CHAPTER 8

The Gene Pool

The Ethics of Genetics in Primary Care

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ABSTRACT

Aim: The purpose of this integrative review is to critically analyze the research literature regarding ethical principles that surround the integration of genetics and genomics in primary care clinical practice. Background: Advanced practice nurses (APRNs) play an important role in the provision of primary care services, in the areas of obstetrics, pediatrics, family practice, and internal medicine. Advances in genetic and genomic science are infiltrating these day-to-day health-care systems and becoming an integral part of health-care delivery. It is imperative for primary care providers to understand the ethical, legal, and social implications of genetics and genomics. Methods: A comprehensive multistep search of CINAHL, MEDLINE, Academic Search Premier, PsycINFO, Web of Science, and Scopus databases was conducted to identify primary research articles published from 2003 to 2015 that evaluated ethical issues related to genetics and genomics in U.S. primary care practice. A sample of 26 primary research articles met the inclusion criteria. Whittemore and Knafl's (2005) revised framework for integrative reviews was used to guide the analysis and assess the quality of the

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studies. Key findings from the studies are discussed according to Beauchamp and Childress's (2009) ethical principles of autonomy, beneficence, nonmaleficence, and justice. Results: Research conducted to date is mainly qualitative and descriptive and the analysis revealed several ethical challenges to implementing genetics and genomics in primary care settings. Conclusion: The review suggests that there are several implications for research, education, and the development of primary care practice that support APRNs delivering genetic and genomic care while incorporating knowledge of ethical principles. More research needs to be conducted that evaluates the actual genetic/genomic ethical issues encountered by primary care providers.

INTRODUCTION

When sequencing of the human genome was completed, it was envisioned that genetic- and genomic-based approaches could be used to predict disease susceptibility and drug response in order to provide individualized medicine based on genetic profiles (Collins, Green, Guttmacher, & Guyer, 2003). It was postulated that genetic services would become part of routine medical care. In the past decade, rapid advances have taken place with regard to genetic technologies and the vision for personalized medicine is becoming more of a reality. Since sequencing of the human genome, science has moved beyond single-gene testing to examining the whole genome and panel testing for multiple genes. Genomic medicine is defined as the study of the function of all the nucleotide sequences present within the entire genome. Innovations in technology have highlighted the role of genomics in common conditions encountered in the primary care setting (Mikat-Stevens, Larson, & Tarini, 2014).

Personalized genomic medicine promises to improve clinical outcomes by providing a more informed process for providers, which can predict disease prior to symptoms, improve patient outcomes, and reduce health-care costs through earlier prediction of disease and individualized interventions that reduce adverse side effects (Lazaridis et al., 2014). Primary care settings, including obstetrics, pediatrics, family and internal medicine, provide entry-level health care for individuals making use of a person-centered approach rather than focusing on disease (Johns Hopkins Bloomberg School of Public Health, 2014).

Primary care was envisioned as the most likely setting for the delivery of many basic genetic services, with practitioners playing a seminal role in the assessment and management of genetic risk in routine practice (Green, Guyer, Manolio, & Peterson, 2011; Kirk, 2000). There are many times throughout the life span that patients and families may require genetic services (Fleck, 2014). It is believed that genomic technology will lead to the delivery of health care that is

precise and personal. The promising aspect of incorporating genetic and genomic medicine into primary care poses many ethical considerations that practitioners should be aware of. An integrative review of the published research literature was conducted in order to evaluate the empirical evidence related to the ethical principles of autonomy, beneficence, nonmaleficence, and justice associated with the provision of genetic and genomic services in the primary care setting.

METHODS

Whittemore and Knalf's (2005) updated integrative review method guided the analysis. This is considered a rigorous method that is useful when there is a need to appraise studies of varying quality and design with diverse research methodologies. Studies were analyzed and grouped based on how the purpose and key findings aligned with Beauchamp and Childress's (2009) four principles of biomedical ethics, autonomy, beneficence, nonmaleficence, and justice.

Search Methods

We systematically searched CINAHL, MEDLINE, Academic Search Premier, PsycINFO, Web of Science, and Scopus databases for articles published between 2003 and 2015, to identify original research studies that evaluated ethical issues related to genetics and genomics in primary care practice. We used combinations of the keywords "genetic," "genomic," "ethic," "legal," "social implications," "primary health care," "family practice," "primary care," "general practice," "family medicine," "physician assistant," "nurse practitioner," and "advanced practice nursing." Original research articles that were conducted in the United States and published in peer-reviewed journals were included in our analysis if they evaluated ethical issues related to genetics or genomics in primary care practice. Nonresearch articles were excluded from our review. Research articles not written in English, not conducted in the United States, not published in peer-reviewed journals, and studies that discussed ethical issues that only applied to research, hospital, or specialty settings were excluded from our analysis (Table 8.1). Research not conducted in the United States was excluded because health-care systems in other countries vary and the impact of some ethical issues may be quite different.

Search Outcome

Our initial search yielded 358 articles. When duplicates were removed, there were 273 abstracts, which were reviewed by hand to identify 40 primary research articles. Each of these 40 research articles was reviewed according to our inclusion/exclusion criteria. Fourteen of the articles were excluded because they were

TABLE 8.1
Literature Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Original research	Reviews, opinion editorials
Conducted in the United States	Conducted outside of the United States
Published in peer-reviewed journal	Non-peer-reviewed articles, abstracts, dissertations
Evaluated ethical issues related to genetics/genomics in primary care	Studies that evaluated ethics of genetics/genomics in research, hospitals, or specialty settings
	Not written in English

studies conducted outside of the United States. We identified 26 studies that met the inclusion criteria. Each study was reviewed, evaluated for methodological rigor and relevance to topic, and grouped according to the ethical principles of autonomy, beneficence, nonmaleficence, and justice that were addressed in the key findings and purpose of the study (Figure 8.1).

Quality Appraisal

All studies were evaluated for methodological rigor using a 3-point scale (1 = low, 2 = moderate, 3 = high) based on qualitative criteria from the "Critical Review Form—Qualitative Studies Version 2" (Letts et al., 2007) and quantitative criteria from the "Quality Assessment Tool for Quantitative Studies" (National Collaborating Centre for Methods and Tools, 2008). Each study was evaluated for relevance to topic using a 3-point scale (1 = low, 2 = moderate, 3 = high) by three reviewers. Each score was determined by consensus of the reviewers. Table 8.2 shows the studies listed by year of publication with each study's relevance to topic and methodologic rigor scores. We included all 26 articles in our analysis since there were so few studies that met our inclusion criteria.

Synthesis

The goal of the synthesis phase was to group all of the data into subgroups in order to identify patterns and relationships among the data (Whittemore & Knafl, 2005). The studies were categorized according to Beauchamp and Childress's (2009) four principles of medical ethics as related to genetics and genomics in primary care and compiled into a matrix located in Table 8.3. The purpose and results of each study were analyzed to identify relationships between the principles of autonomy, beneficence, nonmaleficence, and justice. Analysis strategies

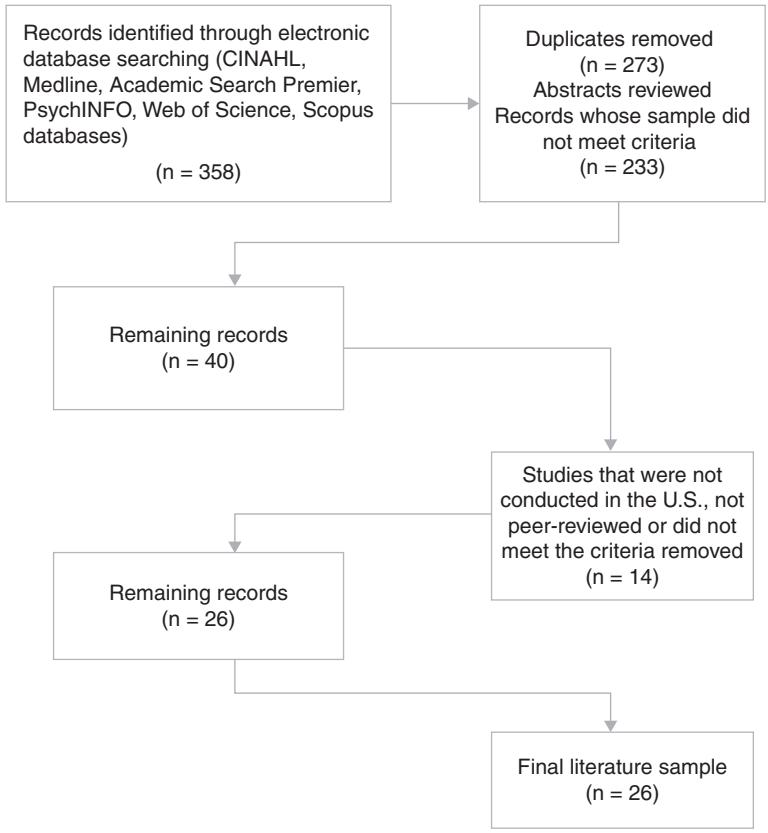

FIGURE 8.1 Search and inclusion process.

included noting intervening factors among the variables. The reorganized and synthesized data formed the basis for this review. Several implications related to ethical issues of genomics in the primary care setting were identified for APRNs, and areas for future research were revealed supported by the textual and numerical ratings.

RESULTS

We identified 26 primary research articles. There were 16 studies with quantitative designs that included mainly descriptive surveys and pretest and posttest designs, 9 studies with qualitative designs including interviews, focus groups, and content analysis of websites, and 1 study that utilized a mixed-method design. The purpose and findings of the studies revealed that 10 of the studies

TABLE 8.2
Quality and Relevance of Appraisal Criteria and Process

Criteria
A = methodological quality (MQ) judgement of overall quality (1, 2, 3)
B = topic relevance (TR) judgement of overall weight (1, 2, or 3)

Author (Year)	Ethical Principle	Design	MQ Score	TR Score	Overall Score
Bell et al. (2014)	Beneficence	Quantitative	1	2	2
Constantine, Allyse, Wall, Vries, and Rockwood (2014)	Autonomy	Quantitative	1	3	2
Goldenberg, Dodson, Davis, and Tarini (2014)	Autonomy	Quantitative	1	3	2
Strong, Zusevics, Bick, and Veith (2014)	Autonomy	Quantitative	1	3	2
Wasson, Cherny, Sanders, Hogan, and Helzlsouer (2014)	Nonmaleficence	Qualitative	1	3	2
Hunt and Kreiner (2013)	Justice	Qualitative	1	3	2
Klitzman et al. (2013a)	Nonmaleficence	Quantitative	1	2	2
Klitzman et al. (2013b)	Nonmaleficence, justice	Quantitative	1	2	2
Christianson et al. (2012)	Justice, beneficence	Qualitative	2	2	2
Haga, Tindall, and O'Daniel (2012)	Nonmaleficence	Qualitative	1	1	1
Hay et al. (2012)	Autonomy	Quantitative	2	1	2
Hurley et al. (2012)	Autonomy	Qualitative	1	2	1

Wasson, Hogan, Sanders, and Helzlsouer (2012)	Autonomy	Qualitative	1	3	2
Lewis, Treise, Hsu, Allen, and Kang (2011)	Autonomy	Qualitative	2	3	2
Srinivasan et al. (2011)	Nonmaleficence	Quantitative	2	3	2
Arar Seo, Abboud, Parchman, and Noel (2010)	Nonmaleficence	Qualitative	2	1	1
O'Neill et al. (2010)	Nonmaleficence	Quantitative	2	3	2
Hindorff et al. (2009)	Justice	Quantitative	1	2	2
Brandt, Ali, Sabel, McHugh, and Gilman (2008)	Nonmaleficence	Quantitative	1	2	1
Lowstuter et al. (2008)	Justice	Quantitative	2	3	2
Trinidad et al. (2008)	Nonmaleficence	Qualitative	1	1	1
Levy, Youatt, and Shields (2007)	Justice	Quantitative	2	2	2
Erde, McCormack, Steer, Ciervo, and McAbee (2006)	Nonmaleficence	Quantitative	2	3	3
Acheson, Stange, and Zyzanski (2005)	Justice	Mixed methods	1	3	2
Hall et al. (2005)	Justice	Quantitative	2	3	3
Maradiegue, Edwards, Seibert, Macri, and Sitzer (2005)	Beneficence	Quantitative	2	2	2

TABLE 8.3
Literature Characteristics

Author (Year)	Ethical Principles Addressed	Design	Sample	Purpose	Findings	Limitations
Acheson et al. (2005)	Justice	Descriptive survey; mixed methods	National random sample of 190 family physicians	Describe genetic issues encountered by family physicians in clinical practice	Most of the physicians reported discussing the genetics of common cancers, cardiovascular disease, and Alzheimer's disease with patients in the past year. 13% of the physicians made a referral for breast/ovarian cancer in the past year. 23% said access to genetic consultation is difficult to obtain particularly in rural areas. Some physicians felt that genetic tests were expensive and that the drawbacks of gaining information about genetics outweighed the benefits.	The researchers cited limitations in the survey instrument, since the survey was based on self-reported recollection of past experience and did not ask how many patients were actually referred for genetic consultation, which could introduce bias in the answers.

Arar et al. (2010)	Nonmaleficence	Qualitative, interviews	20 primary care providers from the Veterans Administration (VA)	Examine providers' intentions toward utilizing genomic services	Most providers thought that primary care plays an important role in genetics but that providers need more training regarding genetic testing and how to make referrals to genetic specialists.	Small sample size. Findings may not be generalizable to providers who do not work for the VA.
Bell et al. (2014)	Beneficence	Randomized controlled trial (RCT) with qualitative Transcripts coded for presence or absence of key topics discussed during a standardized patient encounter	121 community physicians	Evaluate the outcome of an interactive web-based curriculum vs. text curriculum for improving physician practice related to screening for breast cancer	The majority of the standardized patient encounters had inadequate discussion of ethical implications and inadequate history taking.	Possible selection bias. The physicians knew they were being evaluated during the standardized patient encounter. The outcome data collected was not quantitative, which is usually the type of data collected in RCTs.
Brandt et al. (2008)	Nonmaleficence	Descriptive survey	51 primary care and 31 specialist physicians	Provide insight about why, when, and to whom primary care physicians make a referral for cancer genetic testing	Primary care physicians were significantly less comfortable with identifying patients for referral and discussing genetics compared with specialists.	Small sample size. Survey used close-ended questions.

(*Continued*)

TABLE 8.3
Literature Characteristics (Continued)

Author (Year)	Ethical Principles Addressed	Design	Sample	Purpose	Findings	Limitations
Christianson et al. (2012)	Justice, beneficence	Qualitative, focus groups	16 primary care providers	Obtain input regarding incorporation of a family health history risk assessment tool in community practice	Identified several areas of concern regarding genetics in practice including provider's level of expertise, cost of preventive care based on genetics, genetic discrimination, reimbursement, clarity of follow-up guidelines	Self-selected, small sample. Researchers unable to reach qualitative saturation with the responses from the small sample
Constantine et al. (2014)	Autonomy	Descriptive survey	226 female prenatal patients	Evaluate patient's informed consent decision process for quad screen testing	Patients who consent to have the quad screen often lack an understanding about the reason for this test. Having the provider offer the test was viewed by the patient as an endorsement to have the testing done, which was an impediment to the informed consent process.	Possible selection bias, nonresponse error. Findings may not be generalizable because the sample was from one region in the United States.

Erde et al. (2006)	Nonmaleficence	Descriptive survey with hypothetical case studies	165 osteopathic family physicians	Evaluate osteopathic family physician's opinions about disclosing genetic test results to patient's family members	Most providers agreed that adult children should be told about genetic test results if the disease was treatable. Age played a role in disclosure of test results. Most providers agreed they would tell a 22-year-old, were unsure about telling a 17-year-old, and would not tell a person 12 or younger.	Findings may not be generalizable. All providers were from New Jersey, mostly White and male.
Goldenberg et al. (2014)	Autonomy	Descriptive survey	Nationally representative sample of 1,539 parents	Assess parents' interest in whole genome sequencing (WGS) of newborns	74% of the parents were interested in having WGS for newborn screening if it was offered by the state. 70% were interested in WGS if it was offered in a pediatric office. Test accuracy and the ability to prevent a disease from developing were rated as important information for making an informed decision about testing.	Survey asked hypothetical questions and may not represent decisions in actual situations. The researchers suggested that the participants may not have fully understood the benefits and limitations of WGS.

(*Continued*)

TABLE 8.3
Literature Characteristics (Continued)

Author (Year)	Ethical Principles Addressed	Design	Sample	Purpose	Findings	Limitations
Haga et al. (2012)	Nonmaleficence	Qualitative focus groups	21 primary care providers and genetics professionals	Assess attitudes about pharmacogenetic testing	Primary care providers had concerns regarding the impact of pharmacogenetic testing on delay of treatment, clinical utility, insurance coverage, and ability to interpret test results.	Small sample size from one region of the country, may not be representative of the greater population.
Hall et al. (2005)	Justice	Descriptive survey	Multiethnic sample of 86,859 adult primary care patients from 5 U.S. states and 1 Canadian province	Measure concern about insurance problems relating to genetic testing	40% of survey participants were concerned that genetic testing could lead to insurance discrimination.	Assessed insurance discrimination with a question that did not specify the type of insurance (i.e., life vs. health insurance). Participants had already agreed to undergo genetic screening; also does not represent the views of the general public.

Hay et al. (2012)	Autonomy	Descriptive telephone survey	1,772 multiethnic adults who were members of a health maintenance organization (HMO)	Determine if skin cancer awareness, family history, and health information seeking were related to perceived importance of learning about how genes affect health risk	Patients felt that learning about genetics and family history provided important information about health risks.	Self-report of genetic information–seeking behavior, not actual behavioral assessments.
Hindorff et al. (2009)	Justice	Descriptive survey	112 primary care physicians	Investigate primary care physicians' self-reported motivation for ordering Factor V Leiden genetic tests	Many of the physicians felt that lack of availability of genetic counseling services was a barrier that influenced their motivation to order genetic testing.	Self-report responses to hypothetical survey questions. The survey was long and could have introduced inaccurate responses.
Hunt & Kreiner (2013)	Justice	Qualitative interviews	58 primary care clinicians	Explore how pharmacogenetics is integrated in current practice	Pharmacogenetics has led to racial/ethnic profiling instead of individual genetic profiling.	Small sample size. Methods for data collection and analysis are not clearly articulated. Interview questions not provided or discussed in the article.

(*Continued*)

TABLE 8.3
Literature Characteristics (Continued)

Author (Year)	Ethical Principles Addressed	Design	Sample	Purpose	Findings	Limitations
Hurley et al. (2012)	Autonomy	Qualitative interviews	33 carriers of BRCA1/2 mutation	Determine BRCA1/2 carriers' preferences regarding preimplantation genetic diagnosis	Some participants preferred discussing preimplantation genetic diagnosis with a trusted primary care provider.	Small sample size. Results may not be generalizable. Males underrepresented in the study. Noncarrier partners were not interviewed.
Klitzman et al. (2013a)	Nonmaleficence	Descriptive survey	220 internists	Determine internists' views regarding preimplantation genetic diagnosis	Most of the providers felt that they had very little knowledge about preimplantation genetic diagnosis and did not feel comfortable answering patient's questions.	Internists from only two medical centers. Low response rate. High percentage of women in the sample
Klitzman et al. (2013b)	Nonmaleficence, justice	Descriptive survey	220 internists	Determine internists' utilization of genetic testing	The majority of internists surveyed felt that they needed more training about when to order tests and how to counsel patients. Less than 2% of the internists had patients who had testing and experienced genetic discrimination.	Sample not representative of the population of internists in the United States since there was a high percentage of women

Levy et al. (2007)	Justice	Descriptive survey	Random sample of 562 primary care physicians in the United States	Determine the importance of eight factors that influence whether to order a genetic test for smoking cessation treatment	The majority of participants felt that the most important factor influencing decision to order genetic test was if the test would improve cessation outcomes. If the test led to discrimination, this made the physicians less likely to order a test.	Survey was regarding a hypothetical test scenario, not actual patient encounter. Sample may not be representative due to response rate.
Lewis et al. (2011)	Autonomy	Qualitative content analysis of website data	25 direct-to-consumer (DTC) genetic testing company websites	Assess compliance of DTC companies with the American Society of Human Genetics (ASHG) transparency recommendations	The majority of DTC companies did not meet standards for compliance with transparency recommendations issued by ASHG. Most DTC companies did not disclose the limitations of genetic tests to consumers.	Could be some accuracy issues with the data influenced by the dates that the websites were accessed
Lowstuter et al. (2008)	Justice	Descriptive survey	1,181 nongenetic health-care providers	Describe nongenetic clinicians' perception and knowledge of cancer genetic testing and discrimination	The majority of providers felt that testing was of benefit, but believed genetic discrimination was an issue. The majority of providers were not aware of laws that protect against genetic discrimination.	91% of the respondents practiced in urban settings, which could influence survey results.

(*Continued*)

TABLE 8.3
Literature Characteristics (Continued)

Author (Year)	Ethical Principles Addressed	Design	Sample	Purpose	Findings	Limitations
Maradiegue et al. (2005)	Beneficence, nonmaleficence	Descriptive survey	46 advanced practice nursing students	Describe nurse practitioner students' knowledge of genetics	Students perceived that they had minimal knowledge of and training in medical genetics.	Small sample size, self-report
O'Neill et al. (2010)	Nonmaleficence	Descriptive survey	161 primary care providers	Assess primary care providers' willingness to order BRCA predictive testing for adolescents, given a hypothetical case scenario	31% of primary care providers would order BRCA genetic testing for an adolescent.	Small sample size; bias may be present because participants were attendees of a conference. Findings may not be generalizable. Using a hypothetical example does not reflect what may happen in actual clinical practice;
Srinivasan et al. (2011)	Nonmaleficence	Pretest–posttest ethical, legal, social efficacy scale	279 primary care residents	Assess effectiveness of a web-based program to increase knowledge and self-efficacy with genetic ethical, legal, and social implications (ELSI) issues	After participation in the web-based educational program, residents increased their self-efficacy with ELSI skills by 15%. Felt that they could apply content to the clinical setting	There were differences in the way the curriculum was implemented that were not assessed.

Strong et al. (2014)	Autonomy	Descriptive survey	258 primary care providers	Assess views of primary care providers regarding the return of incidental findings	About half of the providers surveyed felt that they would like to have their whole genome sequenced and more than one third would have their child's whole genome sequenced. A little over half of the participants would want to know incidental findings for diseases with no preventive treatment options. Many of the participants did not want to learn about incidental findings even if treatment or preventive actions are available.	The researchers mentioned that the survey was administered after a genetics presentation, which could have introduced biased answers. Sample may not be representative of primary care providers in the United States since the sample size was predominantly female.
Trinidad et al. (2008)	Nonmaleficence	Qualitative telephone interviews	24 primary care providers	Identify primary care providers attitudes toward genetic medicine and their educational needs	Providers were interested in learning more about when and how to order genetic testing and that they would like to have more resources to guide clinical decision making.	Small sample size

(*Continued*)

TABLE 8.3
Literature Characteristics (Continued)

Author (Year)	Ethical Principles Addressed	Design	Sample	Purpose	Findings	Limitations
Wasson et al. (2014)	Nonmaleficence	Qualitative interviews	20 primary care patients who had DTC genetic testing	Explore primary care patient's views, attitudes, and decision-making process related to DTC genetic testing	Most of the participants would disclose information about their genetic test results to their immediate family and less than half of the participants would disclose results to extended family.	Small sample size
Wasson et al. (2012)	Autonomy	Qualitative interviews	29 primary care patients	Explore decision-making process and ethical considerations of primary care patient who had DTC genetic testing	Patients were interested in DTC testing but were concerned about the accuracy and reliability of the testing and were concerned about risk regarding confidentiality of test results.	Small sample size, selection bias. Results are not generalizable.

were related to nonmaleficence, 7 were related to autonomy, 3 to beneficence, and 8 were related to justice. There were two studies that had findings related to two different ethical principles (Christianson et al., 2012; Klitzman et al., 2013b). Detailed characteristics of the literature sample are summarized in Table 8.3. A synthesis of the findings from each of the studies along with commentary for each of the four ethical principles of autonomy, beneficence, nonmaleficence, and justice as they relate to ethical issues of genetics/genomics faced by advanced practice nurses (APRNs) in primary care settings are provided in the following text.

Autonomy

Autonomy implies support for independent decision making by the patient (Beauchamp & Childress, 2009). There were seven studies that had either the purpose or a finding that evaluated aspects of autonomy related to genetics in primary care settings. These studies evaluated decision-making processes and informed consent. Four of the studies were descriptive surveys, two were qualitative interviews, and one study was a qualitative analysis of website content. Five of the studies evaluated patient viewpoints regarding informed consent and the decision-making process for genetic testing. One study evaluated websites of companies that offer direct-to-consumer (DTC) genetic testing to determine if enough information is provided for a consumer to make an informed decision. All of the studies had some methodologic limitations such as selection bias, low response rates, and self-report data. However, the findings from these studies are informative to APRN practice in primary care.

Decision-Making Processes

Studies reveal that there are some patients who are interested in exercising autonomy and seeking information about genetic risk and testing options. A survey of 1,772 patients who were interested in genetic testing and genetic health information concluded that individuals who autonomously seek genetic risk information may be more receptive to prevention and interventions that promote healthy lifestyles (Hay et al., 2012). Relationships with a trusted provider play a role in patient's decision process. A qualitative study of 33 carriers of the BRCA1/2 mutation that explored decisions regarding preimplantation genetic diagnosis reported that some of these patients preferred discussing genetic issues with a trusted primary care provider with whom they have a relationship as opposed to a specialist (Hurley et al., 2012).

It is difficult to separate the decision-making process from informed consent. One of the problems with the process of informed consent is that there are times when patients do not receive enough information to make an

informed decision. A qualitative study of 29 primary care patients who participated in focus groups to discuss interest in DTC genetic testing reported that the patients were interested in testing but were also concerned about the accuracy and reliability of the testing and the risk regarding confidentiality of test results (Wasson, Hogan, Sanders, & Helzlsouer, 2012). Another qualitative study evaluated the websites of 25 companies that offered DTC genetic testing revealed that the majority of these websites did not include enough information to comply with transparency recommendations issued by the American Society of Human Genetics and most did not disclose the limitations of genetic tests (Lewis, Treise, Hsu, Allen, & Kang, 2011). This lack of information makes it difficult for consumers to make informed decisions regarding genetic testing. These findings illuminate the relationship between the decision-making process and the role of informed consent.

Informed Consent

The informed consent process can be inadequate for patients who are considering testing ordered by a primary care provider. An evaluation of the consent process for 226 women for quad screening, a first-trimester prenatal genetic test, concluded that women who underwent this type of testing often lacked understanding about the reason for this test. Findings from this study indicated that having a provider offer the test was viewed as an endorsement for genetic testing, regardless of the level of patient understanding for testing (Constantine, Allyse, Wall, Vries, & Rockwood, 2014). This was an impediment to the informed consent process.

New genomic testing technologies such as whole genome sequencing (WGS) and whole exome sequencing (WES) are increasingly replacing traditional genetic testing procedures and presenting a challenge to informed consent and autonomy. WGS analyzes an individual's entire genetic blueprint and generates data on approximately three billion base pairs. WES analyzes the exome or the 1% of DNA that codes for proteins (Bunnik, de Jong, Nijsingh, & de Wert, 2013). Three applications of WGS and WES technology that primary care providers may encounter are newborn screening, prenatal screening, and DTC personal genome testing. These new genomic technologies are at odds with the principle of respect for autonomy and challenge the process of informed consent because all of the information gained from testing is not immediately interpretable (Bunnik et al., 2013; Hogarth, Javitt, & Metzer, 2008). Therefore, patients may not have the necessary information to make an informed decision about testing because of the possibility of future, incidental findings that may become apparent as more research is conducted that correlates health conditions with these genetic markers.

Incidental findings are defined as likely pathogenic test results that are not apparently relevant to the diagnosis or initial reason for seeking testing. In many instances, it is unclear if these incidental findings are clinically significant and this leads to controversy about what providers should do with this information. In some cases, the significance of incidental findings is not known unless a detailed family history is obtained and additional family members are tested. Family members often need to participate in testing and surveillance in order to decide if incidental findings are significant, which is part of the informed consent process (Crawford, Foulds, Fenwick, Hallowell, & Lucassen, 2013). The ethical challenges of dealing with the large amount of data generated from WGS/WES and how clinicians will disseminate this information has been discussed by a number of authors (Ali-Khan, Daar, Shuman, Ray, & Scherer, 2009; Letendre & Godard, 2004; Sharp, 2011).

There are currently no electronic health records that have standardized protocols for storing and analyzing the vast amount of data or the incidental findings in order to allow for responsible and appropriate disclosure of this information to providers and patients (Hazin et al., 2013; Shoenbill, Fost, Tachinardi, & Mendonca, 2014). According to Biesecker (2012), the nature of WGS and WES is best considered as a health-care resource that can be utilized and interpreted over the patient's life span, rather than a one-time test, and should be written into the patient consent.

Since newborn screening is one of the suggested applications for WGS and WES, this raises the concern of what to do with incidental findings when children are the patients. A nationally representative survey of 1,539 parents to assess interest in WGS of newborns reported that 74% of the parents were interested in having WGS for newborn screening if it was offered by the state and 70% were interested in WGS if it was offered in a pediatric office. However, test accuracy and the ability to prevent a disease from developing were rated as important information in order to make an informed decision about WGS testing (Goldenberg, Dodson, Davis, & Tarini, 2014). The researchers who conducted this study suggested that the participants may not fully understand the benefits and limitations of WGS and that incidental findings may require future follow-up. Another study that assessed the views of 258 primary care providers regarding WGS testing and the return of incidental findings noted that about half of the providers surveyed felt that they would like to have WGS testing and more than one third would have WGS for their own child. Over half of those surveyed wanted to know incidental findings for diseases with no preventive or treatment options. In contrast, some of the participants did not want to learn about incidental findings even if there were treatment or preventive actions available (Strong, Zusevics, Bick, & Veith, 2014).

One way to deal with incidental findings in children is to offer families a choice of which incidental findings they receive during pretest counseling, limit the findings to conditions with childhood onset that have immediate medical interventions, and make findings for adult-onset disease with no preventive measures or carrier status optional (Clayton et al., 2014; Mulchandani et al., 2014). The ethical dilemma is allowing children who are not able to consent for themselves the right to an open future without knowledge of genetic predispositions versus the knowledge of genetic predisposition to disease that may or may not be preventable (Borry, Evers-Kiebooms, Cornel, & Clarke, 2009; Borry, Howard, Senecal, & Avard, 2010; Bush & Rothenberg, 2014).

Historically, responsible laboratory testing and screening have been based on the ethical criteria that a test needed to be meaningful and highly predictive, the condition screened for needed to be serious, and there were follow-up actions or interventions available (Bunnik et al., 2013). The Centers for Disease Control and Prevention (CDC) Office of Public Health Genomics developed the ACCE model for evaluating genetic tests. This model uses 44 targeted questions to evaluate genetic tests according to analytic validity, clinical validity, clinical utility, and ethical, legal, and social implications (ELSI; CDC, 2010). A vast amount of data is generated from WGS and WES, which leads to ethical issues for both practitioners and patients. Data from WGS and WES may not be entirely interpretable at the time of testing, with meaningful results becoming available years later as research reveals new correlations between genetic markers and health conditions. The prospect of incidental findings from WGS and WES has implications for informed consent and disclosure of information. Respecting autonomy would allow patients the right to know or not to know about incidental findings.

Some authorities suggest that practitioners have a duty to recontact patients about incidental findings in order to satisfy the principles of beneficence and nonmaleficence (Clift et al., 2015). The American College of Medical Genetics recommends that patients who have their own or their child's WGS or WES should be informed of incidental findings that are of medical value (Green et al., 2013). There are currently no national or international guidelines about when and how to recontact patients with incidental findings (Otten et al., 2015). Very few research studies have been published about this topic and the implications for primary care settings. The information from the few publications on this topic suggest that patients expect to be recontacted by their health-care provider with new information as it becomes available (Otten et al., 2015). The right not to know should be incorporated into the informed consent process for WGS testing (Hull & Berkman, 2014). Patients should be given control over future data use rather than a one-time consent process that does not accommodate privacy concerns or actively involve patients in relevant future results (Erlich et al., 2014).

Providers need to counsel patients on a case-by-case basis in order to come to an agreement about which incidental findings the patient would like to know. Compassion and advocacy are critically important during and after the genetic testing process.

Nonmaleficence

Nonmaleficence is the responsibility to minimize harm in the technology used (Beauchamp & Childress, 2009). We identified 10 studies with findings related to nonmaleficence, which included 6 descriptive survey studies, 2 qualitative studies, 1 study that utilized focus groups, and 1 study that included a pretest/posttest design. Studies that had findings that addressed issues of nonmaleficence were mainly related to providers' lack of knowledge about genetics/genomics (9 studies) and concerns about confidentiality of genetic test results (2 studies).

Provider's Lack of Knowledge

Although many support integrating genetic/genomic services into primary care, there is an ongoing debate as to whether primary care providers are prepared to provide genetic services. We identified several studies in our analysis that reported providers' lack of knowledge and skills related to the application of genetics in primary care practice. O'Neill et al. (2010) surveyed 161 primary care providers and reported that 31% would order genetic testing for BRCA1/2 for an adolescent. Providers who would order this testing had significantly higher patient volume and frequency of ordering tests. This suggests that primary care providers who are willing to order genetic tests for adolescents may not fully understand the risks and benefits regarding testing of minors for adult-onset diseases (Ross et al., 2013). Two qualitative studies of primary care providers concluded that the providers felt that they needed more education as to how to order genetic testing and when to make a referral to a genetic specialist (Arar, Seo, Abboud, Parchman, & Noel, 2010; Trinidad et al., 2008). A survey of 46 APRN students noted that the students perceived they had minimal knowledge of genetics (Maradiegue, Edwards, Seibert, Macri, & Sitzer, 2005). Similarly, two studies of 220 internists who practice in primary care settings noted that the majority surveyed felt they needed more training about when to order genetic tests and how to counsel patients regarding genetic conditions (Klitzman et al., 2013a, 2013b). Additionally, a survey that compared the comfort of 51 primary care and 31 specialist physicians with initiating a referral for cancer genetic testing reported that primary care physicians were significantly less comfortable making a referral and discussing genetics compared with specialists (Brandt, Ali, Sabel, McHugh, & Gilman, 2008).

It has been suggested that primary care practitioners are lacking in the theoretical knowledge and skills to provide genetic services and that they could provide

information to patients that is misleading (Schmitz, 2010; Shoenbill et al., 2014). Busy clinicians who work in primary care settings may not have the time to adequately counsel patients about genetic testing causing additional distress (Mikat-Stevens et al., 2014). A recent review of case studies with adverse outcomes as a result of genetic testing and counseling provided by primary care practitioners identified that the adverse outcomes were related to wrong tests ordered, misinterpreted results, and unnecessary tests (Brierley et al., 2012). This review also reported lawsuits where practitioners were found to be negligent because insufficient family history was obtained, genetic tests were not ordered, appropriate referral to genetic specialists were not made, and suitable risk reduction options were not provided (Brierley et al., 2012). There are alternative learning methods that could aid with this dilemma. Srinivasan and colleagues (2011) found that a web-based course was effective for improving the self-efficacy of primary care medical residents with ethical issues related to genetics in clinical practice. Primary care providers have an obligation to be up-to-date in their practice and this includes advances in genetics (Badzek, Henaghan, Turner, & Monsen, 2013).

Another area of concern for primary care providers is the lack of knowledge about pharmacogenetics, which is becoming increasingly important for medication management. Qualitative focus groups that included 21 primary care and genetics professionals reported that providers expressed concerns and lack of knowledge about implementation of pharmacogenetic testing in clinical practice. Reasons providers gave for concerns about implementing pharmacogenetics in their practice included delay of treatment, limitations in clinical utility, insurance coverage and reimbursement issues, and inability to interpret test results (Haga, Trindall, & O'Daniel, 2012).

Part of the resistance providers have to implementing pharmacogenomics into practice is related to a lack of clinical decision support tools to guide clinicians to order the correct tests and use genetic data to prescribe medications effectively (Weitzel et al., 2014). Lack of pharmacogenomic knowledge by providers could lead to liability and adverse patient outcomes. For example, a case study reported that a breast-fed newborn who died from morphine poisoning was later genotyped for the cytochrome P450 2D6 genetic variant and found to be an "ultrarapid metabolizer" of codeine to morphine. The mother was taking codeine, which is a commonly prescribed pain medication in the postpartum period (Koren, Cairns, Chitayat, Gaedigk, & Leeder, 2006). In another case, an adult patient who was treated for a cough with codeine cough syrup developed life-threatening opioid intoxication even though only a small dose of medication was prescribed. Genotyping consequently revealed that the patient was an ultrarapid metabolizer of codeine (Gasche et al., 2004). While pharmacogenomic testing for the metabolization of opioids is not yet commonplace, there are several

drugs that do require genetic testing prior to administration, and other drugs where genetic testing is available to prevent adverse outcomes (PharmGKB, 2015; U.S. Food and Drug Administration, 2014).

Confidentiality

Another ethical issue associated with nonmaleficence is confidentiality. Health-care providers are required to keep patient information confidential. This requirement raises ethical concerns with regard to genetic test results. Genetic test results are of significance to not only patients but also entire families, making it challenging for providers who may feel the need to inform family members who are at risk for a genetic condition. A qualitative evaluation of the disclosure decisions of 20 primary care patients who decided to have DTC genetic testing noted that most of the patients would want to disclose information about their genetic test results to their immediate family and less than half wanted to disclose to extended family (Wasson, Cherny, Sanders, Hogan, & Helzlsouer, 2014). This shows that patients would like to be able to have the choice about disclosure of sensitive genetic test results among family members.

An ethical dilemma exists as to whether a provider should breech individual confidentiality in order to provide information to family members who may be at risk for a life-threatening condition versus respecting patient confidentiality (Resnik, 2003). A survey of 165 osteopathic physicians in family practice settings regarding opinions about disclosing test results to patient's family members reported that the majority felt that adults should be told genetic test results but were unsure about disclosing results to teenagers and children (Erde, McCormack, Steer, Ciervo, & McAbee, 2006). This group of providers felt that they needed more guidance about when, how, and whether to disclose genetic testing information to family members. It is highly unlikely that a health-care provider would face legal charges because a family member was not warned (Badzek et al., 2013). Healthcare providers are not legally required to warn family members about genetic risk. They are only required to encourage a patient to inform family members about the results of genetic testing (Badzek et al., 2013). Genetic predispositions can be somewhat uncertain, can take quite a few years to develop into a condition, and the development is often influenced by environmental factors. However, there could be cases where a family member's health would be improved if they had knowledge of a genetic predisposition.

Health-care providers are not legally required to warn family members about genetic risk. They are only required to encourage a patient to inform family members about the results of genetic testing (Badzek et al., 2013). If patients do not object to informing relatives, there are no legal obstacles that prevent health-care providers from informing patients' relatives (Stol, Menko, Westerman, & Janssens, 2010).

Beneficence

Beneficence is defined as patient advocacy and compassion (Beauchamp & Childress, 2009). Few studies were located that evaluated the principle of beneficence as it relates to genetics/genomics in primary care practice. We identified three studies that had findings related to the principle of beneficence. One of these studies utilized videotaped physician–patient encounters that were qualitatively analyzed, one study utilized focus groups, and one study was a descriptive survey.

Patient Advocacy

The first study was a randomized controlled educational trial that evaluated the effects of web-based versus text-based educational programs on the abilities of 121 physicians to interact with a standardized patient who was at risk for inherited breast cancer (Bell et al., 2014). The standardized patient encounters were video-recorded and analyzed. The study found that the majority of the physician–standardized patient encounters had inadequate family history taking and little discussion about genetic testing and ethical implications regardless of the educational program the physicians were exposed to. These findings show a lack of attention to detail that is ethically important for patient advocacy to take place.

A second study of 16 primary care providers (14 physicians and two midlevel providers) who participated in focus groups to discuss integration of family health history and risk assessment in their practice reported several findings related to the principles of beneficence and justice (Christianson et al., 2012). All of the primary care providers in this study reported that they collected family health history information at initial offices visits, but the information collected varied widely with some providers using standardized questionnaires and others using verbal questions. The providers mainly asked patients about family history of breast, colon, and prostate cancer and reported that a positive family history of these disorders initiated different physical exam techniques and screening recommendations (Christianson et al., 2012). Providers in this study were concerned, because given these limitations, they did not know how to best advocate for their patients. Similarly, a third study of 46 APRN students found these students were not comfortable discussing treatment options with a family diagnosed with a genetic condition, nor were they comfortable collecting a family history (Maradiegue et al., 2005). These studies highlight the problem with a lack of standardization for the collection and discussion of family health history with patients in the clinical setting. This lack of attention to the patient's explanations about family health history diminishes the provider's ability for patient advocacy.

Compassion

Another area of ethical concern related to beneficence is how patients react to genetic/genomic information and the ability to empathize with the patient and family members. Considering the inclusion criteria for our review, few, if any, published research studies in the United States have evaluated the principle of beneficence as it relates to patient outcomes of personal genomic testing in primary care settings. What do patients do with the information from genetic tests? An individual who tests negative for an inherited disorder can have a variety of reactions including relief, survivor guilt, or concern over caregiving responsibilities for members of the family who are affected with the disease. Positive test results can lead to increased surveillance, prophylactic surgery, anxiety, and changes in life planning (Ormond, 2008). Some suggest that having knowledge from genetic testing does not necessarily translate into behavioral changes, while others argue that knowledge of genetic susceptibility to disease can actually reduce motivation to participate in preventive measures (Brower, 2004). Genetic testing results are not always informative and need to be interpreted carefully. In order to accurately interpret genetic test results, the individual medical history, family history, and type of genetic test all need to be considered. A negative test result often means that a change was not identified in the genetic material tested, thereby in singularity, not giving any useful information. Genetic testing is a complex process; negative results cannot always confirm or negate a diagnosis (Genetic Home Reference, 2015). The genetic testing process can cause additional problems for the individual and family members potentially leading to stigmatization, family discord, and psychological distress, which need to be dealt with in a compassionate manner (Nyrhinen, Hietala, Puukka, & Leino-Kilpi, 2007).

Justice

Justice includes the principles of impartial, equal, and fair distribution of resources and treatment (Beauchamp & Childress, 2009). We identified eight articles that had key findings or a purpose related to genetics/genomics in primary care practice and the principle of justice. Six of the studies utilized surveys and two of the studies were qualitative interviews. The studies were related to the issues of impartial treatment and access to genetic services.

Impartial Treatment

There is a national and international problem with genetic discrimination (Otlowski, Taylor, & Bombard, 2012). A study examining impartial treatment found the majority of 1,181 nongenetic health-care providers felt that genetic testing was of benefit for patients but thought that genetic discrimination was

an issue that would cause patients to decline testing (Lowstuter et al., 2008). The majority of the providers surveyed were unaware of laws that were in place to prohibit genetic discrimination. This lack of awareness of laws was related to decreased comfort among providers for ordering genetic testing (Lowstuter et al., 2008). Similarly a qualitative study of 16 primary care providers reported that these physicians had concerns with ethical issues related to genetic discrimination and legal liability when ordering genetic tests (Christianson et al., 2012), though few patients have reported genetic discrimination during the testing process (Klitzman et al., 2013b). A random sample of 562 U.S. primary care physicians ranked test results actually leading to improved cessation outcomes as the most important factor for ordering a genetic test for smoking cessation; however, the physicians reported that they would be less likely to order the genetic test if test results led to genetic discrimination (Levy, Youatt, & Shields, 2007). Another survey with a large sample of 86,859 adults in primary care settings regarding their views toward genetic testing reported that 40% of the participants felt that genetic testing might create discrimination related to obtaining health insurance (Hall et al., 2005).

Some fear that the practice of personalized medicine could lead to genetic and racial profiling. For example, advances in pharmacogenetics allow providers to prescribe medications based on an individual patient's genotype results. However, it has been reported that some providers use racial profiling instead of the actual genotype as a basis for prescribing. Interviews of 58 primary care providers suggest that instead of pharmacogenetics leading to individualized medicine, it has led to racial profiling in health care. This is attributed to a lack of knowledge on the part of health-care providers (Hunt & Kreiner, 2013). Genomic scientists are finding that genetic groupings often do not correspond with racial categories. The overlap of socially contrived and genetically bound categories can undermine the potential of personalized medicine, which focuses on the care tailored to the individual based on the identification of genomic risks (Fujimara & Rajaglopalan, 2011). Another consideration in this age of WGS is the possibility that the self-identified race, ethnicity, or nationality of an individual may not represent the genetic ancestry. These factors must be considered when presenting research study results and genomic test results to individuals and families. The distribution of human diversity is complex; therefore, subtleties in race, ethnicity, and nationality are important considerations in the translation of genomic results.

Results of genetic and genomic tests are of interest to a variety of societal institutions and organizations. Employers and insurers have a particular interest in employees' health and genetic and genomic test results, which could

potentially lead to discrimination against employees as these entities seek to make hiring decisions and maintain budgets. In the United States, the Genetic Information Nondiscrimination Act (GINA) of 2008 is a law to protect individuals from genetic discrimination by employers and health insurance companies. However, GINA is not entirely comprehensive since it is limited to the civilian population and does not apply to active members of the military, veterans, and Native Americans served by the Indian Health Service (Badzek et al., 2013). GINA only protects against genetic discrimination for health insurance, but not for life, disability, or long-term care insurance. The possibility for genetic discrimination exists regarding eligibility for these types of insurance. There is a need for additional legislation that protects individuals against genetic discrimination including regulatory and legislative protections for privacy of WGS/WES data to ensure ethical considerations are being upheld when evaluating genomic information (Ginsburg & Willard, 2009).

Access to Genetic Services

Two studies in our analysis reported findings that address the issue of access to genetic services. A survey of 498 family physicians reported that these providers routinely provide a variety of genetic services to patients including consulting for perinatal conditions and familial cancers (Acheson, Stange, & Zyzanski, 2005). In this same study, physicians practicing in rural settings reported that it was difficult to find genetic consultants. A group of 112 primary care physicians were surveyed regarding motivations and barriers associated with ordering genetic testing for Factor V Leiden. Many of the physicians felt that lack of the availability of genetic counseling services was a barrier that influenced their motivation to order genetic testing (Hindorff et al., 2009).

Cost also affects access to genetic services. Although it is projected that genomic discoveries and personalized care will provide cost savings, this is not always the case. As the genomic science moves ahead, there are significant pharmacogenomic discoveries; however, these discoveries often come with a stunning price tag. In an era of health-care policy calling for price controls, this poses roadblocks for educated consumers demanding access to the medications that can provide personalized treatments (Carlson, 2008). For example, the cost of crizotinib, a targeted therapy for non-small-cell lung cancer, is approximately $115,000.00 annually or $10,000.00 per month. Although crizotinib is considered a clinically effective treatment, the cost is prohibitive and insurers are rarely willing to cover the cost of this drug (Djalalov et al., 2014). Access to genetic treatment and services is not always available. In rural areas, there are a lack of available genetic services, which raises concerns about access for patients (Hawkins & Hayden, 2011).

CONCLUSIONS

Sparse research has been conducted on the actual ethical issues encountered by health-care providers in the primary care setting. The majority of research that addresses ethical issues related to genetics and genomics in primary care settings were descriptive surveys or qualitative designs with very few experimental or quasi-experimental designs. There were few studies where the main purpose was to evaluate the ethical issues related to genetics/genomics in primary care practice. Most of the studies included key findings that were pertinent to this topic but few were designed to exclusively evaluate ethical issues related to genomics in primary care practice. Many of the studies had various limitations including small sample sizes, bias associated with self-report data, and samples that were not representative of the general population. These limitations decrease the generalizability of the findings of these studies. Much of the research was based on opinions related to hypothetical case studies and situations presented in survey form. Very few studies have focused directly on the role of primary care providers with genetic and genomic services and the ethical issues faced by this group. It is interesting to note that when the studies are listed by date of publication and topic, more studies have been conducted regarding the topic of autonomy in the past 4 years. This may be influenced by the development of new genomic testing technologies. However, few studies to date have directly evaluated the ethical implications related to advanced technologies such as WGS and WES and their utilization in primary care settings. Little research has been conducted on the actual ethical issues encountered by health-care providers in the primary care setting. More research needs to be conducted that examines the actual experiences of primary care providers with ethical issues associated with genetics and genomics in clinical practice.

Implications for Primary Care Practice

Genomic science is infiltrating day-to-day health care practice and therefore is an integral part of the care delivered by primary care providers. ELSI issues that arise from this science are complex and are too important to be ignored (McCarthy, 2014). Often in the primary care setting, providers take a directive approach with the patient, rather than understanding the perspective and wishes of the patient that are critical to the decision-making process for informed genomic testing. A trusted partnership between patient and provider that is neither judgmental nor compulsory is important to having the patient make an informed choice that is ultimately his or her decision. The current primary care system allots minimal time for patient visits, whereas the time allotments required for pretest and posttest genomic counseling are an hour or longer, often require follow-up visits, and are integral to the management of genomic patient care and assisting with informed decisions. Innovative models of care that address these issues are

required to meet the growing technology that is rapidly entering primary care (American Hospital Association, 2013).

On the horizon is the genomic health record containing WGS that will merge with data from the current electronic medical record actualizing the paradigm of personalized medicine (Fraser & Pai, 2014). Primary care providers including APRNs must understand genomic science and how it will be integrated into clinical practice as well as its impact on the ethical implications for individuals, families, and communities. This requires that primary care providers keep current on this rapidly changing field and integrate new evidence-based genomic information into practice at all levels of care. Medical schools and organizations are addressing the integration of personalized medicine into curricula, and nursing will require leadership skills to incorporate genetic technology into patient care (Demmer & Waggoner, 2014; Huston, 2013). ELSI matters that arise from the science of genetics and genomics are too important to be ignored and cannot be learned in the clinical setting alone. Continuing education regarding ELSI and genetic/genomic services should be a part of staff education using an interprofessional team approach to discuss genetic privacy, screening, and other issues that may impact the individual's care management.

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