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Current and Emerging Technology Approaches in Genomics

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Abstract

Purpose—To introduce current and emerging approaches that are being utilized in the field of genomics so the reader can conceptually evaluate the literature and appreciate how these approaches are advancing our understanding of health-related issues.

Organizing Construct—Each approach is described and includes information related to how it is advancing research, its potential clinical utility, exemplars of current uses, challenges related to technologies used for these approaches, and when appropriate information related to understanding the evidence base for clinical utilization of each approach is provided. Web-based resources are included for the reader who would like more in-depth information and to provide opportunity to stay up to date with these approaches and their utility.

Conclusions—The chosen approaches– genome sequencing, genome-wide association studies, epigenomics, and gene expression– are extremely valuable approaches for collecting research data to help us better understand the pathophysiology of a variety of health-related conditions, but they are also gaining in utility for clinical assessment and testing purposes.

Clinical Relevance—Our increased understanding of the molecular underpinnings of disease will assist with better development of screening tests, diagnostic tests, tests that allow us to prognosticate, tests that allow for individualized treatments, and tests to facilitate post-treatment surveillance.

Keywords

Genetics; genomics; next generation sequencing; genome-wide association studies; epigenomics; gene expression; nursing

Improvements in genomic data collection technologies have been an important driving force behind the increased accuracy and rapidity in which we can currently collect genomic data.

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Improved accuracy and rapidity of data collection are also very important aspects of moving genomic findings into the clinical arena for translation to patient care. This article focuses on four approaches: genome sequencing (Biesecker, 2012; Rizzo & Buck, 2012), genome-wide association studies (GWAS; Marian, 2012), gene expression profiling (GEP; Arao, Matsumoto, Maegawa, & Nishio, 2011), and epigenomics (Emes & Farrell, 2012). Genome sequencing and GWAS both interrogate DNA directly, with the former generating information about the order of DNA nucleotide bases and the latter generating data about genotypes at specific places in the DNA. GEP interrogates messenger RNA (mRNA) that is generated when a gene is "active" and transcribed and therefore gives us information about gene regulation. Epigenomics interrogates the DNA, but unlike genome sequencing and GWAS it generates data related to chemical modifications and structure of the DNA, which impact gene regulation, and not the sequence or genotype information held in the DNA. Each of these approaches has utility and challenges, but all are contributing to our better understanding of important health-related issues and are gaining momentum for clinical value.

Our goal with this article is to introduce the reader to these approaches; discuss their application to current research, their current and potential clinical applications, and challenges related to using the technologies for data collection and interpreting data generated by these technologies; and, if appropriate, provide data related to evidence base for clinical application. This article incorporates a thorough literature review but is not intended to provide an exhaustive coverage of these approaches; however, additional online resources (see Clinical Resources) are provided for the reader who would like to gain more understanding of these approaches and associated technologies and the large-scale projects that are currently using them. We, as the authors, acknowledge that the information about these technologies, particularly in reference to current research findings and clinical applicability, changes rapidly. We hope that the online resources will also allow the reader to stay up to date with these technologies and their application to health care.

Genome Sequencing

Previous methods that allowed DNA sequencing (i.e., determining the order of nucleotide bases in a molecule of DNA) of molecules one by one are being substituted by methods where billions of DNA molecules are sequenced simultaneously. These new technologies, referred to as next-generation sequencing (NGS) or massively parallel sequencing, have dramatically increased the output, reduced the time and cost of sequencing, and allowed for greater coverage of the genome. NGS technology has made it possible to sequence the human genome in a matter of days, whereas the first human genome was sequenced after 13 years of international effort and at a cost of nearly $3 billion dollars (Majewski, Schwartzentruber, Lalonde, Montpetit, & Jabado, 2011). These advances are bringing about a fundamental shift in how medical researchers investigate rare and common disorders and are influencing health care in terms of the diagnosis and understanding of diseases.

Determining the sequence of the entire human genome is referred to as whole-genome sequencing (WGS) and costs on the order of ~$10,000 in a clinical laboratory (Capriotti, Nehrt, Kann, & Bromberg, 2012). In contrast, it can cost one tenth that amount to sequence an individual's exome (the coding sequence of the human genome) in research laboratories. The latter method is referred to as whole-exome sequencing (WES). WES is generally accomplished using an array (or gene chip) that captures the DNA containing the protein-coding regions of genes (exons) from the DNA. This captured DNA is then sequenced. Since an exome represents only about 1% of the genome, it is considerably easier and less costly to sequence than a whole genome but contains greater than 85% of the disease-causing or pathogenic variants with strong effects on disease (Choi et al., 2009). There are

advantages and disadvantages to WGS and WES, which are beyond the scope of this review (Biesecker, 2012).

NGS is a more efficient and relevant diagnostic approach as compared with conventional Sanger sequencing when considering diseases that have multiple genes that may be causal or that have broad presentations (such as heart disease). Sequencing of single-suspect disease genes is effective for diagnosis if distinctive clinical features are present and where minimal genes that might be causal exist. However, the drawback with conventional sequencing results from the inability to prioritize individual genes among many candidates for diagnostic testing. WGS approaches circumvent this difficulty because all candidate genes may be examined simultaneously (Kingsmore & Saunders, 2011). Investigating such extensive amounts of the genome by sequencing results in the identification of many variants, such as single-nucleotide variants (SNVs), which are DNA sequence variations occurring within a single nucleotide that are called common polymorphisms if they exist in at least 1% of the population. These must then be filtered to identify the causal or pathogenic variants and to filter out benign variants (those thought to have no effect on an individual). The highest impact of WES and WGS sequencing is in providing insights into the pathogenesis of rare or uncommon human diseases, which are caused by rare variants that have a large impact on the phenotype (an organism's observable characteristics or traits).

NGS is now beginning to enter clinical practice. As the cost of WGS inevitably drops, it will likely replace the evaluation of many individual genes or panels of genes that are used today in diagnostics (Bick & Dimmock, 2011). As WGS of patients becomes a standard part of health care, it will be important for both bachelor of science in nursing (BSN)-prepared and advanced practice nurses to understand the ramifications of the technology to better inform the public and to engage the public in how this technology can be used (Calzone et al., 2010). One example of how genome sequencing will have clinical utility is the evolving field of predicting an individual's genotype-specific drug responses for commonly used drugs. Recently, a number of pharmacogenomic tests have been translated into clinical practice. Clinical examples include testing breast and gastric tumors for variants in the gene that codes for EGFR proteins, which are sensitive to tyrosine-kinase inhibitors or EGFR-specific antibodies (Sastre, 2011), and testing for the *CYP2C9* and *VKORC1* variants to determine dose requirements (Tucker, Marra, & Friedman, 2009), and hence susceptibility, to adverse drug reactions related to warfarin and statins for coronary artery disease (Ware, Roberts, & Cook, 2012). While pharmacogenomic testing can be done with individual gene testing, pharmacogenomic results can be derived from an NGS sequence, at very little additional cost. An example might be when a specific genotype identifies an individual at increased risk for a particular statin-induced myopathy for which an alternative lipid-lowering therapy may be more appropriate. Due to recent NGS advances, healthcare providers will increasingly rely on pharmacogenomics to guide therapy, often at the point of care.

Healthcare practitioners, including nurses, need to be familiar with the basics of genome sequencing to appreciate both the power and limitations of the data, including error rates. For example, the base-position error rate for NGS sequencers is approximately 0.5% to 2% (Su et al., 2011). A significant false-positive rate can result from a combination of various errors and irregularity arising from the many steps and processes involved in NGS. In addition, healthcare professionals who interpret these test results need to be familiar with a number of genomics resources, most of which are found on the Internet (see Clinical Resources). Reporting the results from NGS raises a number of other issues. The laboratory reporting a WGS result should indicate the genes or exons that did not have a sufficient number of quality reads to permit an accurate analysis. In a patient with an unknown disorder, it will be important to know which genes were not tested. Additionally, the report

will need to specify the types of pathogenic variants that were detected. A report of the sequencing results will also need to focus on the dominant error mode for each NGS device and software tool, since different NGS devices do not all yield the same result when running the same sample. Given that NGS is a new technology, it may be prudent to confirm the genomic results with another established method before issuing a report. Lastly, it is important to recognize that all results that are returned to patients undergo testing in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory ("The Clinical Laboratory Improvement Amendments of 1988," 1989).

There are regulatory and ethical issues to be considered for NGS. WGS and WES will regularly uncover both insignificant and important medical results. Individuals are at risk for learning unwelcome information that may not be directly relevant to the original clinical question, such as the disease-causing variants found in a cancer susceptibility gene during investigation for another disease. This presents additional challenges for clinicians and nurses. How will we report these results to the patient and how should we counsel them about this eventuality? The psychological effects of the unexpected discovery of such results must be planned for and will require provisions for genetic counseling. The National Institutes of Health's *ClinSeq*™ Project is a clinical genomics research study developed to examine the aforementioned technical, medical, and genetic counseling issues associated with large-scale genomic sequencing and its application to personalized health care (Biesecker et al., 2009).

Ultimately, as with other diagnostic tests, uniform analytic methods, variant detection and filtering, and pathogenic variant identification need to be developed and implemented, including the generation of a standardized report interpretable uniformly by clinicians, genetic counselors, and nurses. It is likely for the immediate future that the clinical benefit of NGS will come from an increased rate of disease gene discovery from clinical research, and the application of WES and WGS testing to patients with rare or perplexing diseases that have eluded diagnosis.

Genome-Wide Association Studies

This approach asks the question "does a genetic marker (i.e., a polymorphism) display a relationship with a trait of interest?" These genetic markers are distributed throughout the genome and systematically evaluated for when the answer to the question is "yes, there is a statistically significant difference in the relationship between a genetic marker and the trait of interest." Data for these genetic markers throughout the genome can be collected using a variety of technologies, including those that focus on specifically selected polymorphisms throughout the genome (such as microarray technologies) and those that collect data for all variants throughout the genome (such as NGS). Initially, genome-wide searches in humans were pursued in families that had been measured for the trait or disease of interest (Botstein & Risch, 2003). These family-based studies exploited the concept of cosegregation, where a given genetic marker(s) that underlies a trait will travel with the trait in a given family tree. This approach is typically called linkage analysis. Although linkage analysis has many statistical advantages, such as requiring fewer genetic markers to interrogate the genome and having a known relationship between members of the family (which can be used to yield more robust statistical test results), it requires that the trait in question be possible to measure in a consistent manner in all family members.

Perhaps the greatest limitation is that many traits are not amenable to this approach. Many traits require a certain external event to occur (e.g., pain after surgery, recovery from trauma, post-traumatic stress, fatigue due to chronic inflammation) and multiple occurrences of such events in a given family are rare and have differing contextual factors (i.e., differences in

treatment options over time, the emergence of new therapies). Family size, interpersonal dynamics, and sheer geographic dispersion of members can make recruitment of families of sufficiently large size and number a daunting task that requires considerable human resources, time, and therefore cost. These limitations, coupled with technological advances in the measurement of a very frequent class of genetic markers in the human genome (i.e., single nucleotide polymorphisms, SNPs) and generalization of statistical approaches to dealing with multiple testing, paved the way for the emergence of GWAS as the most common design for genome searches.

Unlike family-based approaches, GWAS focus on the study of unrelated individuals that are measured for the trait of interest. This has the considerable advantage of not requiring resources to recruit and characterize traits in individuals that may not contribute to the analysis of cosegregation in family-based approaches. The most common design is case-control, where individuals either do (i.e., a case) or do not (i.e., a control) have the trait, typically disease status, for which genetic risk factors are being sought. This design relies on a basic statistical approach of testing for differences in the frequency of a genetic variation between cases and controls or with a trait among a group of people. The measurement of SNPs that are close enough to be inherited together more often than not (termed linkage disequilibrium) has allowed for the development of methods where SNPs are combined into more complex genetic markers (termed haplotypes) that can improve the power to detect associations with a trait of interest. Although GWAS are advantageous in that only individuals likely to be informative in the analysis are recruited, they can require considerably larger sample sizes in order to provide the statistical power to detect underlying genetic risk factors. This is due to several reasons, including the complexity of the trait, the effect size of a given genetic risk factor, and the precision of the phenotype (Gibson, 2011; Hakonarson & Grant, 2011).

Given that considerable resources are required to perform GWAS, evidence for the presence and complexity of genetic risk factors for a trait of interest should be established prior to taking this approach. Historically, evidence of heritability was established by examination of identical and fraternal twins (where concordance of a given trait is greater in identical twins), segregation studies in families measured for a given trait (where patterns of inheritance of the trait in a given family conform to patterns predicted by a genetic risk factor), or even evidence of enrichment for a given trait in those with a family history of said trait.

Investigators of the traits that are not amenable to such traditional estimates of heritability have turned to other sources of evidence. Often studies in other organisms have provided biological evidence for the role of certain genes that function in certain pathways reasonably expected to participate in the trait of interest. These candidate genes may often be examined in study populations of more modest size than needed for GWAS. Evidence of an enrichment of genetic markers in a subset of the candidate genes examined is increasingly recognized as a more efficient alternative to classic heritability studies. These studies are ideal for the use of custom SNP genotyping arrays. Ultimately, each trait will require a different combination of approaches and designs due to a complex combination of participant access, trait measurement constraints, resources available, and the skills of the investigative team. New measurement technologies (i.e., NGS, array-based measurements) will undoubtedly influence these considerations.

Epigenomics

Epigenomic evaluation involves looking at modifications that do not involve the nucleotide bases of DNA but instead look at things like chemical modifications or packaging of the

DNA. These non-nucleotide modifications have implications for gene regulation, meaning whether a gene is expressed/actively transcribed or not. Epigenomics in general encompasses histone modifications, localized changes to chromatin structure, activities of non-coding RNAs, and DNA methylation (http://www.ncbi.nlm.nih.gov/epigenomics). The epigenomic modification that currently has the most potential to be used in diagnostic testing is a DNA chemical modification called methylation (Diamandis, Sidransky, Laird, Cairns, & Bapat, 2010). Hypermethylation of DNA prevents a gene from being transcribed, resulting in gene silencing, while hypomethylation of a gene that is supposed to be silenced results in activation of the gene. Methylation of DNA to regulate genes in a cell- or tissue-specific manner is normal and is essential to controlling the cellular environment specific to a particular cell type with a particular job to do (Fernandez et al., 2012). However, hyper- or hypomethylation of genes that are not supposed to be probably explains a lot of the mechanism behind gene regulation abnormalities noted in many disorders such as cancer (Feinberg & Tycko, 2004; Fraga et al., 2004; Lujambio et al., 2008; Su et al., 2012). Epigenomics, like most genomic approaches, plays a dual role in that it can be used to collect data that allow us to better understand a biological phenomenon and as a result better understand health conditions related to that biological phenomenon (Hill et al., 2011), and it can also be utilized in a more focused manner for genetic testing purposes (Ned, Melillo, & Marrone, 2011).

While the current utility of epigenomics may primarily reside in the research arena, strides have been made to move methylation assays to clinical utility for cancer screening. A few exemplars are provided. Methylation assays for colorectal cancer screening have progressed in clinical trials. A DNA methylation assay that focuses on the vimentin gene and is fecal based is the ColoSure™ test. Methylated vimentin has been assessed for sensitivity and specificity to detect colorectal cancer across multiple studies, with sensitivity ranging from 38% to 88% and specificity ranging from 73% to 100% (Ned et al., 2011). Another methylation assay for colorectal cancer screening focuses on a different gene, septin 9, and is blood based instead of fecal based. This assay, currently called ColoVantage®, had an overall sensitivity ranging from 77% to 96% and specificity ranging from 80% to 94% (Warren et al., 2011). ColoVantage® was recently licensed by Quest Diagnostics (corporate headquarters, Madison, NJ). A clinical trial of a methylation-based assay, currently called ProCaM™, that assesses the methylation status of three genes *(GSTP1, RARβ2, APC)* implicated in early prostate cancer has produced promising results. This assay, which utilizes urine, was correlated with prostate needle biopsy findings and had 60% sensitivity, 80% specificity, and an informative rate of 97% (Baden et al., 2011).

The field of epigenomics is aiding our understanding of complex conditions and gaining clinical application; therefore, one can hypothesize that this approach will continue to gain momentum for genomic research. Epigenomic approaches could be used to better understand variability in patient outcomes, therapeutic responses, symptomatology experienced by patients, and so on. While the potential utility of epigenomic approaches is great, one does need to consider some of the limitations and requirements for design and interpretation of a study. One significant issue is that the cell/tissue to be utilized is very important. Analyses that investigate nucleotide composition of DNA (e.g., a study that uses polymorphisms to investigate the genome) have the advantage that the cell/tissue type from which the DNA was extracted does not matter. This is not the case for an epigenomic study because the methylation status and DNA packaging will be specific to the cell/tissue type used. Therefore, when designing or evaluating the literature on epigenomic findings, one should take note of whether the cell/tissue from which the DNA was extracted for the study was appropriate for the phenotype under investigation. Additionally, unlike polymorphism-based DNA analyses, epigenomic status of the DNA is dynamic and can change over time and in response to endogenous and exogenous environments. Therefore, one needs to give

thought to whether samples were consistently collected with respect to potential temporal and environmentally induced changes. For example, if comparing the methylome of individuals before and after a treatment regimen, one would want to make sure that the post-treatment samples were consistently collected from the subjects at the same post-treatment time point and that potential confounding variables were taken into account. On a positive note, one advantage of using an epigenomics approach is that the template of interest, DNA, is more stable than RNA; therefore, it is more amenable to sample collection by patients in the home and sample collection in the field, and there's no need for sample fixation or stabilization (Baumgartel et al., 2011).

Gene Expression Profiling

Though the human genome contains over 20,000 genes, only a fraction within a cell or tissue is active at a given time. Knowledge of which genes are actively being transcribed is important in health-related sciences and for clinical applications. Gene activity, or expression, can be assessed by protein identification; however, gene expression has traditionally been investigated by examining the RNA message, or transcript.

Assessment of gene expression initially focused on one protein-specific mRNA at a time. With sequencing of the human genome came an explosion of efforts in investigating the expression of literally thousands of genes simultaneously. Serial analysis of genome expression (SAGE) and DNA microarrays are two methods that are commonly used for comprehensive gene expression profiling (Weeraratna, Nagel, de Mello-Coelho, & Taub, 2004). The SAGE technique involves isolating sequence tags from an RNA sample, linking the tags together, and sequencing them to generate a digital readout of quantitative gene expression from the cells or tissue of interest (Velculescu, Zhang, Vogelstein, & Kinzler, 1995). DNA microarrays, or gene chips, are small glass slides or postage stamp–sized quartz squares that may contain thousands of genes, either as the complete sequence or as expressed sequence tag (EST) fragments, imprinted on the surface as tiny spots. Quantitative reverse-transcription polymerase chain reaction is also used in gene expression profiling but usually assesses one mRNA at a time.

In the past decade, applications of gene expression profiling have entered the clinical arena and impacted all areas of health. The discovery-to-translation trajectory in cancer has been particularly rapid due in part to extensive genetic abnormalities and heterogeneity within most cancers. These features, coupled with needs for improved prognostic subtype classifications, risk stratification for cancer recurrence, and development and selection of appropriate therapies, serve as a strong impetus for performing gene expression research (Reis-Fulhio & Pusztai, 2011; Yeon et al., 2002).

With breast cancer, an important issue in those diagnosed with early-stage disease is when to include or exclude chemotherapy as adjuvant treatment. For many with small breast tumors that have not spread to the regional axillary lymph nodes, the addition of chemotherapy offers little additional advantage to surgery and radiation, since the risk for recurrence is low (Reis-Fulhio & Pusztai, 2011). The problem is the inability to confidently distinguish those who will benefit from chemotherapy from those who will not, a dilemma that leads to overtreatment of many patients with chemotherapy. Seminal findings were reported by van 't Veer et al. (2002) in which gene expression profiling of primary breast tumors was found to predict treatment outcomes in women diagnosed with early-stage breast cancer without regional lymph node involvement. Using DNA microarray techniques, the investigators began by examining 25,000 genes and sequentially reduced the number of genes associated with outcome to identify 70 genes that predicted those with early-stage breast cancer who were likely to progress to metastatic disease, thus defining a “poor prognostic signature.”

This 70-gene signature identified by van 't Veer et al. (2002) is the basis for MammaPrint (Agendia, Amsterdam, The Netherlands, www.agendia.com), a Food and Drug Administration– cleared microarray-based test used to determine the prognosis of women with stage 1 and stage 2 invasive breast cancer with tumors measuring less than 5 cm and absence of lymph node involvement. Additional gene expression– based assays for breast cancer are available, including Oncotype DX™ (Genomic Health, Redwood City, CA, www.genomichealth.com) and PAM50 (ARUP, Salt Lake City, UT, www.aruplab.com).

It is important to emphasize that although progress has been made using gene expression profiling, continued investigations and technological advances are needed and are indeed occurring. An emerging area is microRNA (miRNA) expression profiling. MicroRNAs are small RNAs that do not code for proteins, but instead regulate mRNA by binding to it. This post-transcriptional regulation can occur by inhibiting translation of the target gene or targeting mRNA for degradation. Over 1,000 miRNAs have been discovered, and continued discovery and validation will enable complete miRNA expression profiling to better characterize and understand diseases such as breast cancer (Ryu et al., 2011).

Other important areas that continue to advance the science are improved technology and information storage. The NGS technology mentioned earlier has greatly increased sequencing speed, capacity, and capability while promising to reduce costs. Whole genomes can now be sequenced from a single cell (Tang et al., 2009), and deep-sequencing methods enable gene expression to be studied at a level of genome-wide transcription start sites (Balwierz et al., 2009). Equally important to NGS methods and the promise they bring is the presence and expansion of open access repository sites such as Gene Expression Omnibus (GEO) at the National Center for Biotechnology Information. GEO is a very large public repository that was designed to house and access volumes of data generated by high-throughput gene expression microarray technology. With NGS techniques in combination with public access repositories and large projects, such as the Cancer Genome Atlas (http://cancergenome.nih.gov/) and the International Cancer Consortium (http://www.icgc.org/), personalized health care that includes nursing care and interventions is not far from being a reality.

Implications for Nursing Practice and Research

The scale and pace of development of genomic technologies and the approaches utilizing these technologies that we have outlined are remarkable, with NGS technologies in particular driving other advances (Wright, 2011). As knowledge and understanding of the molecular mechanisms of disease grow, the potential for clinical impact is profound (Table 1), with developments in screening and testing, diagnosis, individualized treatment, post-treatment surveillance across the life stages, and public health (Human Genetics Strategy Group, 2012). In turn, there are significant implications for nurse education, research, clinical practice, nurse leadership, and the ethical framework within which all must operate.

Perhaps the greatest and most critical initial challenge is for nurse education. Jenkins and Calzone (2012) see a prepared nursing workforce as essential to effective translation of genomic research to benefit patient care, but the knowledge gap is a global concern. Nurses need a sufficient grasp of core scientific concepts to deliver genomic health care to those affected today, concepts they can build upon as future advances are translated into care. They need to be able to explain to patients and families about the implications of screening and testing, putting risk into context, and about treatment choices. Furthermore, they need to be sufficiently prepared to be able to evaluate new developments and their likely time scale for translation to clinical practice, taking a realistic perspective on this (Jenkins & Calzone, 2012). Highlighting the challenges associated with nursing education in genomics along

with resources to assist with this challenge is also the topic of the September 2011 Williams et al. article in the *Journal of Nursing Scholarship*.

The role of nursing faculty is fundamental to preparing the nursing workforce, but the scale of the challenge is such that they cannot achieve this alone. Strong and visionary nurse leadership is needed to drive translation of advances in genomics into nursing practice for the benefit of patients and families, through effecting changes in regulation, policy, education, and practice, informed by a growing evidence base in genomic nursing.

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Clinical Resources

- Cancer Genome Atlas: http://cancergenome.nih.gov
- Catalog of Published Genome-Wide Association Studies: http://www.genome.gov/gwastudies
- Chromatin Structure and Function: http://www.chromatin.us
- ClinSeq: A Large-Scale Medical Sequencing Clinical Research Pilot Study: http://www.genome.gov/20519355
- Collecting family history: http://ghr.nlm.nih.gov/
- Database for DNA Methylation and Environmental Epigenetic Effects: http://www.methdb.de
- Database of Genotypes and Phenotypes (dpGap): http://www.ncbi.nlm.nih.gov/gap
- Database of Noncoding RNAs: http://www.noncode.org
- Epigenomic Datasets: http://www.ncbi.nlm.nih.gov/epigenomics
- Epigenomics Fact Sheet: http://www.genome.gov/27532724
- GeneBank: http://www.ncbi.nlm.nih.gov/genbank/
- GeneCards: http://www.genecards.org/
- Gene Expression Omnibus: http://www.ncbi.nlm.nih.gov/geo
- Genetic home reference (GHR): http://ghr.nlm.nih.gov/
- Genetic Test Registry (GTR): http://www.ncbi.nlm.nih.gov/gtr/
- Histone Database: http://www.research.nhgri.nih.gov/histones
- Human Epigenome Project: http://www.epigenome.org
- Human Gene Mutation Database (HGMD): http://www.hgmd.cf.ac.uk/ac/index.php
- Human genome resources: http://www.ncbi.nlm.nih.gov/genome/guide/human/
- International Cancer Consortium: http://www.icgc.org
- International Human Epigenome Consortium: http://ihec-epigenomes.org/index.html
- Locus Specific Mutation Databases (HGVS/LSMD): http://www.hgvs.org/dblist/glsdb.html
- My Family Health Portrait (Surgeon General's tool): https://familyhistory.hhs.gov/fhh-web/home.action
- National Organization for Rare Diseases (NORD): http://www.rarediseases.org/
- Online Mendelian Inheritance in Man (OMIM): http://www.ncbi.nlm.nih.gov/Omim/
- Orphanet: http://www.orpha.net/consor/cgi-bin/index.php
- Rare Genetic Diseases in Children (RGDC):
- http://mcrcr2.med.nyu.edu/murphp01/homenew.htm

- Talking Glossary of Genetic Terms
- http://www.genome.gov/glossary/

Table 1

Current and Emerging Genomic Approaches: Outcomes and Implications for Health Care

	Approach			
	Genome sequencing	**Genome-wide association studies**	**Gene expression profiling**	**Epigenomics**
Outcomes	Greater volumes of information processed faster and more cheaply, facilitating whole-genome sequencing, with accelerated scale and pace of gene discovery.	Genetic variation between those with and without a specific disease identified through large population studies.	Insights into the role of differential gene expression in normal biological and disease processes.	Growing understanding of gene-environment interaction and influence on gene activity not involving the DNA sequence itself.
Clinical implications and possibilities	More accurate and cost-effective diagnosis and genetic testing; earlier detection of disease and of those at risk for disease; antenatal testing using cell-free fetal DNA; pharmacogenomics; tissue typing and transplantation; rapid response to infectious disease outbreaks through pathogen sequencing.	Greater knowledge of gene loci associated with a broad spectrum of diseases; helps identify genetic contribution to risk. Identifying genetic component(s) of common complex diseases helps identify potential targets for drug development.	Potential for greater accuracy in diagnosis, individualized prognosis, targeted treatment, and post-treatment surveillance, particularly in oncology.	Potential for manipulating epigenetic gene regulation through modifying environmental factors (e.g., nutrition). Of particular relevance during embryogenesis.
Implications for nursing education, practice, and research	*Education:* Keeping up to date with advancing knowledge and understanding of disease mechanisms; educating others, including patients and their families. *Research:* Recruiting patients to studies; building the evidence base for genomic health care in nursing practice. *Clinical care:* Explaining complex risk; dealing with uncertainty; managing patient expectations; explaining treatment choices and targeted treatment. *Public health nursing:* Managing public expectations of personal consumer genomics; translating epigenetic advances to health promotion and education; translating new knowledge to infectious disease management. *Ethical practice:* Upholding autonomy and informed consent in research studies and genetic screening/testing using fresh and stored DNA; managing the implications of intended and incidental findings of (whole) genome sequencing; upholding privacy and confidentiality. *Nurse leadership:* Leading in the translation of new knowledge and understanding into healthcare practices and pathways; driving policies to implement change in nursing regulation, practice, and education to promote competent, evidence-based and holistic care.			