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Integrating genetic and genomic information into effective cancer care in diverse populations

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This paper provides an overview of issues in the integration of genetic (related to hereditary DNA) and genomic (related to genes and their functions) information in cancer care for individuals and families who are part of health care systems worldwide, from low to high resourced. National and regional cancer plans have the potential to integrate genetic and genomic information with a goal of identifying and helping individuals and families with and at risk of cancer. Healthcare professionals and the public have the opportunity to increase their genetic literacy and communication about cancer family history to enhance cancer control, prevention, and tailored therapies.

introduction and background

Cancer is an emerging global health challenge because of the aging of the population and the evolution of new patterns of risk behaviors, including harmful tobacco and alcohol use, unhealthy diet, and physical inactivity. The occurrence of cancer in a population is influenced by several factors including behavioral risk factors, changes in the social and cultural milieu, environmental exposures, and familial cancer history. Worldwide, more than a million cancer deaths are due to tobacco annually [1]. It is estimated that more than 80% of the world's one billion smokers live in low- and middle-resource countries [2]. Public policies instituted to control tobacco have been shown to be cost-effective and cost-saving [3, 4]. At least one-third of cancers are preventable through risk factor modification, but there have been limitations in reducing infections known to increase the risk of cancer—hepatitis B virus in the case of liver cancer and human papilloma virus associated with cervical cancer [5].

The assessment of patients' genetic profiles plays a critical role in the spectrum of cancer care from screening to the use of targeted therapies based on a tumor's molecular signature. Elucidation of the family cancer history remains a low-cost and effective screening tool to target high-risk individuals and families in prevention and surveillance programs [6]. Better understanding of genetic variation offers the possibility of tailored pharmacotherapeutics based on risk, such as stratifying therapy based on a high-risk haplotype in the nicotinic receptor gene cluster that is associated with smoking quantity and success of quitting [7, 8]. Reduction in the cancer burden can be achieved by implementing enhanced surveillance and proven interventions that suit the particular resources and needs of each country [9].

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cancer and genes

Cancer is a genetic condition and as such, attention to risk assessment is particularly important because a significant minority of cancer is due to hereditary susceptibilities. Genetic variation likely underlies a substantial amount of the differences in responsiveness to medications and environmental exposures. Tests that predict the responsiveness of an individual's cancer to specific therapies are increasingly available and integrated in clinical trials and routine cancer care. This is made possible by the availability of a variety of high-throughput sequencing approaches that have enabled the discovery of both prognostic and predictive biomarkers, revolutionizing cancer screening, prognosis, and treatment, including prediction of treatment response. Efforts to improve outcomes in many advanced cancer patients have centered on using targeted therapies directed against key signaling pathways in cancer growth and progression. For example, the use of therapies targeting the epidermal growth factor receptor has resulted in improved survival in patients with advanced colorectal cancer (CRC) [10]. Biomarkers such as those identified in lung and CRC also help to stratify patients according to the likelihood of benefit from targeted therapies (in lung cancer, epidermal growth factor receptor (EGFR)-positive patients benefit from erlotinib and gefitinib and echinoderm microtubule-associated protein like 4-anaplastic lymphoma kinase-positive patients benefit from crizotinib), or being deriving no benefit from the use of these targeted therapies (patients with v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog wild type not likely to benefit from cetuximab and panitumumab in CRC) [11, 12].

family history and risk assessment

Family history is a fundamental element of health information. Obtaining systematic family history information is currently important for addressing cancer risk variation in high-resource countries, but could be more generally used [13, 14]. With the help of a genetic counselor, it can serve as an important

predictor of cancer risk and a basis to recommend stratified prevention strategies in various populations aimed to reduce morbidity and early mortality in cancer. Survey data suggest a broad understanding of the importance of family health history among the public, but that it is often not documented [15, 16].

The use of family history as a tool in assessing familial cancer risk may have some limitations in culturally diverse settings [17]. The construction of the pedigree and the assessment of risk may be complicated in cultures, wherein polygamous, polyandrous, and/or consanguineous relationships are prevalent [18]. Additionally, since cancer is still often stigmatized and not disclosed, patients may not be aware of their cancer family history [19]. Finally, patients and their families may not readily disclose a family history of cancer for fear that it may negatively impact other family members—causing them emotional distress and shame [20].

Hereditary forms of cancer offer the opportunity for early detection and prevention in family members. For example, the Lynch Syndrome and familial adenomatous polyposis, as well as their associated gene profiles, have been identified to convey an increased risk of developing CRC. In this setting, secondary prevention with the use of nonsteroidal anti-inflammatory drugs has been shown to reduce the incidence of colorectal adenomas [21–23]. In some other cancers, e.g. like breast cancer, high-risk status (e.g. >20% lifetime risk), derived in part from family history information, may impact recommended screening modalities, such as magnetic resonance imaging [24].

Despite the availability of genetic tests, some populations may be hesitant to undergo them. The cultural factors associated with refusal of genetic testing are important to explore as targets for interventions. A study conducted among Asian women who refused genetic testing did so for fear of emotional stress and burden of genetic information (16%), perception of no change in medical management (16%), concerns with how family members will accept the information (15%), and reluctance of family members to be tested for fear of emotional burden (15%) [25]. Low acceptance of genetic testing in African Americans has been attributed to concerns about racial discrimination and stigmatization, and higher anticipated levels of negative emotional reactions to positive results [26–28]. Barriers to genetic counseling and testing may also include worry about passing a genetic change to children and concern about the communication of this information [29, 30]. In adhering to the tenets of Jewish law, orthodox Jewish women may not wish to know whether they are at high risk of developing breast cancer as it may conflict with a responsibility to preserve health, including emotional health [31, 32]. Preferences for family-centered care in Islamic cultures may be more important than confidentiality concerns and lead to less information-sharing even though genetic information may affect other family members [18, 19]. Differing cultural beliefs, mental models of disease, and propensities to fatalism can impact the interpretation of genetic information and thus, require effective communication skills in cancer care.

challenges in the integration of genetic/genomic information into cancer care

Even with improvements in the understanding of the role of genetic information in cancer care, health care providers globally face challenges in providing competent genetically guided health care [33]. Access to point-of-care cancer risk tools, with integrated family history information in electronic health records, is not widely available. Family history review is potentially widely available, but genetic counseling and testing that identify individuals who carry gene mutations that increase the risk of developing cancer are generally more widely used in high-resource countries. The diversity of family structures, genetic interrelatedness, and family traditions necessitate an open approach to addressing genetic issues. The 'ask-tell-ask' approach to communication (i.e. ask the patient/family to describe their current understanding of the issue). Tell them in straightforward language what you need to communicate. Ask them to tell you what they understand with attention to evidence-based guidelines where they exist, can provide a framework for the integration of family history information in cancer care [34]. Interventions that are aimed to improve screening and prevention must take, in account, the role of cultural traditions, variations in literacy, and allocation of health care resources, so that disparities do not escalate. The assessment tools used in resource-rich and more homogeneous populations may need to be adapted to local needs.

Despite advances in our understanding of the genetics and the molecular bases for cancer, most of the cancer patients are not yet receiving therapy tailored specifically to their tumor biology, both for the lack of resources and evidence bases. Over the past 10 years, international and national efforts to develop therapeutic standards and guidelines have been associated with substantial improvements in survival in resource-rich countries [35]. However, the first international consensus guidelines for advanced breast cancer did not address genetic testing issues [36]. Furthermore, the inclusion of genetic counseling in specialized multidisciplinary cancer units is not yet standard, even in high-resource countries [37].

Populations in low- and middle-resource countries as well as minority populations in the developed world may not benefit from our increased understanding of the molecular basis of cancer and genetic risk. They have historically had delayed access to care and worse treatment outcomes when compared with their high-resource country counterparts [38–40]. Extraordinary differences in access to treatment, chemotherapy, radiotherapy, genetic risk assessment, and individualized health care exist across the world. With minority populations under-represented in clinical trials, we may not be able to appropriately assess the effectiveness of these newer therapies in diverse populations. Numerous studies have identified differences in non-Caucasian patient populations with regard to tumor biology and epigenetic factors and the distribution of known prognostic and predictive markers [41, 42]. These differences may, in part, explain the disparities in cancer outcomes currently seen.

Addressing family communication about family cancer history with a goal of optimizing prevention, moderating risk, and tailoring treatment is a strategy to consider globally. Public health campaigns addressing cancer prevention could include information about the utility of family health history [43]. The World Health Organization (WHO) 2010 community genetics report has focused on reducing the prevalence and health impact of congenital disorders and genetic diseases while noting

Table 1. Integration input of genomics/genetics into international cancer care

International cancer care	Genetics/genomics input with examples	Needs and challenges
Knowledge and communication about FH in families	• 'My Family Health Portrait'—US Surgeon General [86] • 'Health Heritage' [87]	• Issues related to family structure, communication, misconceptions, and privacy
Provider knowledge about FH and genetic risk	• ASCO cancer genetics education module [88]	• Effective training of health care workforce
Integration of FH in care	• Provider asks and documents FH • CDS in GPM	• Time and prioritization
Integration of point of care cancer risk assessment tools	• Evidence-based risk assessment tools • CaGene in EHRs	• Efficient tools to assess risk for clinical decision support
Referral mechanisms for high-risk patients/families	• Genetic counseling services • FQHCs and PCPs	• Shortage of training programs globally • TAGC and GPCI
Informed consent	• Standards for the protection of participants	• International variation • Health literacy variation
Molecular testing for hereditary susceptibility syndromes	• Genetic testing laboratories with quality standards • Risk assessment models	• Accessibility and affordability • Patent issues • Systems-compatible algorithms • VUS
Molecular tumor diagnosis	• State of art techniques—ability to run whole genome sequencing	• Standards in interpretation • Accessibility and affordability • Evolving knowledge of genome • Harmonized nomenclature
Individualized molecularly tailored Rx	• Genomic map of tumor biology	• Accessibility and affordability • Clinical trials mechanism
Cancer registries and public health/heath care organization programs	• Inclusion of information on cancer in relatives • Screening policies	• Resource variation • Legal and ethical issues
Survivorship	• Access to DNA banking/genetic counseling and testing with integration of FH in palliative medicine [89, 90]	• Access to services • Integration of evolving genetic understanding throughout lifespan
Nondiscrimination protections	• Genetic information nondiscrimination act (GINA)	• International discussion and standards
National policies	• Genomic test regulation • Professional society standards • Advisory committees	• Legal and regulatory framework • Standardization • Evaluation measures
Resources	• Genetic support groups • Multilingual advocacy groups	• Culturally and family-centered awareness, discussion, and materials

ASCO, American Society of Clinical Oncology; CDS, clinical decision support; EHR, electronic health record; FH, family health history; FQHCs, federally qualified health centers; GPCI, genetics in primary care institute; GPM, genetically guided personalized medicine; PCP, primary care physicians; Rx, treatment; TAGC, transnational alliance of genetic counselors http://tagc.med.sc.edu/quarterly.asp; VUS, variants of unknown significance.

challenges in the lack of resources related to inadequate genetic services, low genetic literacy, costs, fear of stigmatization, and lack of trained professionals as barriers [44]. The WHO action plan does not yet include an international community goal for increasing the understanding and application of information about family history-associated risk and genetic variation in cancer care [45]. Similarly, the WHO's plan for control of chronic diseases does not directly address family and inherited aspects of cancer or tiered prevention and treatment strategies based on genetic variation [2]. It emphasized the importance of establishing and strengthening national policies and plans for prevention and control, including robust health promotion units, high-quality surveillance, and monitoring systems that enable implementation and monitoring of standards and evidence-based guidelines, cost-effective approaches for the early detection of certain cancers, strengthened health care provider training, and improved education and tools for self-management. While proven cost-effective strategies for incorporating genetic and genomic information in cancer plans have not been demonstrated internationally, several models for

the regional address of particular cancers have been proposed that could incorporate strategies to address familial aspects of cancer [46–48]. Table 1 summarizes evolving areas in international cancer care where the utilization and understanding of genetics and genomics can have impact, along with some of the associated needs and challenges.

communication and advocacy issues

Cultural competency and respect for differences occupy a significant place in cancer care. Patient-centered communication in cancer care encompasses the functions of: exchanging information, fostering healing relationships, recognizing and responding to emotions, managing uncertainty, making decisions, and enabling patient self-management and navigation [49]. A patient-centered approach includes identifying and negotiating different styles of communication across cultures, decision-making preferences based on cross-cutting cultural and social issues, roles of family, sexual and gender issues, cohesion, flexibility, and issues of mistrust, prejudice, and racism [50]. Genetic counseling facilitates the inclusion of cultural competency, advocacy, and the ongoing communication of survivorship in cancer care. The National Society of Genetic Counselors recommends genetic counseling in cancer care from the step of gathering personal medical and family history data. Genetic counseling impacts psychosocial assessment and support, derivation of personalized risks, discussion of cancer and mutation risk, facilitation of informed consent process and likelihood of identifying a mutation with genetic susceptibility testing, disclosing results, discussing medical management options, and reviewing genetic discrimination issues [51]. Expanded genetic counselor training and extensive programs for health care providers in genetics are needed worldwide to adapt these guidelines and to enhance practices in cancer care across different populations [52].

strategies for action

The incorporation of expanding genetic understanding and genomic information in cancer care requires both infrastructure enhancements (i.e. the use of clinical tools, registries, and biobanks with expanded access, research, and workforce training) and patient and population interventions (e.g. enhanced access, health education, culturally adopt interventions). The distribution of prognostic and predictive biomarkers likely varies by population [41]. In diverse populations, different susceptibility loci and variations in allele frequency may explain biologic differences of cancer across ethnic and racial populations [53–57]. An extensive epidemiological assessment of populations in the developing world with international collaboration is needed to better understand the interaction between genetic susceptibility and environmental exposure and to develop the evidence to support specific interventions [58–60]. Extensive characterization of cancer genomes in diverse populations may lead to improved approaches to prevention and treatment [61]. The ethnic differences in the epidemiology of known prognostic and predictive markers should be taken into account when conducting global clinical trials that include different ethnic groups. As strides are made to build research infrastructure in resource-challenged countries, attempts may be made to include diverse population subgroups in ongoing clinical trials in resource-rich countries.

It has been estimated that 80% of the world's population is not covered by a population-based cancer registry [62]. This is in contrast to 99% and 40% of the USA and European populations, respectively [63]. In a five continent survey of population-based cancer registries, only 5 of 62 such registries in Africa produced sufficiently good data to be included in a publication of worldwide cancer registries [64]. Data from population-based registries can help researchers, practitioners, and policy-makers to better characterize the magnitude of the cancer burden and to better deploy resources to addressing the issue. Furthermore, bio-specimen banks can help determine whether allocation of resources to genetically based therapies is appropriate and may help elucidate potential targets for therapy that are unique to other populations given differences in ethnicity, lifestyles, environmental exposures, and stage at presentation (e.g. EGFR-positive adenocarcinomas of lung in nonsmoking Asian women). International barriers to bio-banking may include the lack of financial resources, poor literacy among patients, physicians regarding the importance of bio-specimens, and the lack of infrastructure [65]. Consortia are developing both nationally and internationally to address the implementation of pharmacogenomic testing, including those specifically addressing cancer treatments in an effort to reduce toxic effects [66]. The rate of diffusion of next-generation sequencing into regular laboratory medicine and genomic knowledge translated into cancer therapeutics is likely to vary [67]. Prevention strategies incorporating family history and genetic understanding are evolving in their scientific evidence base and sufficient public and professional awareness to affect practice and care [68]. For example, while first-degree relatives of persons CRC have a 1.6–8× higher lifetime risk of CRC than those without a positive family history, a combination of familial susceptibility and unhealthy behaviors increases the risk of CRC substantially [69, 70]. Behavior change programs targeting high-risk groups may be more effective than those targeting the general population [71–74]. Screening recommendations varying by genetic risk (e.g. positive family history) are continuing to evolve as evidence is accrued [75]. For example, family history of breast and colon cancer is included in the US Services Preventive Task Force and National Comprehensive Cancer Network Guidelines on breast and colon cancer [24, 76, 77]. As health literacy spreads, campaigns emphasizing the importance of family health history to cancer risk may be integrated in education and self-management [78]. Health care providers' capacity to document and use an accurate cancer family history for risk assessment may benefit from enhanced decision support, including the point of care tools [13, 79, 80].

conclusions

A framework for integrating genetic/genomic understanding into cancer care in diverse populations must recognize social, cultural, and economic heterogeneity and how genetic factors may impact individual and population health. Cancer care

guidelines that are developed in resource-rich countries may be limited in their application in resource-challenged settings [81]. This underscores the importance of modifying guidelines and practice to take into account competing health care demands, the gaps in resources and infrastructure, and the social and cultural milieu.

Progress toward more individualized and family-centered care throughout the world requires enhanced understanding of genetic and genomic information by patients and providers [82]. Workforce competencies and educational objectives in training programs in cancer genetics are being developed. Awareness of family history offers a bridge for communicating health risks, their complexity, and the importance of health behaviors between patients and providers. The development of genomic-biomarker testing that assesses cancer susceptibility and precancerous conditions has the potential to reduce the burden of late diagnosis [83]. International collaboration on the development of evidence-based guidelines is an important strategy for improving care [84]. As the cost of genetic sequencing continues to decline, cancer management in all countries may benefit from efforts to integrate genetic information in risk stratification, prevention, and treatment. It is estimated that, by 2050, approximately two-thirds of cancer cases will occur in low- and middle-income countries [85]. It is hoped that the enormous costs associated with the use of cancer drugs can be curbed by unnecessary treatment. In order for the gap to be closed, comprehensive plans that include developing and validating less-expensive molecular technologies that provide the same information, investment in human capital, infrastructure building, and prevention policies that address cancer control earlier in its genetic progression are needed.

resources

National Coalition of Health Professionals in Genetics, http://nchpeg.org/. National Institutes of Health: National Human Genome Research Institute, http://www.genome.gov. National Genetics Education and Development Center, http://geneticseducation.nhs.uk/. National Genetics Education and Development Centre: Telling Stories, http://www.tellingstories.nhs.uk/index.asp. World Health Organization Human Genetics Programme, http://www.who.int;genomics/en/.

disclosure

The authors have declared no conflicts of interest.

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