Human Services (DHHS)[8,9] produced a position statement proposing that personalized health care should be transformed to include genome data.[10,11] Clinical translations of genome discoveries from bench to bedside are recommended for optimal health care.[12] Health care systems will evolve by far the greatest magnitude in human history with the clinical translations of genome discoveries from clinical to bedside and the complex science-based personalized genomics.[1,2] This article will review advances in genome research and personalized genomics, including the implications for nursing research and practice.

Genetics to Public Health Genomics

Genomic studies include all genes, the gene-environment interactions, and other psychosocial and cultural factors in the human genome, with much greater and common occurrence in populations. Prior to the 1990s, genetics was practiced in the care of children and families mostly by the diagnosis and classification of common hereditary diseases from single genes and chromosomal conditions, which comprised less than 1% occurrence.[13] In 2007 and 2008, the National Office of Public Health Genomics (PHG) at the Centers for Disease Control and Prevention (CDC), called for the integration of genomics into public health research, policy and programs.[14,15] The impact of genes interacting with diet, behavior, and environment on the health of populations is the focus of PHG. PHG emphasizes using genome data for early disease detection to improve

outcomes such as newborn screening. Emphases are given for genome application on services program research (third stage of research translation or T3), and for policy as well as large network services evaluation for greater impact on health care (fourth stage of research translation or T4). Note that, according to Khoury and others,[15] the first stage of translation (T1) involves human models translated from animal models (animal models being T0), and the second stage of translation (T2) involves synthesis of evidence for evidence-based practice.

Personalized genomics is where individual genomes are assessed to determine individual susceptibility to diseases and response to specific drugs so that treatments can be customized to the individual patients.[3] Hence, the advances in personalized genomics will help to achieve personalized health care with improved understanding of responses to therapies,[3] by taking individual characteristics into consideration when delivering the customized care strategies.[16-19] Personalized genome data include the collection of genetic profile analyses with detailed family health history with at least a three generational family pedigree that includes disease risk factors, disease characterization, and patient characteristics.[12,20,21] Whereas, phenotype analyses include observable traits or physical and biochemical characteristics of an organism such as color, weight, presence of diseases, and different progression or development of diseases.[3,17,20-25] Genome related analyses include the genotype analyses [DNA mutation, single nucleotide polymorphism (SNP), gene sequencing and analyses to examine the inherited genetic alterations] of blood cells, tissues, and stem cells, as well as gene expression profile microarrays and proteomics.[22-24]

In 2007, the complete human genome sequencing (CHGS) was completed with a new highthroughput 454 Pyrosequencing technology (454 Life Sciences, Branford, Connecticut). Watson's CHGS was accomplished 78 times faster, in two months rather than 13 years, and 3,000 times less expensive, at one million dollars rather than the previous three billion dollars.[26,27] As the cost for the individual human genome sequencing decreases to an affordable expense for some people, the era of the personalized genomics is becoming an approachable reality in health care. The cost of CHGS, based on the target set forth by the National Human Genome Research Institute (NHGRI) of National Institutes of Health (NIH), will decrease to $1,000 by 2014 or earlier.[28] The $1,000 cost will make personalized genomics feasible for routine care. For example, in Canada where one million babies are born each year, the cost of CHGS would be about $1 billion per year, or about 1% of Canada's total heath care budget. With the targeted lower cost of CHGS, personalized genomics could become a reality for routine newborn screening and clinical care.[15]

Bioinformatics analysis for individual genome, disease association of gene and loci, are already being investigated at various sequencing centers in the world.[29-31] Private companies have also become involved in providing partial genotyping, most focusing on selected disease risks. Relatively simple saliva and cheek cell samples are required to test a portion of genome, range of 600,000 to1 million

SNPs to estimate 20 and more disease risks, with racial-ethic related profiles. Though the cost or these genome data is reduced ($399 and lower over time), there is not yet a formalized standard regulation for these private laboratories beyond their own internal standards.[32]

Functional genomics involves the investigation of the functional elements in the human genome including gene transcription and protein-protein interactions.[33] [33(cont.)] [33(cont.)] [34] In September 2003, the NHGRI launched the ENCODE (ENCyclopedia Of DNA Elements) project, a critical public research consortium to investigate functional elements.[33] [33(cont.)] [33(cont.)] [35,36]The transcription of the annotations discovered 10 times more non-coding transcripts than the number of protein-coding genes, for the linkage structure of human genome and mapping loci for complex diseases. The second phase of ENCODE was launched in late 2007 to identify and list all biologically functional elements in human genome.[37,38]

A large fraction of the genome sequences involves the elements of ribonucleic acids (RNAs). These RNAs include micro RNAs (miRNA, single-stranded RNA molecules), small regulatory RNAs, small interfering RNAs (siRNA, also called silencing RNAs, double-stranded RNA molecules), and longer non-coding RNAs.[39-41] MiRNAs are small RNA molecules, encoded by the genes that are transcribed from DNA but not translated into protein.[42] Mature miRNA molecules are partially complementary to messenger RNA (mRNA) molecules, with main functions to down-regulate gene expression by interacting with the mRNAs. SiRNAs interferes with the expression of a particular gene and can be exogenously introduced into cells to knockdown a gene of interest.[43-45] Essentially any gene of which the sequence is known can be targeted with an appropriately tailored siRNA,[46] an important tool for drug development in the post-genomic era. Hence, these small RNA molecules are investigated for their potential therapeutic properties in the development of diseases.[47] Molecular imaging involves the identification of small molecules as probes and potential therapeutics to identify targets in the cell for future therapeutics.[48]

Research Opportunities

Funding opportunities for genome research continue to increase in the current post genomic era, which includes integrative comprehensive analyses of multi-genome analyses and functional genomics. Special calls for proposals are being announced with the need for faster clinical translations of genome research for personalized genomics. For example, the new National Institutes of Health (NIH) Roadmap Transformative R01 (T-R01) program was announced in late 2008 with the goal to foster the development of exceptionally innovative, high risk, original and unconventional research with the potential to challenge existing scientific paradigms (NIH RFA-RM-08-029). Symptom management and genome care for individuals and families has been prioritized as a major focus for nursing research.[49-51] The National Institutes for Nursing Research (NINR) has a

Graduate Partnerships Program (GPP) in bio-behavioral research with the focus on symptom management and genetics.

Started in 2008, research proposals are requested from CDC for genome research translation.[14] Khoury and others estimated that less than 3% of research so far has involved research translation into practice.[15] Thus, continued increased funding opportunities are needed to address epigenomics of human health and diseases; for research translation of genome into clinical application; and for educational, behavioral, or social studies. Following the genome sequencing projects, substantial research will be needed to link the risks associated with the new genome variations with clinical practice. Research opportunities for nursing and health care in personalized genomics will continue to grow, with the emergence of new genome research paradigms.

Cancer genome sequencing research emphases. One example of the major advances of genome sequencing research is in the study of cancer. In 2008, Tumor Sequencing Projects (TSP), launched by the NHGRI sequenced exons of 1,000 candidate tumor gene specimens for lung adenocarcinoma,[52,53] involving comprehensive genomic characterization and evaluation of molecular utilities in diagnosis, prognosis, and treatment.[54]In 2005, NHGRI and the National Cancer Institute (NCI) of NIH jointly launched The Cancer Genome Atlas (TCGA) to accelerate the understanding of molecular basis of cancer. Glioblastoma multiform (GBM), a brain tumor, was selected as a first candidate to sequence on 1,200 candidate tumor genes in 500 patients,[55] due to its low survival rate of less than a year and the hope that the treatments using different genomic inhibitors might be tailored for the patients based on the genome alterations. Because large cohorts of high-quality tumor samples are difficult to obtain from a single institution in many serious cancer types, large research network groups have been formed to construct tissue banks using cutting edge genome analyses.[56-60] Thus, data are shared to accumulate large databases for association with populations.[61]

The analyses of cancer genomics in the post-genome era involve multi-dimensional analysis of DNA sequencing, proteomics, and functional genomics.[62] Biomarkers are discovered using tissue samples, blood, and fluids by using various technologies. Basic scientists on cell cycle control, invasion and micro-environmental alterations, apoptosis, cell signaling, immunology, and clinicians, oncologists, surgeons, pathologist, and epidemiologists collaborate to investigate cancer progression. Additional genome sequencing emphases are on the virus and bacterial species, such as the West Nile virus,[63] Escherichia coli,[64] and HIV virus,[65] for the treatment and prevention of infectious diseases.

Guidelines have been established on tissue repositories and quality control procedures to prevent contamination and degradation of the samples, especially as RNAs may lose its integrity after five years if not frozen and stored appropriately.[59,66-69] Surgeons, pathologists, technicians, genomics scientists, as

well as nurses should be informed of different collection procedures for DNA, RNA, and protein samples. Tissue samples should be stored using de-identification techniques. Matched blood samples are commonly collected in conjunction with the tissue samples (tumor tissues and surrounding normal healthy tissues). Clinical information databases are generally stored on web-based servers with restricted access, in compliance with the Health Information Portability and Accountability Act (HIPAA).[70,71] Material transfer agreements and data sharing policies are important for such tissue resource networks and organizations. For the ENCODE project, as the biological functions of DNA sequence elements may be linked to the clinical utility for licensing in genomic inventions, data sharing policies have been established.[38] NHGRI recommended a 9-month protection period during which scientists can freely use the ENCODE data, but cannot submit papers for publication without prior consent of releasers or until the data releasers have published first using the data.

Opportunities with environmental factors and bio-behavioral susceptibility to disease. Genomics have brought a significant paradigm shift from acute intervention to prospective preventive personalized care to reduce risk behaviors and environmental toxic exposures.[72,73] Current genome-wide studies have identified DNA sequencing variations with chronic diseases. However, less than a moderate degree of associations suggests that other factors including interacting environmental factors may play a more important role.[74] Nursing research has been reported in relation to gene-wide associations with signs, symptoms, and healthy behaviors for patients with breast cancer, for individual resource needs.[75] While lifestyle factors in cardiovascular genome studies included smoking, alcohol, and stressors,[76-81] future investigations are pointed to nutrition and epigenetics from childhood and early development for the prevention.[82-84] Nursing research can be designed to investigate healthy behaviors including nutritional intake and epigenetics from early development (fetal stage to early childhood) in family context.

For nurses and health care providers who are exposed to anti-neoplastic drugs, in comparison to nurses who are not exposed, genotoxicity was reported with increased DNA damages in blood and epithelial cells.[85-87] Thus, nurses and health care providers are at high risk for environmental exposure for genotoxicity. Healthy work environment initiatives could be useful strategies for nursing research to prevent or repair DNA damages and altered gene expressions for nurses and their off-springs from pregnancy to life-long development.

The human genome is constantly exposed to the environmental mutagenic stressors, endogenous reactive metabolites, as well as chemical toxins and harmful materials that challenge its integrity.[88] MiRNAs (functional genomics) regulate biological processes such as metabolism, proliferation, apoptosis, hematopoiesis, and oncogenesis. A combination of miRNAs is associated with the differentiation of pancreatic cancer with benign pancreatic tissues and a 24-month survival.[89] Mi-RNA-122a is found to be down-regulated in 70% of

hepatocellular carcinoma.[90] A combination of mi-RNAs is silenced in colorectal cancer.[91-94] In the immune system, several miRNAs are involved in endotoxin shock, inflammation, and hematopoietic cells.[95-97] Thus, miRNA profiling can be associated with clinical and nursing care outcomes, which might provide further insights for disease mechanisms and therapeutic strategies.

The developmental epigenetics research includes the investigations of gene-environment interactions or adaptive phenotypes, where functional variations in gene expression in response to environmental exposures are assessed for the risk of diseases.[17] Genome research for newborn screening may include genetic polymorphisms for variations in DNA sequences (substitutions, insertions, and deletions of DNAs). Environmental exposure to synthetic chemicals, pollutants, and lifestyle choices may alter adaptive phenotype during early development (fetus and early childhood) causing increases in certain diseases for modern lives,[17,98-100] and thus the ability to respond to environmental toxic exposures or the plasticity in building capacity. Chemical pollutants disrupt endocrine functions, and are most commonly associated with altered gene expression through DNA methylation (methyl groups added to the base cytosine of DNA). Increased DNA methylation is associated with gene silencing, and decreased DNA methylation is associated with gene activation, changing responses to disease development later in life and increasing the vulnerability for developing cancer.[98,99] Based on animal model studies, these epigenetic programming modifications may cause permanent changes and be inheritable for generations.[99-102] Thus, early interventions in children and families to prevent exposure to toxic substances and DNA methylation can reduce health disparities in vulnerable populations.

Recent findings on environmental exposure to the electromagnetic fields (EMF) on increasing cancer risks,[103] particularly breast cancer risks,[104] also have been confirmed with altered gene expression.[105] Alterations in genes involved the changes of metabolism, cellular processes, signal pathways, and immune functions after the EMF exposure. The potential mechanisms for the changes were connected to endocrine changes on insulin-secreting cells by attenuating insulin secretion and by affecting calcium influx through calcium channels.[106-108] Thus, functional genomics can be a part of nursing research to examine the biological mechanisms of genome changes under various pollutants, during pregnancy or childhood to improve life-long development and to reduce health disparities in vulnerable populations.
Research findings have also connected resilience, mental disorders, and cognition to the genome. SNP identifications in the mental health area included bipolar disorder,[109,110] cognition and schizophrenia,[111] and post-traumatic stress.[112] Resilience has been associated with positive affect and optimism, cognitive flexibility, coping, social support, emotional regulation, as well as mastery of hardships such as stress and pain.[114] To improve functional outcomes, psychological resilience carries significant promise in designing and evaluating interventions with genome basis, aimed at building plasticity during

early childhood development.[113] Neuro-imaging technologies are used to identify key brain regions for reconsolidation of fear memory, and to associate with resilience. The endocrine basis for increased resilience has been associated with higher levels of neuropeptide Y and increased ratio of dehydroepiandrosterone (DHEA)/cortisol fraction.[112] Additional research has found functional differences on language measure to be associated with a 37 base-pair insertion/deletion polymorphism of a LRPAP1 gene in individuals with Alzeimer's disease.[115] Furthermore, family related variables have been investigated on family resilience in adaptation to hereditary diseases.[116,117] Future nursing research may continue to examine the association of personalized genomics and strengthened resilience, and improving resources for children during early development and families to prevent disease development and to reduce health disparities.

The Impact of Personalized Genomics on Clinical Practices

Following the CHGS, major agencies of the US government health care systems have set guidelines and goals to integrate personalized genomics in the clinical care and research.[8,9,14,118] To achieve best health care outcomes, the DHHS[8,9] recommended the development of personalized genomics medicine and surgery (PGMS).[119,120] Following is an example of PGMS model sequence in pancreatic cancer. A patient's pancreatic cancer tissues are sampled for prototype of pancreatic and duodenal homeobox factor 1 (*PDX-1*), induced through siRNA suppression on the expression of a target gene.[121-123] Then, a given molecular target (or its mutations) is identified by the genomic analysis and microarray analysis. Thereafter, molecular diagnostics using molecular imaging techniques are tested using small molecules, siRNA, and gene therapy using non-viral delivery systems against human pancreatic cancer cells in mouse models. Finally, these preclinical animal studies are translated into the clinical trials to tailor the therapy based on the individual's genomic profile. These clinical trials include choosing the most effective therapy for the individual's disease subset, based on but not limited to individual weight, age, kidney functions, metabolic and enzyme activities, and dosing resistance.[124,125]

Ethical, legal, social implications of genome testing. Profound implications of ethical, legal, and social consequences are an integral part of genome testing.[20,70,71,126,127] With a rapid growth in the discovery of human genome and related molecular functions (molecular targets and genome treatment), comprehensive genetic counseling for consumers and family members have been suggested to help consumers and their families for informed decision making on their participation in the genome testing. The consumers and care providers need to be educated on the genetic influences of diseases. The consumers and family members may also need to be educated on the impact of genetic testing on the relationships with their family members. Increasingly, genome data have been used to determine paternity in child-custody disputes and to link forensic evidence in criminal processes. To protect individual privacy,

all tissue storage and publication of the genomic data must be unlinked to the identity of the individual.[70]

Informed consent for the genome data has been modified to reduce the risk of potential distress and the negative consequences of distress to consumers.[70,71] Potential personal risks associated with genome sequencing and genetic testing could include introducing hardship for life in securing jobs or insurance, as well as consenting and understanding, and the withdrawal options for the individuals with unwanted information. As individual genome data may be used to trace back to individual identity even with the de-identified data, CDC has informed the public that the genome data is blocked to general public access.[14,128] For genome research networks, only limited investigators would have the access to the network genome data. For the clinically relevant findings, reports may be sent to the consumers when the new associated research results become available. Legal liability for the research team and health care institutions may be heightened with genome data. The consumers may need additional genetic counseling with new genome research findings.[129-132]

Because the genome data could become easily linked to an individual, potential discriminations have been identified, particularly if the genome data is to be disclosed to the insurance companies and the employment settings when genome data becomes part of the standing medical record. Two legislations were passed by the US House and Senate delegates, then, signed by the US president in 2008, to reduce the risk of discriminations and to plan for better health care for newborn babies in relation to the advances in genomics.

The *Genetic Information Nondiscrimination Act* was signed by the U. S. president on May 21, 2008, following almost unanimous votes by the House and Senate delegates to pass the legislation.[133] This act was introduced to prohibit discrimination by insurance companies and employers based on the individual's genetic information such as the genetic risk factors for breast cancer or other cancer types, or any increased risk for genetic diseases.[134,135] This legislation is significant to prohibit discrimination of individuals based on genetic information, particularly with the newest genome research findings on cancer risks and the concerns for discriminations, which may ignite fear for women to participate in breast cancer risks genome testing. However, this law does not apply to military enrollment, life insurance, long term disability and care, or preexisting genetic conditions. Thus, further legislation is needed to reduce the risks of potential discriminations based on genome data, in order to decrease health care disparities.

The *Newborn Screening Saves Lives Act* was signed April 24, 2008 by the US president to establish grant programs to support genome research for newborn screening.[136] Additional focus for this Act includes increasing consumer awareness and knowledge of family support services, improving laboratory quality standards, and establishing a central online clearing house for genome

research translation. Based on these focused priorities, nurses can develop educational and coordination programs to improve clinical services for the newborns to save lives and to reduce health disparities. Nursing support to parental decision making in relation to children's genomics and coordination of care will be emerging areas for much needed services research.[137]

Summary

Major strides have been made with genome research. It is evident that in the next ten years, more progress will be made with personalized genomics health sciences and health care research. Gene-environment interactions, with the focus of bio-behavioral susceptibility for diseases and health, present great promise for nursing research. Epigenetics focuses on developing plasticity and resilience among children also offers promise for nurses' participation to help children and families to reach their optimal capacities and functions for health. Nursing interventions may be designed to improve the resilience among children and families through identification of vulnerabilities. Changes will occur in health care, calling for multi-disciplinary research teams and for true collaborations, with the increased emphasis on research translation. Nursing research is at the turning point of sharing the great promise of personalized genomics to improve health care outcomes for the best interests of children, families, and future generations.

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