CA CANCER J CLIN 2011;61:327–359

Genetics, Genomics, and Cancer Risk Assessment

State of the Art and Future Directions in the Era of Personalized Medicine

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Abstract

Scientific and technologic advances are revolutionizing our approach to genetic cancer risk assessment, cancer screening and prevention, and targeted therapy, fulfilling the promise of personalized medicine. In this monograph, we review the evolution of scientific discovery in cancer genetics and genomics, and describe current approaches, benefits, and barriers to the translation of this information to the practice of preventive medicine. Summaries of known hereditary cancer syndromes and highly penetrant genes are provided and contrasted with recently discovered genomic variants associated with modest increases in cancer risk. We describe the scope of knowledge, tools, and expertise required for the translation of complex genetic and genomic test information into clinical practice. The challenges of genomic counseling include the need for genetics and genomics professional education and multidisciplinary team training, the need for evidence-based information regarding the clinical utility of testing for genomic variants, the potential dangers posed by premature marketing of first-generation genomic profiles, and the need for new clinical models to improve access to and responsible communication of complex disease risk information. We conclude that given the experiences and lessons learned in the genetics era, the multidisciplinary model of genetic cancer risk assessment and management will serve as a solid foundation to support the integration of personalized genomic information into the practice of cancer medicine. **CA Cancer J Clin 2011;61:327-359. ©2011 American Cancer Society.**

Introduction

Scientific and technologic advances in genomics are revolutionizing our approach to genetic counseling and testing, targeted therapy, and cancer screening and prevention, fulfilling the promise of personalized medicine. Features of genetic counseling that pose emerging challenges to oncology and other health care providers include the focus on the family as well as the individual, the emerging role of testing for common as well as rare genomic markers of cancer susceptibility, and the role of the oncologist in the communication of nononcologic health risks. For physicians, genetic counselors, nurses, and other members of a multidisciplinary cancer care team, the future of personalized medicine is now; however, the current enthusiasm about personalized genomics follows several decades of scientific discovery and clinical translation in human genetics. By analyzing the lessons learned

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DISCLOSURES: Supported in part by National Cancer Institute grant R25CA112486 and grant RC4CA153828 from the National Cancer Institute and the Office of the Director, National Institutes of Health to Jeffrey Weitzel and City of Hope, and also by support to Kenneth Offit from the Robert and Kate Niehaus Clinical Cancer Genetics Initiative, the Sharon Levine Corzine Fund at Memorial Sloan-Kettering Cancer Center, the Lymphoma Foundation, and the Esther and Hyman Rapport Philanthropic Trust.

We are grateful to Peter Thom, MS, for his help with designing Figure 1; to Dr. Stephen Gruber for his critical reading of the article; and to Tracy Sulkin and Shawntel Payton for assistance with preparation of the article. We also thank participants in the City of Hope Community Cancer Genetics and Research Training Intensive Course (National Cancer Institute grant R25CA112486; PI: J.N.W.) for providing insights about the challenges and rewards of providing genetic cancer risk assessment in community-based practices and the Cancer Genetics Community of Practice.

 doi:10.3322/caac.20128.

Available online at http://cacancerjournal.com

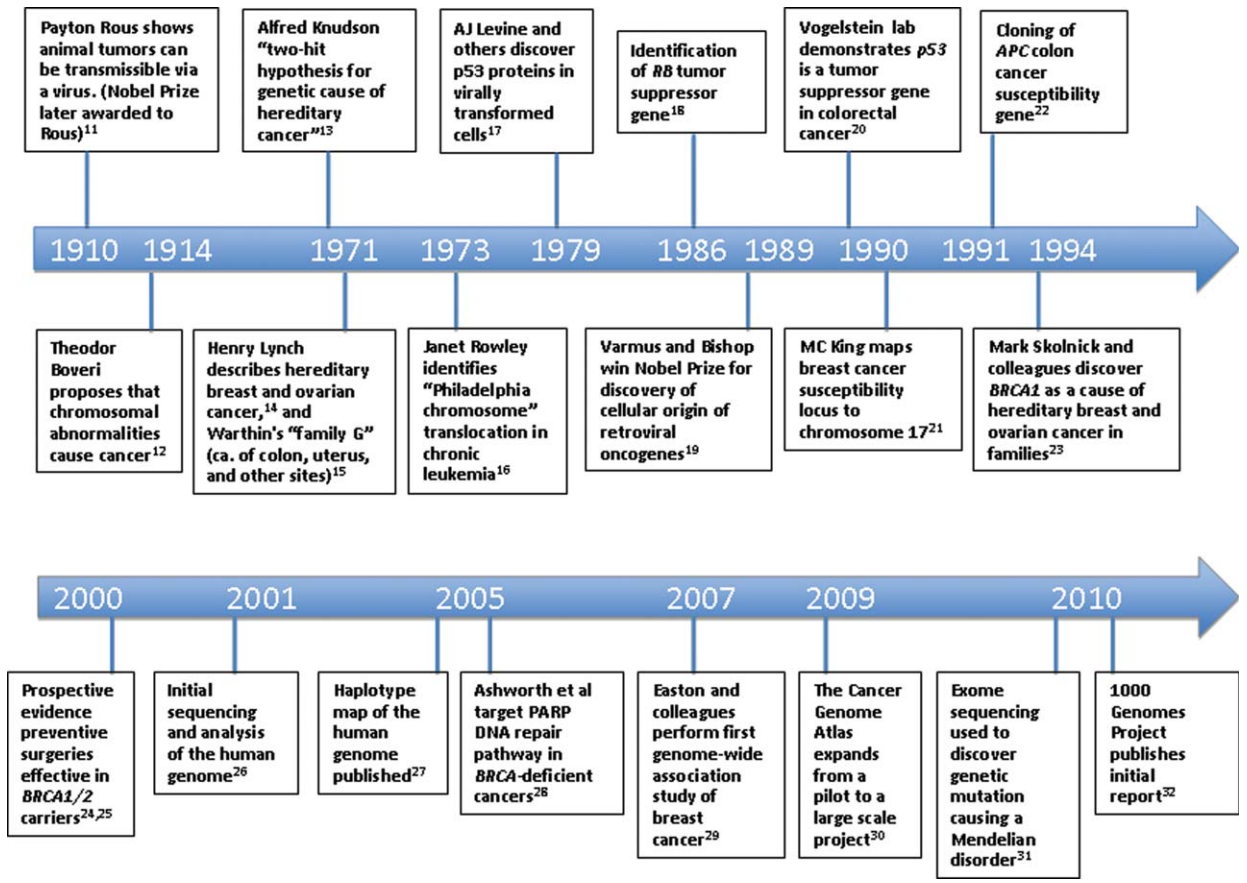

FIGURE 1. Timeline of Cancer Genetics to Genomic Discovery. Depicted is a snapshot of scientific developments capturing a century of experience in the translation of research in genetics and genomics to the practice of cancer medicine. *Rb* indicates retinoblastoma tumor suppressor gene; *APC*, adenomatous polyposis coli; PARP, poly(ADP-ribose) polymerase.

during the development of genetic cancer risk assessment (GCRA) and management, we will define the scope of the challenges currently faced by practitioners seeking to integrate genomic technologies into medical practice.

The Genetics of Hereditary Cancers: The First Decades of Discovery and Translation

Today, personalized medicine, informed by a molecular understanding of disease, has resulted in new classification systems as well as more effective preventive and therapeutic interventions. The National Cancer Institute (NCI) defines personalized medicine as "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease."[1] Simply put, the field of genetics refers to the study of single genes, and the emerging field of genomics refers to the study of all of a person's genes.[2] While the computational challenges of genomics are daunting, the translation of genomics to clinical care derives squarely from genetics practice. Indeed, single or multiplexed genetic profiles (DNA analysis of a single gene or set of genes) have been applied to presymptomatic risk assessment, as well as to diagnostic, prognostic, and therapeutic application in several fields, notably cancer care. In oncology, the use of presymptomatic genetic testing and "targeted therapies" tailored to the genetic profiles of tumors is part of the recommended evaluation for cancers of the colon, lung, breast, and other sites.[3-7]

The discussion presented here assumes that personalized genomics must meet the same evidentiary standards as other components of personalized medicine. Thus, it is important to state at the outset that the perspective offered here does not recognize a special claim to the "personal utility" of genomic tests for medical conditions outside of a medical context. Requirements for the clinical validity and utility of genomic tests are discussed elsewhere,[3,8] and the roles for alternate models of provider delivery of genetic and genomic information are

TABLE 1. Genes Associated With Hereditary Cancer Predisposition

SYNDROME (OMIM ENTRY)	PRIMARY COMPONENT TUMORS[a]	INHERITANCE	GENES
HEREDITARY BREAST CANCER SYNDROMES			
Hereditary breast and ovarian cancer (113705, 600185, 605724-*FANCD1*)	Breast cancer, ovarian cancer	Dominant	*BRCA1, BRCA2*
	Prostate cancer, pancreatic cancer, melanoma	Dominant	*BRCA2*
	Fanconi anemia (*FANCD1*) in biallelic carriers, medulloblastoma	Recessive	*BRCA2*
Partner and localizer of *BRCA2* (610355)	See *BRCA2* above	Dominant	*PALB2 (FANCN)*
BRCA1-interacting protein 1 (605882, 609054-*BRIP1)*	See *BRCA1* above; Fanconi anemia (*FANCJ*) in biallelic carriers	Recessive	*BRIP1*
Li-Fraumeni syndrome (151623)	Breast cancer, sarcomas (soft tissue/ osteosarcoma), brain tumors, adrenocortical carcinoma	Dominant	*p53*
Cowden syndrome (158350-*PTEN*, 612105-*Killin*)	Breast, thyroid, endometrial cancers	Dominant	*PTEN, KILLIN*
Bannayan-Riley-Ruvalcaba syndrome (153480)	Breast cancer, meningioma, thyroid follicular cell tumors	Dominant	*PTEN*
Ataxia telangiectasia (208900)	Leukemia	Recessive	*ATM*
Other hereditary breast cancer (604373)	Breast cancer (2-fold risk)	Dominant	*CHEK2*
HEREDITARY GASTROINTESTINAL MALIGNANCIES			
Lynch syndrome (also known as HNPCC) (120435, 613244-*EPCAM/TACSTD1*)	Colon, endometrial cancers; gastric, hepatobiliary, ovarian, pancreatic, renal, pelvis, small bowel, and ureteral cancers	Dominant	*MLH1, MSH2 (including EPCAM), MSH6, PMS2*
Includes Turcot syndrome (276300)	Glioblastoma		
Familial adenomatous polyposis, including attenuated phenotype (175100)	Colon cancer; gastric, duodenal, ampullary cancers	Dominant	*APC*
Includes Turcot syndrome (276300)	Medulloblastoma		
MYH-associated polyposis (608456)	Colon cancer	Recessive	*MYH*
Mismatch repair cancer syndrome (276300)	Colon, CNS, hematologic, and other cancers	Recessive	*MLH1, MSH2 MSH6, PMS2*
Hereditary diffuse gastric cancer (137215)	Gastric cancer; lobular breast cancer	Dominant	*CDH1*
Juvenile polyposis (174900)	Gastrointestinal cancers; Pancreatic cancer	Dominant	*SMAD4 (DPC4), BMPR1A*
Peutz-Jeghers syndrome (175200)	Colon, small bowel, breast, ovarian, and pancreatic cancers	Dominant	*STK11*
Hereditary pancreatic cancer (600185, 260350)	Pancreatic cancer; breast and ovarian cancers	Dominant	*BRCA2, PALB2*
Hereditary melanoma pancreatic syndrome (606179)	Pancreatic cancer, melanoma	Dominant	*CDKN2A (p16)*
Hereditary pancreatitis (167800)	Pancreatic cancer	Dominant	*PRSS1*
Familial gastrointestinal stromal syndrome (606764)	Gastrointestinal stromal tumors	Dominant	*KIT*
Oligodontia-colorectal cancer syndrome (608615)	Colon cancer	Dominant	*AXIN2*
GENODERMATOSES WITH CANCER PREDISPOSITION			
Melanoma syndromes (155600, 155601, 609048, 608035)	Malignant melanoma	Dominant	*CDNK2 (p16), CDK4, CMM*
Basal cell carcinoma/nevus syndrome/Gorlin syndrome (109400)	Basal cell cancers; medulloblastoma, ovarian cancer	Dominant	*PTCH*
Cowden syndrome	See above	Dominant	*PTEN*
Neurofibromatosis 1 (162200)	Neurofibrosarcoma, pheochromocytoma, optic gliomas, meningiomas	Dominant	*NF1*

TABLE 1. (Continued)

SYNDROME (OMIM ENTRY)	PRIMARY COMPONENT TUMORS[a]	INHERITANCE	GENES
Neurofibromatosis 2 (101000)	Vestibular schwannoma	Dominant	*NF2*
Tuberous sclerosis (191100)	Renal cancer, multiple bilateral renal angiomyolipoma, myocardial rhabdomyoma, ependymoma, giant cell astrocytoma	Dominant	*TSC1, TSC2*
Carney complex (160980, 605244)	Myxoid subcutaneous tumors, primary adrenocortical nodular hyperplasia, testicular Sertoli cell tumor, atrial myxoma, pituitary adenoma, mammary fibroadenoma, thyroid carcinoma, schwannoma	Dominant	*PRKAR1A*
Muir-Torre syndrome (variant of Lynch syndrome; 158320)	Sebaceous neoplasia (adenoma, keratoacanthoma, carcinoma); see Lynch syndrome above for other component tumors	Dominant	*MLH1, MSH2, MSH6*
Xeroderma pigmentosum (278730, 278700, 278720, 278760, 274740, 278780, 278750, 133510)	Skin cancer, melanoma, leukemia	Recessive	*XPA-G, POLH*
Rothmund-Thomson syndrome (268400)	Basal and squamous cell carcinoma, osteogenic sarcoma	Recessive	*RECQL4*
LEUKEMIA/LYMPHOMA PREDISPOSITION SYNDROMES			
Bloom syndrome (210900)	Leukemia, carcinoma of the tongue, squamous cancers, Wilms tumor	Recessive	*BLM*
Fanconi anemia, several complementation groups (227650)	Leukemia; squamous cancers; hepatoma; and brain, skin, vulvar, and cervical cancers; see hereditary breast cancer above (*FANCD1, J*)	Recessive	*FANCA, B, C, D2, E, F, G, I, L, M, N (FANCH is FANCA)*
Shwachman-Diamond syndrome (260400)	Myelodysplasia, acute myelogenous leukemia	Recessive	*SBDS*
Nijmegen breakage syndrome (251260)	Lymphoma, glioma, medulloblastoma, rhabdomyosarcoma	Recessive	*NBS1*
Canale-Smith syndrome (601859)	Lymphoma	Dominant	*FAS, FASL*
Hodgkin lymphoma (236000)	Hodgkin lymphoma	Recessive	*KLHDC8B*
IMMUNODEFICIENCY SYNDROMES			
Wiskott-Aldrich syndrome (301000)	Hematopoietic malignancies	X-linked recessive	*WAS*
Severe combined immune deficiency (102700, 300400, 312863, 601457, 600802, 602450)	B-cell lymphoma	X-linked recessive Recessive	*IL2RG, ADA, JAK3, RAG1, RAG2, IL7R, CD45, Artemis*
X-linked lymphoproliferative syndrome (308240)	Lymphoma	X-linked recessive	*SH2D1A*
GENITOURINARY CANCER PREDISPOSITION SYNDROMES			
Hereditary prostate cancer (176807, 601518)	Prostate cancer	Dominant	*HPC1, HPCX, HPC2/ELAC2, PCAP, PCBC, PRCA*
Simpson-Golabi-Behmel syndrome (312870)	Embryonal tumors, Wilms tumor	X-linked recessive	*GPC3*
Von Hippel-Lindau syndrome (193300)	Hemangioblastomas (retina and CNS), renal cell cancer (clear cell), pheochromocytomas, endolymphatic sac tumors	Dominant	*VHL*
Beckwith-Wiedemann syndrome (130650)	Wilms tumor, hepatoblastoma, adrenal carcinoma, gonadoblastoma	Dominant	*CDKN1C, NSD1*
Wilms tumor syndrome (194070)	Wilms tumor	Dominant	*WT1*
Wilms tumor, aniridia, genitourinary abnormalities, mental retardation (WAGR) (194072)	Wilms tumor, gonadoblastoma	Dominant	*WT1*
Birt-Hogg-Dubé syndrome (135150)	Renal tumors	Dominant	*FLCN*
Papillary renal cancer syndrome (605074)	Papillary renal tumor	Dominant	*MET, PRCC*

TABLE 1. (Continued)

SYNDROME (OMIM ENTRY)	PRIMARY COMPONENT TUMORS[a]	INHERITANCE	GENES
Constitutional t(3;8) translocation (603046)	Renal cell cancer	Dominant	*TRC8*
Rhabdoid predisposition syndrome (601607)	Rhabdoid tumors (see below)	Dominant	*SNF5/INI1*
Testicular tumors (273300)	Seminoma, embryonal carcinoma, teratoma, choriocarcinoma, endodermal sinus tumor	Dominant	*KIT, STK11, FGFR3*
CNS/VASCULAR CANCER PREDISPOSITION SYNDROMES			
Hereditary paraganglioma (115310, 600857, 185470, 602413, 602690, 16800, 613019, 613403)	Paraganglioma, pheochromocytoma	Dominant	*SDHA, SDHB, SDHC, SDHD, SDH5, TMEM127*
Retinoblastoma (180200)	Retinoblastoma, osteosarcoma	Dominant	*RB1*
Rhabdoid predisposition syndrome (601607)	Rhabdoid tumors, choroid plexus tumors, medulloblastoma	Dominant	*SNF5/INI1*
SARCOMA/BONE CANCER PREDISPOSITION SYNDROMES			
Multiple exostoses (133700, 133701)	Chondrosarcoma	Dominant	*EXT1, EXT2*
Leiomyoma/renal cancer syndrome (605839)	Papillary (type II) renal cell carcinoma, uterine leiomyosarcomas	Dominant	*FH*
Carney complex	See above	Dominant	*PRKAR1A*
Werner syndrome (277700)	Sarcoma/osteosarcoma, meningioma	Recessive	*WRN*
ENDOCRINE CANCER PREDISPOSITION SYNDROMES			
MEN1 (131100)	Pancreatic islet cell tumors, pituitary adenomas, parathyroid adenomas	Dominant	*MEN1*
MEN2 (171400)	Medullary thyroid cancers, pheochromocytoma, parathyroid hyperplasia	Dominant	*RET*
Hyperparathyroidism (145000, 145001, 610071)	Parathyroid carcinomas, Wilms tumor, pancreatic adenocarcinoma, renal cortical adenoma, papillary renal cell carcinoma, Hurthle cell thyroid carcinoma	Dominant	*HRPT1, HRPT2, HRPT3*
MISCELLANEOUS SYNDROMES			
Chordoma (215400)	Chordomas, skull (sphenooccipital, nasopharyngeal) and spine (sacrococcygeal, vertebral)	Dominant	*CHDM*
Costello syndrome/faciocutaneoskeletal syndrome (218040)	Epithelioma, bladder carcinoma, rhabdomyosarcoma, vestibular schwannoma	Dominant	*HRAS*
Dyskeratosis congenita (127550)	Squamous cell carcinoma	Dominant	*TERC, TERT, TINF2*
Mosaic variegated aneuploidy (257300)	Wilms tumor, nephroblastoma, rhabdomyosarcoma, leukemia	Recessive	*BUB1B*

ADA indicates adenosine deaminase; *APC*, adenomatous polyposis coli; *ATM*, ataxia telangiectasia mutated; *AXIN2*, axis inhibition protein 2; *BLM*, Bloom syndrome, RecQ helicase-like; *BMPR1A*, bone morphogenetic protein receptor, type IA; *BRIP1*, *BRCA1*-interacting protein 1; *BUB1B*, budding uninhibited by benzimidazoles 1 homolog beta (yeast); *CDH1*, cadherin-1; *CDK4*, cyclin-dependent kinase 4; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; *CHEK2*, human gene CHK2 checkpoint homolog; *CMM*, cutaneous malignant melanoma/dysplastic nevus; CNS, central nervous system; *ELAC2*, elaC homolog 2; *EPCAM*, epithelial cell adhesion molecule; *EXT1*, exostosin-1; *EXT2*, exostosin-2; *FANCA*, Fanconi anemia, complementation group A; *FANCJ*, Fanconi anemia group J; *FASL*, FAS ligand; *FGFR3*, fibroblast growth factor receptor 3; *FH*, fumarate hydratase; *FLCN*, folliculinc; *GPC3*, glypican 3; HNPCC, hereditary nonpolyposis colon cancer; *HPC*, hereditary prostate cancer; *HRPT1*, hyperparathyroidism 1; *HRPT2*, hyperparathyroidism 2; *HRPT3*, hyperparathyroidism 3; *IL2RG*, interleukin-2 receptor subunit gamma; *ILR7*, interleukin 7 receptor alpha chain; *JAK3*, Janus kinase 3; *MEN*, multiple endocrine neoplasia; *MEN1*, multiple endocrine neoplasia 1; *MLH1*, MutL homolog 1, colon cancer, nonpolyposis type 2; *MSH2*, mutS homolog 2, colon cancer, nonpolyposis type 1; *MSH6*, mutS homolog 6; *MYH*, MutY human homologue; *NBS1*, Nijmegen breakage syndrome; *NF1*, neurofibromin 1; *NF2*, neurofibromin 2; *NSD1*, nuclear receptor binding SET domain protein 1; OMIM, Online Mendelian Inheritance in Man; *PALB2*, partner and localizer of *BRCA2*; *PCAP*, predisposing for prostate cancer; *PMS2*, postmeiotic segregation increased 2; *POLH*, polymerase (DNA directed), eta; *PRCA*, candidate susceptibility gene for prostate cancer; *PRCC*, papillary renal cell carcinoma (translocation-associated); *PRKAR1A*, protein kinase, cAMP-dependent, regulatory, type I, alpha (tissue specific extinguisher 1); *PRSS1*, protease, serine, 1 (trypsin 1); *PTCH*, protein patched homolog; *PTEN*, phosphatase and tensin homolog; *RAG1*, recombination activating gene 1; *RAG2*, recombination activating gene 2; *RB1*, retinoblastoma 1; *RECQL4*, RecQ protein-like 4; RET, ret proto-oncogene; *SBDS*, Shwachman-Bodian-Diamond syndrome; *SH2D1A*, SH2 domain-containing protein 1A; *SDH5*, succinate dehydrogenase complex, subunit 5; *SDHA*, succinate dehydrogenase complex, subunit A; *SDHB*, succinate dehydrogenase complex, subunit B; *SDHC*, succinate dehydrogenase complex, subunit C; *SDHD*, succinate dehydrogenase complex, subunit D; *SMAD4*, SMAD family member 4; *STK11*, serine/threonine kinase 11; *TERC*, telomerase RNA component; *TERT*, telomerase reverse transcriptase; *TINF2*, TERF1-interacting nuclear factor 2; *TMEM127*, transmembrane protein 127; *TSC1*, tuberous sclerosis 1; *TSC2*, tuberous sclerosis 2; *VHL*, Von Hippel-Lindau tumor suppressor; *WAS*, Wiskott-Aldrich syndrome (eczema-thrombocytopenia); *WRN*, Werner syndrome, RecQ helicase-like; *WT1*, Wilms tumor 1.

Modified from Garber JE, Offit K. Hereditary cancer predisposition syndromes. *J Clin Oncol*. 2005;23:276-292.

[a]Most common syndromic tumors are listed followed by other less common tumors; this list is not exhaustive.

presented later in this monograph. The scientific foundation for personalized genomics draws on a range of disciplines including basic genetics, population genetics, genetic and clinical epidemiology, behavioral science, and emerging regulatory science. The clinical foundation of personalized genomics is the practice of medicine; indeed, many clinicians have been integrating personalized genetic services as part of their practice for many decades.[8-10] It is therefore instructive to review some of the insights gleaned from the recent period of scientific discovery and translation to the practice of genetic medicine, since the lessons learned are directly relevant to the challenges facing personalized genomics.

The Impact of Genetics and Genomics on the Practice of Cancer Medicine

As depicted in Figure 1,[11-32] there is now more than a century of experience in the translation of research in genetics and genomics to the practice of cancer medicine. At the turn of the century, the seeming conflict between the "infectious" and "chromosomal" models of cancer causation, represented by the work of Rous[11] and Boveri,[12] respectively, was resolved when the roles of proto-oncogenes and retroviruses were unraveled a half a century later. There was a revolutionary aspect in the discovery that human homologues of retroviral oncogenes were present in the normal human chromosomal complement, and that these same genes were dysregulated by chromosomal abnormalities observed in both liquid and solid human tumors.[33] More relevant to the model of human cancer susceptibility was the derivation of the "Knudson 2-hit model" of retinoblastoma, and its empiric validation in the discovery of "tumor suppressor genes" observed as heterozygous mutants in the germline, but with both alleles missing or mutated in the tumor genome.[13]

The positional cloning of genes associated with susceptibility to common cancers of the breast, ovary, and colon in the late 1990s was followed by clinical translational studies.[3-5,33,34] Over the course of the past 2 decades, more than 50 highly penetrant cancer susceptibility syndromes have been linked to inherited mutations in specific genes (Table 1). The rational integration of "high-risk" family testing within preventive oncology practice was a major accomplishment of cancer medicine in that time period.[3-5,9,10,35-39] Lessons of that experience included the observation that in some cases, a germline mutation in one of several genes presents a very similar clinical phenotype (eg, *BRCA1* and *BRCA2* both are associated with breast and ovarian cancer). This concept of genetic heterogeneity has profound implications on strategies for clinical testing. In other cases, a mutation occurring in a different part of the same gene can correlate with different clinical manifestations (eg, *RET* mutations in multiple endocrine neoplasia type 2 [MEN2A] and familial thyroid cancer); this concept of genotype-phenotype correlations is also an important consideration in clinical translation.[33] Furthermore, interactions between genes and between genes and environmental exposures may also occur, and this polygenic and multifactorial etiology of cancer is a vital concept that applies to both genetic and genomic tests for disease risk. Recently, the application of high-throughput genomic technologies has ushered in a second wave of discovery of both rare and common genetic variants of intermediate penetrance, and has also made possible the genomic profiling of tumors for diagnostic and prognostic uses, facilitating the emerging molecular targeting of cancer therapies.[7]

As shown in Figure 2, the highly penetrant cancer susceptibility mutations (shown on the left side of Fig. 2) are relatively rare, with the exception of certain "founder mutations" in genetic isolates (eg, Ashkenazi Jews). Genetic variants discovered recently by scans of hundreds of thousands of single-nucleotide polymorphisms (SNPs) in populations of thousands of individuals have for the most part represented common but very low-risk markers, as seen at the far right side of Figure 2.[40] As will be discussed in a later section of this monograph, with the completion of the map of the human genome and the cataloguing of its normal variation, and with the impending availability of affordable whole-exome or whole-genome sequence information, this new wave of genomic application is about to impact the practice of cancer medicine. Sequencing technologies are already being applied to detect mutations in human tumors, with the aim of guiding therapy. In the process, comparisons are commonly made between the tumor genome and the germline genetic sequence. For this reason, it is likely that physicians, genetic counselors/nurses, and other allied cancer care providers will be on the front lines of the translation of germline genomics to clinical practice.

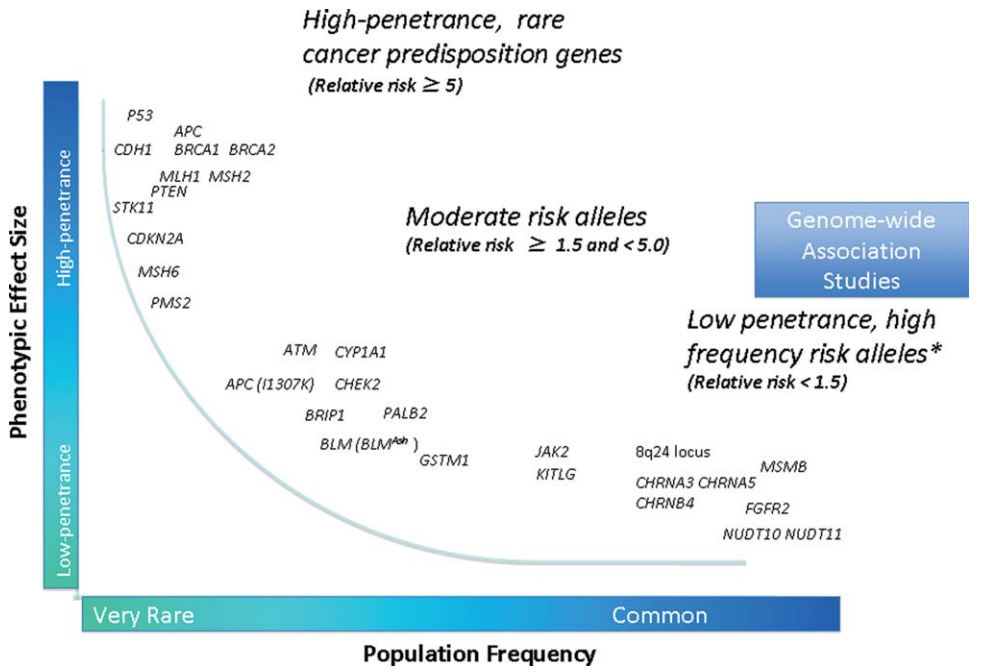

FIGURE 2. Phenotypic Effect Size and Frequency of Occurrence. In humans, mutations in highly penetrant cancer susceptibility genes are rare, whereas mutations in genes conferring low-to-moderate cancer risks are common. *Named genes only reflect the most likely candidate genes to be implicated by the marker single-nucleotide polymorphisms identified from the genome-wide association studies. *APC* indicates adenomatous polyposis coli; *CDH1*, cadherin-1; *MLH1*, MutL homolog 1, colon cancer, nonpolyposis type 2; *MSH2*, mutS homolog 2, colon cancer, nonpolyposis type 1; *PTEN*, phosphatase and tensin homolog; *STK11*, serine/threonine kinase 11; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; *MSH6*, mutS homolog 6; *PMS2*, postmeiotic segregation increased 2; *ATM*, ataxia telangiectasia mutated; *CHEK2*, human gene *CHK2* checkpoint homolog; *BRIP1*, *BRCA1*-interacting protein 1; *PALB2*, partner and localizer of *BRCA2*; BLM, Bloom syndrome, *RecQ* helicase-like; *GTSM1*, glutathione S-transferase Mu 1; *JAK2*, Janus kinase 2; *KITLG*, KIT ligand; *MSMB*, microseminoprotein, beta; *CHRNA3*, cholinergic receptor, nicotinic, alpha 3; *CHRNA5*, cholinergic receptor, nicotinic, alpha 5; *CHRNB4*, cholinergic receptor, nicotinic, beta 4; *FGFR2*, fibroblast growth factor receptor 2; *NUDT10*, nudix (nucleoside diphosphate linked moiety X)-type motif 10; *NUDT11*, nudix (nucleoside diphosphate linked moiety X)-type motif 11. Reprinted with permission from Stadler ZK, Thom P, Robson ME, et al. Genome-wide association studies of cancer. *J Clin Oncol*. 2010;28:4255-4267. Reprinted with permission.

Before embarking on the challenges and approaches characterizing the era of personalized genomics, it is important to recognize certain "hard lessons" learned from the practice of "personalized genetics" in cancer medicine. One of the most obvious is that the accuracy of the clinical laboratory is as critical as the accomplishments of the research laboratory. Catastrophic results may follow an analytic failure of a single genotype.[41] In the genomics era, disparate results of genomic testing for disease susceptibility have already been noted, suggesting suspected analytic or postanalytic error.[42–44] Encouraged by calls from professional societies,[3] and as required by statute in some states such as New York, the same quality assurance standards required for genetic tests are being requested of genomic "profiles."[45] A second lesson of the genetics era is the importance of clinical utility, as this is likely to drive integration into clinical care and third-party reimbursement. Just as laboratory practices must be standardized, established models in genetic medicine may serve as a useful framework for the clinical practice of genomic risk assessment for cancer.[3,9,46–48]

State of the Art and Evolving Models in the Practice of GCRA

The Specialty Practice of GCRA

GCRA is an interdisciplinary medical practice that employs a growing arsenal of genetic and genomic tools to identify individuals and families with inherited cancer risk. Identifying and deciphering the heritable risk factors for cancer in a given individual or family are complex, and raise considerable psychological, social, and ethical considerations. Consequently, GCRA has emerged as a specialized clinical practice that requires knowledge of genetics, oncology, and patient and family counseling skills, and involves more provider time than most other clinical services.[9,49–52] The American Society of Clinical Oncology (ASCO), the National Society of Genetic Counselors (NSGC), the Oncology Nursing Society (ONS), and other health care professional organizations have set forth guidelines outlining standards for the practice of cancer risk counseling, risk assessment, and genetic testing.[3,46,53–55] Table 2 summarizes the key components and activities of

TABLE 2. Key Components of the GCRA Process[39,53,56-62]

GCRA COMPONENT AND ACTIVITIES
Introduction/engagement • Establish rapport, agenda with patient • Assess patient concerns, motivations for GCRA • Clarify misconceptions • Identify potential contraindications (depression, coercion, etc)
Document patient and family cancer history • Construct pedigree (3-4 generations in both lineages, current ages, ages at death) • Document: - Pertinent medical information (general, surgeries, major illnesses) - Diagnostic characteristics of reported cancers (primary site, age at diagnosis, pathologic features, treatments) - Endogenous cancer risk factors (age at first menarche, fertility history) - Factors that impact disease penetrance/expression (ie, surgeries, chemoprevention, early deaths, truncated family, no access to information) - Health behaviors/exposures (tobacco/alcohol use/exercise/food intake/medications/exogenous hormone intake) - Cancer screening history (mammograms, MRI, colonoscopy) • Request additional documentation as needed to confirm etiology/characteristics of key reported cancers (pathology reports, clinic notes, death certificates)
Assess psychosocial and interpersonal dynamics • Elicit social and psychosocial history • Assess: - Family dynamics/communication - Experiences with/perception of cancer (personal, family, others) - Support system - Cultural and religious beliefs (related to health, illness, genetics, etc)
Discuss basic principles of cancer genetics • Convey medical, genetic, and technical information (in terms understandable to patient) • Define cancer genetics: sporadic vs hereditary • Describe features of hereditary cancer syndromes • Explain relevant Mendelian and other inheritance patterns
Assess/interpret personal and family medical history to establish the differential diagnosis • Identify features/patterns associated with hereditary cancers (malignant and nonmalignant) • Assess the contribution of tumor characteristics (histopathologic features, ER/PR, MSI, IHC status) • Consider factors that limit interpretation and assessment (limited family structure, lack of information, sex-limited expression, variable expressivity, limited disease penetrance, risk-reducing surgeries, chemoprevention) • Establish and prioritize the differential diagnoses
Assess mutation probabilities/empiric risks • Employ hereditary cancer mutation probability models (eg, BRCAPRO, Couch, Myriad, MMRpro) • Interpret the significance of tumor characteristics (eg, hormone receptor status, IHC, MSI) • Calculate disease risk estimates using empiric risk models if genetic testing is not pursued (eg, Gail/Claus)
Develop genetic testing strategies • Identify the best individual(s) to test; prioritize order of testing • Prioritize order of tests if more than one to consider (including germline testing, tumor analysis) • Understand test methods (techniques, limitations, sensitivity/specificity, research vs clinical testing) • Identify and select testing resources/vendors • Obtain specimens needed for testing

TABLE 2. (Continued)

GCRA COMPONENT AND ACTIVITIES
Facilitate informed consent when testing pursued • Describe: - Genetic testing process (include points above) - Potential test outcomes (positive, true-negative, uninformative) - Cost/turnaround time/insurance coverage • Assess/address psychological, cultural, communication, ethical issues: - Patient concerns, anxieties, distressors - Genetic discrimination (concerns, protections) - Potential coercion - Protection of anonymity, privacy, confidentiality - Communicating genetic information to at-risk family members/medical caregivers - Testing children/vulnerable populations (as applicable) - Alternatives to testing
Physical examination • Perform targeted physical examination to identify features associated with hereditary cancer syndromes (as appropriate within scope of practice): - Evaluation of skin, head circumference, tongue, thyroid, chest/lungs, abdomen • Review: - Cancer screening guidelines as appropriate (clinical breast examination, colonoscopy, prostate screening) - Preventive health behavior practices
Disclose/interpret test results • Interpret/communicate test results (sensitivity, specificity, significance, limitations) • Address psychological, ethical concerns • Identify at-risk family members who would also benefit from genetic testing and/or increased screening/preventive care • Discuss communication of results to at-risk family members (strategies, resources, barriers) • Arrange contacts, resources for patient and at-risk family members
Develop personalized risk management plan • Apply evidence-based guidelines and resources to develop personalized risk management recommendations to include: - Risk-appropriate screening plan - Cancer prevention/risk reduction (surgical, chemopreventive) - Empiric risk screening and prevention recommendations in setting of uninformative genetic test results • Identify research options/clinical trials appropriate to patients and at-risk family members • Summarize and disseminate personalized risk management plan with patient and patient-authorized care providers
Case administration and management • Case preparation: - Electronic/manual pedigree construction - Patient information data entry • Insurance authorization for: - GCRA consultation - Genetic tests • Identifying genetic testing vendors • Phlebotomy/preparing and shipping specimens • Identifying research resources • Dictations/chart notes • Post-GCRA patient/provider communications • Other patient-related administration and follow-up duties

ER indicates estrogen receptor; GCRA, genetic cancer risk assessment; IHC, immunohistochemistry; MRI, magnetic resonance imaging; MSI, microsatellite instability; PR, progesterone receptor.

comprehensive GCRA, which entails one or more consultative sessions with the patient and may vary based on practice setting and available resources.[39,53,56-62] In the context of this article, GCRA practice includes genetic testing as appropriate and the management of at-risk individuals so that they can make informed choices about cancer screening[63-65] and surgical[66-70] and chemopreventive risk management options,[71-75] as well as genetically targeted cancer treatment therapies.[76,77]

Tools of GCRA Practice

There are several tools that can enable and enhance state-of-the-art GCRA practice. In contrast to most medical practice, wherein the focus is on the individual, the focus in genetic risk assessment includes the family.[10] Similar to the photograph in dermatology or the video in endoscopy, a pedigree drawing is the most concise and informative means of depicting family relational data. The pedigree is also an essential source of the data required for most of the validated cancer gene mutation probability and empiric cancer risk predictive models. However, there are numerous challenges to obtaining, qualifying, and recording a multigenerational family history. An overview of family history tools and resources is described below, followed by a summary of the key features of predictive models for both genetic mutation probability and empiric cancer risk.

Family History

The challenge of getting clinicians to obtain, review, and update family history is of global relevance to the goals of personalized medicine. Approaches to obtaining and documenting family history for common diseases such as cancer vary considerably.[78-80] Other than an earlier than expected age of cancer diagnosis (eg, colon cancer diagnosed before age 50 years), family history is the single most important indicator of strong (single gene) hereditary cancer risk for which early recognition and intervention could be lifesaving. While our focus in this monograph is on cancer, there is a genetic component to most chronic diseases; hence, obtaining a thorough family history may also reveal potential risk for complex diseases such as diabetes or heart disease.[81] Moreover, failure to recognize features that signal potential hereditary cancer risk may result in malpractice lawsuits.[82,83] Health care clinicians must therefore be prepared to discuss, document, and update family history with their patients on a regular basis.

Obtaining an accurate and detailed family history is the cornerstone of genetic counseling,[53] cancer prevention,[84,85] and health promotion.[38,39,86-90]

Details of the family history are most readily apparent when displayed in the graphical representation of a pedigree,[61] using standardized nomenclature depicting family relationships including adoption, consanguinity, and use of assisted reproductive technology.[91] Using standardized nomenclature also facilitates communication among clinicians and may reduce medical errors. The pedigree format assists in the identification of disease transmission patterns and recognition of hereditary cancer syndromes, and also serves to visually depict gaps in family structure (ie, few family members who have attained or lived to an age wherein it would be possible to observe a pattern of disease, such as cancer) that may limit evidence of these syndromes.[92]

Key features associated with hereditary cancer and a list of tools and resources to support family history documentation are summarized in Table 3. While the primary care setting presents a clear opportunity for clinicians to identify patients who could benefit from increased screening, risk reduction interventions, and/or genetics referral,[93,94] taking a family history can be time-consuming for the busy clinician, and many are not adequately trained to efficiently obtain and document the family cancer history.[95,96] The validity of patient-reported family history can also be a challenge. A large study utilizing data from the 2001 Connecticut Family Health Study found that reports of breast, colorectal, prostate, and lung cancer were significantly more accurate for first-degree than for second-degree relatives.[97] In addition, the family history is a dynamic measure, with births, deaths, and new diagnoses that should be documented at regular intervals.

Family History Tools and Referral Prompts

There are a growing number of resources available to help document family history and identify candidates for cancer risk assessment. A recent review by Qureshi et al identified 18 family history tools developed for (or applicable to) collecting a family history of breast, colorectal, ovarian, and/or prostate cancers in the primary care setting.[98] Each tool assesses at least

TABLE 3. Things All Clinicians Can Do Now to Improve Patient Access to GCRA and Personalized Preventive Care

RECOGNIZE AND DOCUMENT PERSONAL AND/OR FAMILY HISTORY THAT WARRANTS CONSIDERATION FOR GENETIC CANCER RISK ASSESSMENT

Features that suggest hereditary cancer:

- Early onset of cancer (eg, breast cancer before age 45 y, colorectal cancer before age 50 y).
- More than one primary cancer in an individual.
- Cancers occurring in multiple generations on the same side of the family.
- Constellation of cancers consistent with specific cancer syndromes (eg, breast with ovarian, colon with endometrial, or pancreatic with melanoma).
- Rare cancers, with or without additional cancers in a family (eg, retinoblastoma, adrenocortical carcinoma).
- Unusual presentation of cancer (eg, male breast cancer, ocular melanoma).
- Uncommon tumor histology (eg, medullary thyroid carcinoma).
- Geographic or ethnic populations known to be at risk for hereditary cancer due to a founder effect (eg, Ashkenazi Jewish heritage and *BRCA1*/*BRCA2* mutations).
- Key elements of a well-documented family cancer history are described in Table 2

TOOLS AND RESOURCES TO SUPPORT FAMILY HISTORY DOCUMENTATION

Family history documentation can be time-consuming for the busy clinician. Strategies and tools to help clinicians efficiently obtain and document a thorough and accurate family history include:

Web-based tools to help health care professionals collect and assess family health history:

- Genetic Risk Easy Assessment Tool (GREAT) family history collection program, available at: http://www.greatprogs.com/index.html
- Family Health*Link* at https://familyhealthlink.osumc.edu/Notice.aspx.
- Progeny pedigree drawing program, available at: http://www.progenygenetics.com/lab/index.html
- Cyrillic pedigree drawing program, available at: http://www.cyrillicsoftware.com/
- Hughes riskApps program, available at: http://www.hughesriskapps.net/
- University of Texas Southwestern Medical Center at Dallas CancerGene program, available at: http://www4.utsouthwestern.edu/breasthealth/cagene/

Patient-completed tools to collect family history:

- American Medical Association Adult Family History Form, available at: http://www.ama-assn.org/resources/doc/genetics/adult_history.pdf
- US Surgeon General/My Family Health Portrait, available at: https://familyhistory.hhs.gov/fhh-web/home.action
- Centers for Disease Control/Family History Resources, available at: http://www.cdc.gov/genomics/famhistory/famhist.htm

RESOURCES TO HELP IDENTIFY PATIENTS WHO MAY BENEFIT FROM GENETIC CANCER RISK ASSESSMENT

- National Comprehensive Cancer Network (NCCN) Practice Guidelines, available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
- National Cancer Institute Physician's Data Query (NCI PDQ), available at: http://www.cancer.gov/cancertopics/pdq/genetics
- GeneTests/GeneReviews, available at: http://www.ncbi.nlm.nih.gov/sites/GeneTests/

SUPPORT EFFORTS TO INCORPORATE FAMILY HISTORY INTO QUALITY MEDICAL CARE

- Encourage the promotion and monitoring of quality family history information in the medical record by professional organizations across the spectrum of health care disciplines, such as the American Society of Clinical Oncology (ASCO) Quality Oncology Practice Initiative, available at: http://quopi.asco.org/
- Integration of a well-structured and/or graphical and revisable family history representation in the EHR is a critical technological challenge. Inclusion of structured, multigenerational, relational data in the EHR will allow application of GCRA-related clinical decision support tools and prompts.

TABLE 3. (Continued)

HOW TO FIND A GCRA PROFESSIONAL IN YOUR AREA
The following Web sites can help clinicians locate health care providers with experience in the delivery of cancer genetics services: • NCI PDQ/Cancer Genetics Services Directory, available at: http://www.cancer.gov/cancertopics/genetics/directory/ • National Society of Genetic Counselors/Find a Genetic Counselor, available at: http://www.nsgc.org/ • GeneTests/Clinic Directory, available at: http://www.ncbi.nlm.nih.gov/sites/GeneTests/
SUPPORT HEALTH CARE POLICIES THAT ENCOURAGE THE INTEGRATION OF GCRA INTO PRACTICE
• Ongoing health care reform efforts provide an opportune moment to emphasize the need to improve payment for cognitive medical services such as GCRA consultation to encourage the integration of these preventive services into practice

EHR indicates electronic health record; GCRA, genetic cancer risk assessment.

one type of these cancers via self-administered paper- or Web-based surveys or structured interviews. The review includes useful tables describing the cancer type, clinical implementation, and other features of each tool. Full details of the review are presented in the 2007 Agency for Healthcare Research and Quality of the US Department of Health and Human Services report.[94]

One example of a simple, single-disease focused tool that can be completed by patients prior to the clinic visit or in the waiting room is the FHS-7, a 7-question, paper-based tool used in a public hospital setting in Brazil to identify women with features suggestive of hereditary breast cancer risk.[99] Another is the 3-question Colorectal Cancer Risk Assessment Tool, which is best used as a first pass at identifying persons who may be at hereditary risk for colorectal cancer.[100] A breast cancer-focused, Web-based tool for use by either patients or providers is the Breast Cancer Genetics Referral Screening Tool (B-RST), which can be completed in fewer than 5 minutes (available at: http://www.brcagenscreen.org/).[101] While relatively easy to implement in most clinical settings, brief screening tools and those with a single disease focus do not elicit a thorough family history. Although in the interim these single-disease tools will identify many persons appropriate for a genetics referral, efforts to develop simple tools that recognize multiple common hereditary cancer syndromes are warranted.

More complex tools that collect information on multiple cancers include the Genetic Risk Easy Assessment Tool (GREAT) and Family Health*Link*. The GREAT program systematically collects family cancer history extending to third-degree relatives via a patient-completed computer telephone interview.[102] The data go directly into the pedigree drawing program, Progeny (Progeny Software, South Bend, Ind),[103] which automatically provides the patient's 3- to 4-generation pedigree to the health care provider. Depending upon the individual family characteristics, GREAT may take the patient from a few minutes to nearly an hour to complete.

The Family Health*Link* is an in-office touch screen family history computer kiosk designed to be completed by patients.[104] The program generates a tailored letter to the patient, outlining qualitative level of cancer risk and recommendations for screening and genetics consultation if appropriate. Responses serve as a screening tool to trigger clinician in-depth review and confirmation of the family history.

Given increasing time constraints in the clinical setting, tools that allow direct entry of family cancer history by patients can facilitate data collection, allowing the practitioner to be fully engaged in review and analysis of the information, rather than simply transcribing it.[105] One patient-friendly Internet-accessible tool is the US Surgeon General's "My Family Health Portrait."[106] A copy of the resulting pedigree can be printed, and the unique identifier associated with the family can be used to import the data into other pedigree drawing programs using a Health Level Seven translator ([HL7] a national standard for transmission of health care information).[107] Other layperson-oriented "family tree" software programs are also available.

GCRA programs often use a formal family history questionnaire to obtain information on first-, second-, and third-degree relatives. In some

programs, written questionnaires have been adapted to a scannable format for ease of entry into a pedigree drawing program.[60] In other settings, the cancer risk counselor or other staff will telephone patients prior to the consultation to elicit the family history and prompt patients to seek missing information. These strategies help limit the amount of time spent eliciting the family history during the consultation.

Pedigree Drawing and Database Programs

Many GCRA programs utilize a relational database and pedigree drawing program to store and represent family history data. One example of this type of program is Progeny (Progeny Software).[103] Progeny is not specific to cancer; can be customized to clinical and research needs; and is available as a stand-alone, multiclient server or Web version with a recently developed patient entry interface.[108] Another example is Cyrillic (Cherwell Scientific Publishing, Inc., Oxford, UK), which has a standard database version with risk calculation capability and a version for working with genetic marker and haplotype data that can be exported to linkage analysis programs.[109] Pedigree data can also be assembled in CancerGene,[110] which has a suite of breast/ovarian, colorectal/uterine, pancreatic, and melanoma gene mutation probability and cancer risk estimation models, including, respectively, BRCAPRO,[111] MMRpro,[112] PancPRO,[113] and MelaPRO.[114]

The Hughes riskApps[115] system allows patients or clinical staff to enter family cancer history data by answering a series of questions via a tablet or desktop PC, which can also interact with the My Family Health Portrait pedigree program.[105] Breast and ovarian cancer risks are generated and printable along with family history and a graphical pedigree. While both CancerGene and Hughes riskApps are also able to use a Web server version of BRCAPRO (described below),[111] neither can be modified to create custom data fields that may be important in risk assessment.

Family History and the Electronic Health Record

The adoption of the electronic health record (EHR) to store health data poses challenges to providing quality care. Currently, only a text-based description of family history can be included in most EHR systems. Consequently, there are limitations in the ability to generate automated prompts for genetic risk evaluation based on family history content in the EHR. While guidelines and criteria based solely on individual patient characteristics may be a feasible basis for such prompts even in the absence of family history, an accurate and thorough family history is necessary to take full advantage of mutation probability and empiric risk models. The Health Information Technology for Economic and Clinical Health (HITECH) Act and the Patient Protection and Affordable Care Act place new emphasis on the widespread and meaningful use of EHRs.[116,117] Thus, it is critical that the EHR be adapted to accommodate the multigenerational relational data depicted in the family pedigree diagram, ideally conforming to standardized pedigree nomenclature.[91] The EHR can only have a major impact on quality of care if it contains structured data and if it interacts with robust clinical decision support tools.[105] Furthermore, we need initiatives such as the ASCO Quality Oncology Practice Initiative[118,119] to ascertain and monitor the incorporation and use of family history across the spectrum of medical practice.

Armed with knowledge about key features of hereditary cancer and standard-of-care referral guidelines, clinicians should be able to discern and address the concerns of the "worried well," who are at average or minimally increased cancer risk, from those persons at higher risk who warrant genetic risk evaluation.

Developing the Differential Diagnosis

After a pedigree is taken, the cancer risk assessment process includes consideration of a differential diagnosis of cancer syndrome(s), which is based on the types of cancer in the family. Excellent reviews of the malignant and benign clinical features of each syndrome are available.[120,121] Knowledge of each of these syndromes is essential for a thorough consideration of the differential diagnosis for cancer genetics assessment. For example, hereditary breast-ovarian cancer syndrome, caused by a *BRCA1* or *BRCA2* mutation, typically involves breast and/or ovarian cancer but may also include prostate or pancreatic cancers; Lynch syndrome, caused by the mismatch repair genes, primarily involves colon and endometrial cancer but may also include ovarian, gastric,

and other cancers. Some families with breast cancer combined with unusual features may require consideration of rare syndromes. For example, breast cancer onset before age 30 years may be suspicious for Li-Fraumeni syndrome, patients with a large head circumference and thyroid nodules would be considered for Cowden syndrome, and mucocutaneous hyperpigmentation could suggest Peutz-Jeghers syndrome. Often a physical examination to evaluate the presence or absence of physical features of a suspected cancer syndrome is needed. A review of pathology reports may also be necessary to confirm the cancers in the family and distinguish between histological subtypes associated with specific cancer syndromes. Published referral guidelines often highlight patterns associated with specific genes.[50,122-124]

Models and Criteria Used to Estimate Mutation Probability

Several tools are available to estimate the likelihood of detecting a cancer-predisposing mutation. If a *BRCA* gene mutation is suspected, there are numerous models available to estimate the probability of an individual carrying a mutation (Table 4). Such models have been reviewed elsewhere[125-128] and include the Couch,[129] Penn II,[130] Myriad,[131] BRCAPRO,[132-134] Tyrer-Cuzick,[135] and BOADICEA models.[136] Each of these models incorporates breast and ovarian cancer in first- and second-degree relatives, age of onset of cancer, and Ashkenazi Jewish ancestry, and some are starting to incorporate other racial/ethnic backgrounds. Beyond that, each of the models incorporates different factors as shown in Table 4 and each are utilized selectively based on the characteristics of the patient's personal and family history.

The use of mutation probability models is important for several reasons. First, calculating the probability of a mutation can help clinicians determine who is an appropriate candidate for testing. Second, due to the high cost of genetic testing, numeric calculations of mutation probability may provide supportive evidence for insurance companies. Some major insurers are willing to consider probability estimates for patients who do not meet their specific testing criteria. Third, for psychosocial reasons, patients who are counseled with a numeric estimation of the probability of a mutation may have more realistic expectations about the possibility of a positive result. Finally, for concerned patients with a low probability of a mutation, the numeric presentation may provide substantial reassurance supporting recommendations based on empiric cancer risks in lieu of genetic testing.

Similar models exist for mutation probability in Lynch syndrome, including MMRpro,[137] Wijnen,[138] MMRpredict,[139] and PREMM1,2,6[140] (Table 5). However, in the genetic assessment of colon cancer families, it is more common to use established criteria as an indication for testing, including the Amsterdam I,[141] Amsterdam II,[142] or revised Bethesda Guidelines[143]; the Bethesda Guidelines determine eligibility for tumor analysis to detect abnormalities associated with Lynch syndrome that would lead to germline genetic testing. The identification of patients with Lynch syndrome using population-based testing of colorectal tumors has been reported.[144] A recent study highlighted possible health benefits and the cost-effectiveness of primary genetic screening for Lynch syndrome in the general population.[145]

As shown in Table 5, there are established diagnostic criteria and mutation probability models for Cowden[146,147] and Li-Fraumeni syndromes,[148,149] as well as mutation probability models for a melanoma-predisposing gene (*p16*)[150] and a hypothetical pancreatic cancer syndrome gene.[151]

The decision to order genetic testing should be based on clinical judgment and medical necessity, not by probability models alone. Several models may underestimate mutation probability in certain situations such as a limited family structure[92] or specific tumor characteristics.[143,152] Therefore, probabilities predicted by a model must be interpreted in the context of a patient's overall personal and family history. The National Comprehensive Cancer Network (NCCN) publishes guidelines on an annual basis to help clinicians determine which patients are appropriate candidates for genetic referral and genetic testing.[122,123]

Interpretation of Personal and Family History (Absolute Risks) and Use of Risk Prediction Models

In the absence of an identified gene mutation, counseling unaffected individuals about their empiric risk of cancer requires careful consideration of the patient's personal and family history.

TABLE 4. Models Used to Estimate *BRCA1/BRCA2* Mutation Probability and Breast Cancer Risk

	MODEL/ PREVALENCE TABLE	TYPE OF MODEL	BREAST CANCER/ OVARIAN CANCER IN PROBAND AND FEMALE FDR/SDR; AGE AT BREAST CANCER ONSET	BREAST CANCER/ OVARIAN CANCER IN TDR	RELATIVE'S CURRENT AGE OR AGE AT DEATH	HALF-SISTERS	TWINS	AJ	BRCA TEST RESULT	ER/PR STATUS OF BREAST TUMOR	BSO	DCIS	BILATERAL BREAST CANCER	MALE BREAST CANCER	PANCREATIC CANCER AND PROSTATE CANCER
MUTATION PROBABILITY MODELS	Couch[a,b]	Logistic regression	x	x				x							
	Penn II[c]	Logistic regression	x	x				x					x	x	x
	Myriad prevalence tables[b,d]	Empiric	Breast cancer included if diagnosed at age <50 y only	Only if FDR/SDR had breast cancer at age <50 y or ovarian cancer				x				x		Proband only	
	Family structure[e]	Empiric	Absent in FDR/SDR					x							
MUTATION PROBABILITY AND RISK ASSESSMENT MODELS	BRCAPRO[b,f]	Bayesian	x		x			x	x	x	x		x	x	
	Tyrer-Cuzick[g,h,i]	Logistic regression	x	Cousins only	x	x		x	x				FDR only		
	BOADICEA[f,j]	Genetic	x	x	x	x	x	x	x				x	x	x
RISK ASSESSMENT MODELS	Gail[b,h,i]	Logistic regression	Breast cancer in FDR only												
	Claus[b,i]	Genetic	Breast cancer only												

Abbreviations: AJ, Ashkenazi Jewish; BSO, bilateral salpingo-oophorectomy; DCIS, ductal carcinoma in situ; ER, estrogen receptor; FDR, first-degree relative; PR, progesterone receptor; SDR, second-degree relative; TDR, third-degree relative.

[a]Couch model probabilities are only calculated for *BRCA1* and for the family member with breast/ovarian cancer; for unaffected relatives, degree of relationship to the affected must be used to modify the calculation.

[b]Model calculations can be made by CancerGene for Desktop, available at: http://www4.utsouthwestern.edu/breasthealth/cagene/.

[c]Penn II can be accessed online at http://www.afcri.upenn.edu/itacc/penn2/.

[d]Myriad prevalence tables are downloadable and available at http://www.myriadtests.com/provider/brca-mutation-prevalence.htm.

[e]Family structure influences accuracy of BRCAPRO and BOADICEA when there is only a single case of breast cancer occurring at age younger than 50 years.

[f]Model calculations for BRCAPRO and BOADICEA can be made using pedigrees in Progeny version 8.

[g]The Tyrer-Cuzick model can be calculated by IBIS for Desktop, available at: http://www.ems-trials.org/riskevaluator.

[h]The Gail and Tyrer-Cuzick models incorporate personal risk factors including age of menarche, age of first live birth, breast biopsies, and atypical hyperplasia; additional risk factors included in the Tyrer-Cuzick model include body mass index, age at menopause, hormone replacement therapy use, and lobular carcinoma in situ.

[i]Model applicable to unaffected women only.

[j]BOADICEA model can be accessed at http://www.srl.cam.ac.uk/genepi/boadicea/boadicea_home.html.

TABLE 5. Mutation Probability Models and Clinical Criteria for Other Hereditary Cancer Syndromes

	EVALUATION TOOL	TYPE	CANCERS INCLUDED	OTHER CLINICAL AND PATHOLOGIC FEATURES	AGE OF ONSET	FDR/SDR WITH CANCER, AGE OF ONSET
LYNCH SYNDROME (*MLH1, MSH2, MSH6* ONLY)						
Clinical criteria	Amsterdam criteria	Clinical criteria	CRC		x	x
	Amsterdam II criteria	Clinical criteria	CRC, endometrial, small bowel, ureter, renal pelvis		x	x
	Revised Bethesda guidelines	Clinical criteria	Lynch-associated cancers[a]	MSI-high histology[b]	x	x
Mutation probability models	MMRpro[c]	Bayesian	CRC, endometrial	MSI/IHC results; proximal vs distal CRC	x	x
	Wijnen (MLH1/MSH2 only)	Logistic regression	CRC, endometrial		x	x
	MMRpredict[d]	Logistic regression	CRC, endometrial	Proximal vs distal CRC	Only if at age <55 y	FDR only
	PREMM1,2,6[e]	Logistic regression	Lynch-associated cancers[a]	Adenoma, age of onset	x	x
LI-FRAUMENI SYNDROME (p53)						
Clinical criteria	Chompret criteria	Clinical criteria	Sarcoma, brain, breast, ACC		x	x
Mutation probability model	Gonzalez prevalence tables	Empiric	Sarcoma, brain, breast, ACC		x	Only if at age <50 y
COWDEN SYNDROME (*PTEN*)						
Clinical criteria	International Cowden Consortium criteria for Cowden syndrome	Clinical criteria	Breast, endometrial, thyroid, kidney	x[f]		
Mutation probability model	Cleveland Clinic calculator for estimation of PTEN mutation probability[g]	Empiric	Breast, endometrial, thyroid, kidney	x[f]		
PANCREATIC CANCER SYNDROME (HYPOTHETICAL)						
Mutation probability model	PancPRO	Bayesian	Pancreas		x	x
HEREDITARY MELANOMA (*P16*)						
Mutation probability model	MelaPRO	Bayesian	Melanoma		x	x

ACC indicates adrenocortical cancer; CRC, colorectal cancer; FDR, first-degree relative; IHC, immunohistochemistry; *MLH1*, MutL homolog 1, colon cancer, nonpolyposis type 2; *MSH2*, mutS homolog 2, colon cancer, nonpolyposis type 1; *MSH6*, mutS homolog 6; MSI, microsatellite instability; *PTEN*, phosphatase and tensin homolog; SDR, second-degree relative.

Note: For references to evaluation tools, see text.

[a]Revised Bethesda guidelines include cancers of the colon, endometrium, stomach, ovary, pancreas, biliary tract, and small intestine; brain tumors (usually glioblastoma as seen in Turcot syndrome); sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome; hepatobiliary cancer; and transitional cell carcinoma of renal pelvis or ureter.

[b]Presence of tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern.

[c]Model calculations can be made by CancerGene for Desktop, available at: http://www4.utsouthwestern.edu/breasthealth/cagene/.

[d]MMRPredict model can be accessed online at: http://hnpccpredict.hgu.mrc.ac.uk/.

[e]PREMM1,2,6 model can be accessed online at http://www.dana-farber.org/pat/cancer/gastrointestinal/crc-calculator/default.asp.

[f]Cowden syndrome evaluation tools also consider head circumference, benign mucocutaneous lesions, and thyroid abnormalities associated with this syndrome.

[g]Cleveland PTEN mutation probability calculator can be accessed online at http://www.lerner.ccf.org/gmi/ccscore/.

Several models exist that allow for empiric breast cancer risk estimation including the Gail,[153] Claus,[154] BRCAPRO,[132-134] Tyrer-Cuzick,[135] and BOADICEA[136] models (Table 4). All of these models incorporate first-degree relatives with breast cancer, but beyond that they differ vastly in which known breast cancer risk factors are incorporated.[125-127] Several published tools are also available to assess risks for colon, ovarian, lung, melanoma, and other cancers, although few are validated.[155]

Numeric estimates of cancer risk may guide recommendations for appropriate screening and preventive care. For example, the American Cancer Society recommends breast magnetic resonance imaging (MRI) screening for women whose risk exceeds a 20% lifetime breast cancer risk[156] as calculated by the Claus, BRCAPRO, Tyrer-Cuzick, or BOADICEA models. Similarly, chemoprevention with tamoxifen has been approved by the US Food and Drug Administration (FDA) for women with a 5-year breast cancer risk of greater than 1.66% as calculated by the Gail model, based on a 50% risk reduction for breast cancer observed in that population.[157] Risk assessment also plays a role in guiding recommendations for colorectal cancer screening. For example, for patients with a first-degree relative with colorectal cancer diagnosed between ages 50 and 60 years, the NCCN recommends colonoscopy screening every 5 years beginning at age 40 years.[158] In summary, the calculation of cancer risk may trigger thresholds of risk, allowing for tailored recommendations based on the patient's personal and family history.

Clinical Utility and the Role of Multidisciplinary Team Risk Management

A central concept to GCRA, which is applicable to genomic cancer risk assessment and management, is clinical utility. Risk assessment and management of highly penetrant cancer predisposition syndromes were shown to increase adherence to surveillance, which is associated with the diagnosis of earlier stage tumors.[159,160] One of the first discernable examples of "proof of principle" of the clinical utility of personalized genetics was the identification of early stage malignancies likely to be associated with better survival following GCRA for hereditary adult and pediatric tumors.[70] The detection of microscopic foci of medullary thyroid cancer following "prophylactic" thyroidectomy for MEN2A presaged the observation of microscopic foci of ovarian cancer in risk-reducing oophorectomy specimens in the setting of *BRCA*-linked hereditary breast and ovarian cancer,[24] as well as the detection of microscopic cancer in prophylactic hysterectomy specimens in the setting of Lynch syndrome.[161] Indeed, GCRA and risk-reducing surgeries are now well-established aspects of preventive oncology.[70] The often difficult decision between prophylactic surgery of the breasts versus intensified radiographic screening was informed by emerging prospective data regarding the efficacy of both surgery as well as MRI screening.[6,160] Strikingly, evidence of a decrease in cause-specific mortality, as well as all-cause mortality, was recently described in the setting of risk-reducing surgery following *BRCA* testing.[69] Insights about the role of the *BRCA* genes in DNA repair have led to the first targeted therapies for *BRCA*-associated cancers.[77,162,163] Similarly, colonoscopic screening has proven efficacy in the early detection and/or prevention of colon cancer in patients with Lynch syndrome.[164] Even before these studies demonstrated decreased mortality, the available body of evidence for the relative efficacy of interventions following genetic risk assessment for cancers of the breast, ovary, and colon was subjected to formal evidence-based documentation of clinical utility.[165-167]

Another key aspect of GCRA is the multidisciplinary involvement of genetic counseling and risk management teams. While some genetic counselors work independently or with generalist physicians, nurses, psycho-oncologists, laboratory scientists, ethicists, and support groups also play important roles in personalizing the process of GCRA. Increasingly, genetic counselors, master's level specialists in both the biology and psychology of genetic risk assessment and testing, are teamed with oncologists, medical geneticists, and other medical specialists to deliver comprehensive hereditary cancer risk management. In the era of genomic counseling, the multidisciplinary model will become even more important, as medical geneticists, computational biologists, genetic epidemiologists, molecular pathologists, and a new generation of laboratory scientists trained in

high-throughput sequencing will play a vital role in managing the impending tsunami of personalized genomic data.

Barriers to Access and Effectiveness of GCRA

In addition to the published consensus guidelines noted above, since 1999 the NCCN has published annually updated guidelines indicating when a person should be referred for genetics assessment.[122,123] Providers by geographical location may be found through resources such as the NSGC (available at: http://www.nsgc.org/FindaGeneticCounselor/tabid/64/Default.aspx), the NCI cancer genetics services directory Web site (available at: http://www.cancer.gov/search/geneticsservices/), and the National Institutes of Health Gene Tests Web site (available at: http://www.ncbi.nlm.nih.gov/sites/GeneTests/clinic). However, only a small fraction of individuals with a personal or family history warranting risk assessment are provided GCRA services. Limited access to and uptake of GCRA services stems from multiple systemic and personal barriers.

Systemic Barriers

Despite efforts to integrate cancer genetic services into mainstream medicine, one significant barrier is the lack of accessible GCRA programs, particularly for persons residing in rural areas far from a major cancer center.[168,169] The dearth of available GCRA services is in large part related to the limited number of health care providers adequately trained in the relatively new field of clinical cancer genetics (workforce needs are discussed below). Other systemic barriers to receiving GCRA care include the lack of a regular primary care provider or recommendation for GCRA, and limited linguistically and culturally competent providers.[168,170-172] As noted above, limited knowledge among physicians about who should be referred, the value of referral, and how to refer also contributes to low referral levels.[168,169,171] Time constraints of busy clinicians, perceived low practice priority,[173] physician concerns for the cost of counseling/testing,[169] and the oft-held misconception that genetic testing will result in genetic discrimination may also discourage referrals.[171,174] Furthermore, failure to obtain and update the family cancer history during patient encounters hinders recognition of potential hereditary cancer predisposition syndromes.[175] Low reimbursement relative to the time required impedes the provision of adequate risk counseling, particularly for physicians outside of an academic setting.[176]

Where GCRA services are available, the primary barrier is lack of or insufficient health insurance coverage for genetic consultations, genetic testing, and recommended follow-up care.[177-180] While insurance coverage and cost is a patient-related barrier, the root issue is also systemic in health care finance in the United States. In contrast, many public health care systems outside the United States provide more support for genetic services. Most published studies of GCRA uptake and outcomes involve populations dominated by higher socioeconomic and educational status.[181,182] Although difficult to quantify, many people who are referred never make an appointment, or cancel appointments due to lack of coverage or high deductibles or copayments.[183] Furthermore, there are circumstances where genetic testing is clinically indicated and it simply is not a covered benefit. This is especially the case for at-risk individuals whose affected family members have died. NCCN and other guidelines do not clearly address the value of genetic counseling, risk assessment, and even genetic testing in these circumstances. The US Preventive Services Taskforce recommendations[48] may be overly restrictive and fail to recognize the potential bias against individuals with small families, limited knowledge of their family history, or families with relatives who have not lived long enough to express a hereditary cancer pattern. The NCCN and some insurers have explicitly acknowledged the special circumstance of limited family structure.[92,122]

Patient-Related Barriers

Understanding and acting on genetic/genomic information is a critical rate-limiting step for both clinicians and patients in the translation of this information to preventive practice.[8] To make informed decisions about genetic counseling/testing and risk reduction interventions and lifestyle choices, and to promote the effective dissemination of information within families, it is essential that patients understand how genetics/genomics information influences their personal and family's health. A challenge for providers in effectively conveying risk information is to ensure that patients understand numeric and graphical representations used to discuss risk, which may be difficult even for highly educated patients.[184,185] Providing written information

may aid comprehension of complex health information and decision-making,[186,187] and is especially warranted for persons with poor health literacy.[188] Furthermore, women undergoing evaluation for hereditary breast cancer risk have expressed the need to balance the time required to assimilate the volume and complexity of information provided during genetic counseling with the need to make timely decisions.[185,189] Decision aids can help these women contemplate their options, decrease decisional conflict, and increase decision satisfaction,[190] allowing more time for addressing the emotional elements essential to effective genetic counseling.[191]

Additional barriers to the uptake of GCRA services include lack of awareness of these services or the reason for referral,[192] limited knowledge of one's family cancer history, genetic discrimination, privacy and confidentiality concerns, and fear of the stigma and medical consequences associated with a genetic mutation being identified. As noted above, perception of high out-of-pocket costs may also interfere with presenting for GCRA as well as proceeding with recommended genetic testing.[193] While many insured individuals will have genetic consultation and testing coverage, some may be unable or unwilling to pay for copayment or deductible expenses. In addition, patients referred at the time of cancer diagnosis may find the intercurrent stress of the diagnosis and multiple medical appointments deters their full engagement in the GCRA process.

Similar to other health care services, minority populations are less likely to have access to or uptake of GCRA, partly due to lack of adequate insurance coverage and discrimination fears.[172,194,195] Mistrust in the medical system,[196] anticipated guilt about passing on a mutation to children, and the stigma associated with having a genetic condition also contribute to negative perceptions of breast cancer risk counseling and testing among African American women.[197] Access to care may be hampered by few ethnically sensitive and culturally competent health care providers, unfamiliarity with the US health care system, and linguistic isolation.[198-200] Some studies have suggested that a lower level of acculturation for Latinas and African Americans influences uptake of genetic testing for cancer risk.[201-203] Although studies have found that race/ethnicity[204,205] and socioeconomic status (SES) influence uptake of genetic testing, a recent study suggests that regional differences account for a lack of awareness of genetic testing for disease risk and attitudes toward this testing more so than ethnicity or SES.[206] Nonetheless, the use of bilingual/bicultural cancer risk counselors and Spanish language counseling aids can result in good uptake and effectiveness of GCRA,[172,207] suggesting a positive impact of the availability of culturally tailored services.

Family Communication

A primary motivator for GCRA is concern for and perceived duty to inform relatives of cancer risk.[208-213] Several studies have found that genetic test results are often shared with at least first-degree relatives.[208-215] Little is known about communications to potentially at-risk distant relatives or what information is communicated beyond the test result. Various factors, including lack of confidence in communicating complex information, gender and age differences, relationship issues (eg, estrangement/loss of contact), and cultural norms affect risk communications and the quality of the information shared.[208,209,211,216,217] Studies also indicate that positive test results are shared more often than uninformative results.[213] The lower uptake of genetic counseling/testing for identified *BRCA* mutations among at-risk paternal relatives and men[218] may reflect a lack of understanding of the health care implications.

Despite the described challenges and barriers to care, the central clinical utility and efficacy of GCRA in promoting risk-appropriate cancer screening, prevention, and targeted therapy warrant efforts to develop and expand access to competent clinical services.

Current Models for Delivery of GCRA Services

The initial delivery models for cancer risk assessment services emerged out of the academic health care setting, where GCRA is conducted by a multidisciplinary team that includes genetic counselors, advanced practice nurses, one or more physicians (generally a medical geneticist or oncologist), and often a mental health professional.[47,219] Rapidly evolving knowledge of the genetic basis of cancer, national policy mandates, and direct-to-consumer and provider marketing by commercial genetic testing vendors has catapulted the onslaught of cancer genetic services offered in the community setting.[71,220-225] A number of alternative practice models, such as those described in Table 6, have evolved to extend GCRA services beyond

TABLE 6. Evolving Models of Practice for GCRA

MODEL	BENEFITS	LIMITATIONS
ACADEMIC MODEL		
Academic/medical center model: patients referred to cancer genetics program, seen by interdisciplinary team (genetic counselor, nurse, physician); pregenetic and postgenetic testing, counseling, and integrated risk assessment	• Comprehensive state-of-the-art personalized GCRA delivery including genetics-focused physical examination and medical management • Level of care expected of a cancer center setting; billable patient visits • Critical research linkage	• Through-put may be limited by physician availability, personnel costs, and time intensity of providing comprehensive GCRA service • Possible community clinician barriers to referral
COMMUNITY MODELS		
Collaborative model: community center partners with academic center of excellence	• Advanced practice-based support from the academic center for community center clinicians • Time commitment for quality assurance activities	• Possible fees for academic oversight • Patients receive high-level care • Access to the academic center clinical and research data forms and genetics research
Medical practice model: oncologist as genetic consultant or other trained/designated physician initiates genetic testing[a]; only refers patients with positive or ambiguous results to genetics provider (who may or may not be onsite)	• Immediate offering of genetic test may be effective means of GCRA delivery for carefully selected patients • Complicated cases referred to genetics provider for thorough counseling and risk assessment • Bill as usual fee-for-service • Potential downstream revenue generation	• Nuances of GCRA underestimated; possible errant test/testing approach; patient and family may be falsely reassured • Patient may not be given sufficient information to make informed decision for genetic testing/testing strategies
Genetic referral model (or cancer risk referral model): patient referred to community-based cancer risk counselor (GC/APN) for genetic counseling/testing; summary note sent to referring physician	• Meaningful counseling and risk assessment service provided by qualified personnel	• Patient given general vs tailored risk reduction recommendations • No or limited billable GCRA service, no or limited physical examination to help guide assessment • Cancer genetics research participation limited
Triage model[a]: APN performs initial personal/family history screening; triages to GC or further assessment; referring physician provides patient recommendations	• Streamlined referral process • Patients requiring individual counseling identified and seen in a timely manner • Efficient use of limited genetics provider resources	• APN/GC may not have adequate cancer genetics knowledge to triage/assess appropriately • Referring physician may not be familiar with current risk level-based medical management • Cancer genetics research participation limited
Group model[a]: at-risk individuals attend a group-focused cancer genetics presentation, followed by individual counseling sessions as indicated based on risk and/or as desired by patient	• Efficient for providing overview of GCRA and prescreening referred patients • Efficient use of limited genetics provider resources	• Ineffective for anxious patients, particularly if recent cancer diagnosis • Time constraints to address individual questions • Group session not a billable service • Patient confidentially/privacy may be compromised
Telemedicine model: community center servicing a geographically or socioeconomically underserved population partnered with an academic center of excellence	• Patients gain access to academic center-level of clinical care, including opportunities for research participation • Efficient use of limited genetics provider resources	• Requires telemedicine set up and time commitment for quality assurance • Consultation services may not be billable • May require funding to establish partnership
Remote open-access model[a]: educational materials and telephone and/or Internet counseling provided by for-profit company	• Counseling may be scheduled at the convenience of the patient (possibly from home) • May be cost savings	• Few quality outcomes data • Possible lack of local clinician communication or follow-up • No research opportunities

APN indicates advanced practice nurse; GC, genetics counselor; GCRA, Genetic Cancer Risk Assessment.

[a]Practice may be limited to GCRA for specific cancers such as breast/ovarian and colon.

	Tests for Which Clinical Utility is Accepted	Tests for Which Clinical Utility is Uncertain
Professionally Mediated	**Quadrant 1** HCP-ordered testing for high-penetrance mutations (eg, *BRCA1/2, MLH1/MSH2*)	**Quadrant 2** HCP-ordered testing for low-to moderate-penetrance mutations (eg, *CHEK2*)
Not Professionally Mediated	**Quadrant 3** DTC testing for high-penetrance mutations (eg, *BRCA1/2, MLH1/MSH2*)	**Quadrant 4** DTC testing for low-penetrance variants of uncertain clinical utility (eg, breast cancer risk SNPs)

FIGURE 3. Clinical Utility of Genetic and Genomic Tests. When considering the future development of germline genetic testing in oncologic care, it is useful to think of tests with regard to their position along 2 axes. The first axis identifies whether or not the test can be said to have accepted clinical utility. The second axis describes whether the test was obtained through the mediation of a health care provider (HCP) with whom the individual being tested had an ongoing relationship or through a direct-to-consumer (DTC) channel. To date, most genetic testing for cancer susceptibility can be categorized as professionally mediated and of accepted clinical utility (quadrant 1). As the fields of oncology and genetics continue to progress and become increasingly intertwined, HCPs will need to develop a working knowledge of tests that fall under the other 3 quadrants. MLH1 indicates MutL homolog 1, colon cancer, nonpolyposis type 2; MSH2, mutS homolog 2, colon cancer, nonpolyposis type 1; CHEK2, human gene CHK2 checkpoint homolog; SNPs, single-nucleotide polymorphisms. Reprinted with permission from Robson ME, Storm CD, Weitzel J, Wollins DS, Offit K; American Society of Clinical Oncology. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol*. 2010;28:893-901. Reprinted with permission.

the confines of the academic health care delivery system to the broader community. A community-of-practice model that leverages the experience and multidisciplinary nature of academic programs in partnership with community-based providers has many attractive features.[226,227]

It is important to note that all of the models described in Table 6 involve some degree of professional mediation of the GCRA process by clinicians with cancer genetics training and experience. Some of these models, particularly those that employ an interdisciplinary team-based approach, combine efficient patient care with best practices in GCRA, while others may not adequately address important nuances inherent in the GCRA process that inform several aspects of patient care, such as optimal testing strategies, appropriate interpretation of uninformative test results, consideration of alternate genetic etiologies, and psychosocial and family communication dynamics. Despite efforts to expand community-based best practices in GCRA, market forces are compelling an increasing number of clinicians with no training or expertise in GCRA to prescribe and interpret predictive genetic tests.[35,59,221,222,225,228-231] Problems related to absent or inadequate counseling range from genetic testing issues, including inappropriate or incomplete testing and misinterpretation of test results by both patients and clinicians (eg, considering a variant of uncertain significance to have implications for patients/relatives' cancer risks, believing that a "negative" result equates to no risk in families where a causative mutation has not been identified), to inappropriate cancer screening/prevention recommendations and psychological issues.[3,232,233] Moreover, direct-to-consumer genetic testing has created a third rail of access to personal genetic information that completely circumvents professional mediation, including access to high-risk genetic traits for which there is known clinical utility as well as emerging low-penetrance genomic variants. As highlighted in the recent ASCO policy update,[3] creating appropriately supported models for the delivery and interpretation of genomic information and defining clinical utility for emerging moderate and low-penetrance variants pose major challenges (Fig. 3).

Genomic Discovery: The Next Generation of Personalized Medicine

One of the concerns accompanying the emergence of genomics in oncology is the risk of "premature translation" of genomic tests to clinical practice. Indeed, as discussed in the prior sections, the majority of both cancer and non-cancer–associated common variants discovered by whole-genome association studies are not believed to be medically "actionable."[3,166] Unlike the genetic mutations discovered during the past decade, new cancer-associated

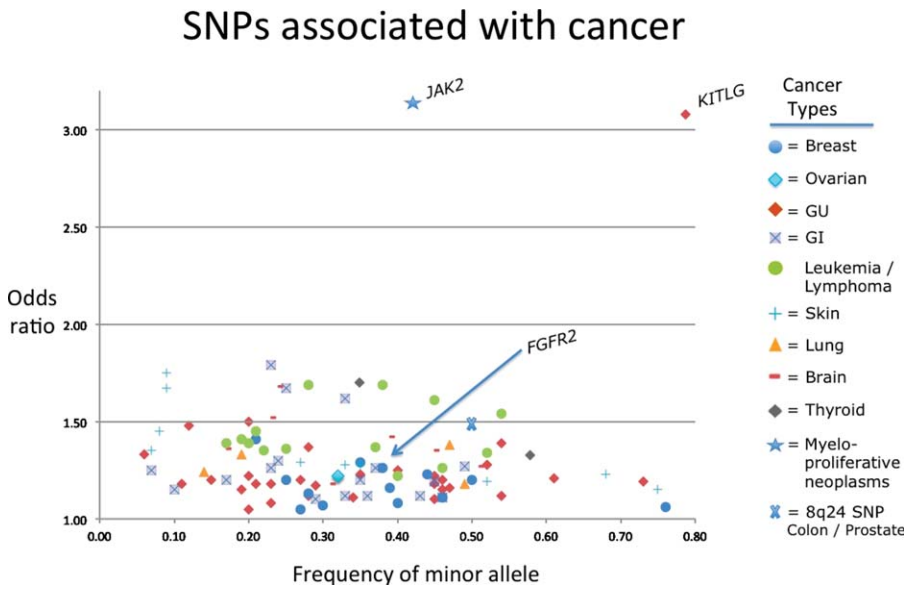

FIGURE 4. Genome-Wide Association Studies for Cancer. The left axis represents the odds ratio (OR). The horizontal axis depicts the frequency of minor alleles. As shown, the OR associated with developing cancer for most of the alleles is low. Exceptions are the marker single-nucleotide polymorphisms (SNPs) mapping to KIT ligand (*KITLG*) in testicular germ cell cancer and Janus kinase 2 (*JAK2*) in myeloproliferative neoplasms, which have ORs of approximately 3.0, with allele frequencies ranging from 20% to 40%. FGFR2 indicates fibroblast growth factor receptor 2; GU, genitourinary; GI, gastrointestinal. Adapted from data from Stadler ZK, Thom P, Robson ME, et al. Genome-wide association studies of cancer. *J Clin Oncol*. 2010;28:4255-4267.

"genomic" variants are, for the most part, not associated with readily identifiable syndromes or sufficient risk thresholds to spur preventive interventions. During the genetics era, the use of linkage or "reverse genetics" led to discoveries of the basis of single-gene disorders such as breast cancer,[234] prompting further scientific research into the mechanisms of disease causation, as well as proof of the clinical efficacy of interventions. Nonetheless, more than 15 years after the advent of testing for *BRCA1*, its numerous cellular roles continue to be defined,[235] complicating prediction of the functional (hence clinical) significance of some of the mutations (those resulting in single amino acid changes) routinely detected.[236]

This same pattern is unfolding in the clinical translation of genomic research exploring the functional role of the estimated 50,000 to 200,000 SNPs that may contribute to disease.[237] As in the genetics era, these genomic studies have revealed novel pathways of disease causation, such as the complement pathway in adult-onset blindness due to macular degeneration.[238] As mechanistic research continues, translation to practice will also occur. For example, it may soon be possible to offer testing for risk modifying variants affecting *BRCA2* penetrance,[239,240] even in the absence of knowledge of their function. As shown in Figure 4, while most of the findings of genome-wide association studies have produced relative risks too low for actionability, in at least 2 examples, familial testicular cancer and familial myeloproliferative disorders, the point estimates of risk are high enough to consider notifying patients within a research context.[40] In the case of other SNPs, it is also true that a very small subset of the population will be at significantly higher risk if they carry 2 copies of multiple disease-associated variants, and that multiplicative interactions between SNPs may eventually approach thresholds for actionability.[241] Analogous to the translation of genetics into clinical practice, the translation of newly discovered cancer genomic risk markers into practice should be carried out in the context of longitudinal research studies, leading to the promulgation and embrace of evidentiary standards.[242]

While the proof of the clinical utility of genetic or genomic disease predictive markers does not depend on a complete understanding of the biological function of the genetic variant in question, such an understanding remains critical for pharmacologic targeting. The lack of functional models for most disease-associated SNPs remains a significant impediment to the development of "preventive" drugs. Ultimately, a mechanistic understanding of all the genomic as well as epigenomic changes affecting the

germline will be required to accurately predict cancer risk.[36,243] Epigenetic phenomena such as "silencing" of genes by the addition of methyl groups that affect critical control regions ("promoter methylation") do not change the DNA sequence and are not detected on first-generation genome scans. Similarly, the emerging role of small RNA molecules that also regulate gene expression (microRNAs) will also need to be taken into account as part of personalized cancer genomic profiles, since both of these epigenetic and genetic mechanisms may affect risk for diseases such as cancer.

As next-generation sequencing technologies are now being deployed to analyze tumor and constitutional genomes, an impending "data deluge" has descended on cancer genomics. The cost of "next-generation" sequencing technologies continues to decrease, facilitating the availability of terabytes of genomic data per patient in the next decade. At the current rate of technological developments, human whole-genome sequencing could cost US $1000 by the year 2014, and as little as US $100 by the year 2020.[7] However, efforts to deduce potentially pathogenic mutations from the genome of just a single 40-year-old male took over a year of work by a multidisciplinary team at one center.[244] The challenges facing the routine translation of genomics to practice include the limitations of current sequencing platforms (eg, failure to detect structural genomic changes or to distinguish mutations on the same or different chromosomes), the absence of a central repository of rare and disease-causing variants, and the need for longitudinal follow-up to update counseling based on new information.[245] It is now estimated that 50 to 100 variants implicated in inherited disorders are identifiable in the "personal genome" of the average individual.[246] The interpretation of these findings will require a vastly improved human reference sequence annotation, which is needed as a comparison group to deduce clinical significance from the data.[247] It has been observed that the conventional clinical GCRA model of 2-hour, multivisit counseling for a single gene disorder must scale up for counseling for dozens or hundreds of genetic markers of risk.[245] One needed resource for counselors and patients will be interactive computer-assisted aids to transmit components of the genomic risk assessment.

Even with advances in computer-assisted risk assessment and counseling, the therapeutic and reproductive aspects of genomic counseling will continue to require interpersonal interaction, support, and follow-up. The therapeutic implications of genomic information are becoming well established in cancer medicine.[7] A new class of drugs already appears to be of particular benefit to oncology patients with germline *BRCA* mutations.[77,162,163] The current practice of clinical oncology is being transformed by the growing number of pharmacologic agents targeted to specific tumor-derived genomic alterations.[7] This is only the first ripple in the tsunami of genomic information that will inform oncology practice. While the Cancer Genome Atlas Project has led to new scientific insights, the translation of these findings to personalized therapeutics requires an ability to scan gigabytes of genome sequence and remains a research-in-progress.[248,249] It is also important to emphasize the parallel yet distinct progress in germline and somatic (tumor-associated) genetics in oncology. At present, tailoring cancer treatment to either germline (eg, pharmacogenetic) or somatic tumor profiles (eg, Oncotype DX©,[250] epidermal growth factor receptor, *BRAF*) is a process distinct from GCRA, although the same oncogenic signaling pathways may be involved in disease susceptibility as well as targeted therapy.

Interpreting and counseling patients about the medical implications of individual germline or cancer-derived genome sequences will likely entail greater investment of human capital and more potential liability than experienced during the genetic era.[247] Given that it will be easier to generate genomic data than to counsel about it, new approaches to genomic risk notification will require paradigm shifts in both the models of delivery of information to consumers in a medical context and education of health care professions. However, the core principles of GCRA, based on a foundation of evidence-based counseling regarding the clinical utility of testing, should remain a prerequisite for the responsible translation of genomic technologies. The successful implementation of personalized genomics will also hinge on the continued training of a multidisciplinary work force.

Preparing an Expanded Genomics Workforce

Advances in genetic technology and market-driven pressures notwithstanding, leading stakeholders in medicine strongly recommend that predictive

genetic testing be conducted in the context of pretest and posttest counseling, conducted by suitably trained health care providers.[3,5,122,165,251] This recommendation is supported by the nuanced nature of hereditary disease patterns, complex genetic and genomic test information, appropriate prescription of personalized risk management procedures, and the growing body of evidence that documents the emotional and psychosocial needs of the patients who undergo GCRA.[44,92,181,189,213,252-257]

As there is no subspecialty practice credential in cancer genetics, a comprehensive roster of experienced GCRA professionals is not available. Currently, most experienced physician GCRA practitioners are licensed and/or credentialed in oncology or genetics. Among allied health professionals who practice GCRA, most are genetic counselors or advanced practice nurses. As of March 2011, the NCI listed 563 cancer genetics specialists in its Cancer Genetics Services database,[219] representing an approximate 70% increase in self-registrants who met the criteria for inclusion in this clinical service resource since March 2006. Although similar increases have also been observed in recent years on other clinical service registries (such as http://www.genetests.org) and among such professional memberships as the cancer genetics special interest groups of the NSGC and the ONS, there is still a dearth of professionals with interdisciplinary training and expertise in GCRA.

Despite priorities set forth by policy and leadership stakeholders emphasizing the need for cancer genetics education,[38,46,58,190,258-265] GCRA education and training resources remain limited. Professional societies and some academic institutions offer cancer genetics seminars, workshops, and Web-based GCRA resources, and the ASCO Curriculum: Cancer Genetics and Cancer Predisposition Testing is a self-teaching resource for oncologists and other health care providers.[39,266] Toward the goal of promoting practitioner-level competence in GCRA, a multimodal course (supported in part by NCI R25 grant funding) developed by several authors of this monograph combines 12 weeks of distance and face-to-face interdisciplinary team training followed by ongoing practice-based support for community-based clinicians.[96,226,227] To date, 220 community-based clinicians from 47 US states and 7 countries outside the United States have completed the course, and despite its rigorous participation requirements, each course offering generates 4 times more applicants than can be accommodated for training.

It is in this setting of limited GCRA professional workforce, education, and training resources that we face the challenge of integrating genomics information into clinical care. Beyond the core interdisciplinary knowledge and skills currently employed in the practice of GCRA, translating complex genomic information into clinically meaningful applications will require an understanding of the inferences of gene-gene and gene-environment risk interactions; epidemiologic, noncancer risk information; and other nuanced genomic factors that will contribute to the practice of genomically informed personalized medicine.

It would be close to impossible for the individual health care practitioner to master and apply this expanding range of knowledge and skills. Thus, similar to the pivotal role of the multidisciplinary team to the integration of genetic discovery into clinical practice, training and promoting multidisciplinary clinical/research teams (comprised of genetics/genomics and oncology specialists, pathologists, biostatisticians, informatics/computational specialists, epidemiologists, behavioral scientists, pharmacists, etc) will be essential to support the effective and responsible translation of genomic information into clinical utility. Table 7 outlines a number of useful resources and activities available to help clinicians learn more about cancer genetics, genomics, and cancer risk assessment.

Discussion

It is now widely anticipated that the rapid progress in genome science occurring over the past decade, coupled with the declining cost of sequencing technologies, will hasten the arrival of new tools for personalized medicine, with an immediate impact in the field of cancer medicine.[7,267] The computational and counseling challenges resulting from the emerging deluge of next-generation sequencing data constitute a barrier that will need to be surmounted to translate genomics research to practice, and to surmount the

TABLE 7. Resources and Activities to Help Clinicians Learn More About Cancer Genetics and Genomics

LEARN MORE ABOUT GENETICS, GENOMICS, AND CANCER RISK ASSESSMENT

Online genetics, genomics, and cancer genetics education resources include:

- The National Human Genome Research Institute (NHGRI) lists several self-teaching resources, available at: http://www.genome.gov/Education/
- National Coalition for Health Professional Education in Genetics (NCHPEG) has a clearing house of genetics and genomics educational resources, available at: http://www.nchpeg.org/
- NCI PDQ Genetics Resources Guide, available at: http://www.cancer.gov/cancertopics/pdq/genetics/overview/HealthProfessional/page5
- Evaluation of Genomic Applications in Practice and Prevention (EGAPP) provides evidence-based reviews of genetic and genomic translational applications, available at: http://www.egappreviews.org/default.htm

Key published cancer genetics and genomics resources include:

- Hodgson SV, Foulkes WD, Eng C, Maher ER. A Practical Guide To Human Cancer Genetics. 3rd ed. Cambridge, UK: Cambridge University Press; 2007.
- Offit K. Clinical Cancer Genetics: Risk Counseling and Management. New York: Wiley-Liss Inc, 1998.
- Lindor NM, McMaster ML, Lindor CJ, Greene MH; National Cancer Institute, Division of Cancer Prevention, Community Oncology and Prevention Trials Research Group. Concise handbook of familial cancer susceptibility syndromes-second edition. J Natl Cancer Inst Monogr. 2008;(38):1-93.
- ASCO Curriculum: Cancer Genetics and Cancer Predisposition Testing, last updated in 2004, is a robust primer in cancer genetics. The course is no longer available through ASCO University, but the curriculum is an excellent resource.

Cancer genetics continuing medical education and training courses include:

- City of Hope's Intensive Course in Community Cancer Genetics and Research, a 3-phase program of interdisciplinary training, available at: http://www.cityofhope.org/education/health-professional-education/Pages/default.aspx
- The Fox Chase Personalized Cancer Risk Assessment: Genetics and Genomics in Nursing Practice, a 3-d to 4-d course for nurses, available at: https://cmetracker.net/FCCCNURSE/
- Seminars, 1-d or 2-d workshops, and Web-based self-teaching resources focused on topics in clinical cancer genetics and genomics are offered by professional genetics, oncology, and nursing organizations, including:
  - ASCO, available at: http://www.asco.org/
  - National Society of Cancer Genetics (NSGC), available at: http://www.nsgc.org/
  - Oncology Nursing Society (ONS), available at: http://www.ons.org/

LEARN ABOUT AND SUPPORT GENETICS AND GENOMICS EDUCATION AND POLICY INITIATIVES

- Efforts to address the significant need for genetics and genomics education and training resources across the spectrum of health care, including current and future medical workforce needs, are outlined by the Department of Health and Human Services Secretary's Advisory Committee on Genetics, Health, and Society Report (February 2011), available at: http://www.nchpeg.org/
- The Federation of American Societies for Experimental Biology (FASEB) Web site is a resource for updates and activities related to the promotion of progress and education in biological and biomedical sciences through service to its member scientific societies and collaborative advocacy, available at: http://www.faseb.org
- Policy, legislation, and translational research efforts related to the standards and ethics of patient care in the genomics era can be found on the NHGRI Website, available at: http://www.genome.gov/Issues/

approaching eventuality of what one senior geneticist has termed the era of "the $1000 genome and $100,000 analysis."[268]

Just as the rapid progress in genome technologies has outstripped the pace of clinical practice, these genomic breakthroughs now are requiring new regulatory and ethical anticipation and accommodation. For example, in the past year, the United States House Energy and Commerce Subcommittee on Oversight and Investigations issued a report on direct-to-consumer marketing of genomics, and held open hearings. Following concerns about the need for new regulatory efforts in this area, device notification letters were sent by the US FDA.[45] It can be anticipated over the next decade that commercial genetic testing companies will work with laboratories that are Clinical Laboratory Improvement Amendments (CLIA) approved and seek evidentiary proof of the clinical validity and utility of tests offered. The for-profit pressure to directly market genomic tests for disease risk will continue to recede in the face of perceived economic inefficiencies and regulatory requirements for clinical utility, as well as the consumer risks inherent in uncoupling medical tests from a context of medical support and follow-up. Federal efforts to support the creation of an evidentiary database for genomic medicine have included the Evaluation of Genomic Applications in Practice and Prevention.[269,270] However, in the face of continued debate and limited budgets, the future of these vital "impartial brokers" of genomic information may be threatened.

It is important to promote translational behavioral research on factors influencing uptake and responses to genetic/genomic counseling/testing as well as uptake of recommended primary or secondary preventive interventions following risk assessment. As the pace of genomic technologies also tests ethical precepts, the current emerging consensus in the bioethical community is that the issue is no longer if genomic information should be returned to consenting individuals but how to do this while avoiding harm.[271] As mentioned in the course of this discussion, a pressing issue limiting the translation of genomics to personalized medicine is equity and access; there is the risk that these technologies will be available only to the affluent.[247] These same concerns have accompanied the clinical dissemination of preimplantation genetic diagnoses for cancer predisposition syndromes.[8,272]

The rational and appropriate use of genomic technologies in cancer medicine can be based on several decades of experience in the use of genetics in cancer medicine.[3,8] To a great extent, the challenges facing the practitioner of genomic medicine are similar in substance but far greater in scale when genomic technologies are involved. The model of GCRA outlined here offers a solid blueprint for the foundation of genomic applications in cancer prevention and management. This model will need to be supplemented with next-generation interactive teaching and counseling aids, more efficient means to collect and interpret family history as well as genomic and environmental risk information, a new synthesis of these approaches in training multidisciplinary cancer genomic risk assessment and management teams, and continuing education to promote a genomically informed health care workforce. Furthermore, the predictive landscape is likely to be augmented in the future by allied sciences such as metabolomics and environmental exposure monitoring.

Efforts to reform public and private health care policy and coverage are needed to address gaps in insurance coverage for genetic/genomic analyses as a component of preventive care, and to improve reimbursement relative to the time required for adequate risk counseling, particularly for physicians outside of an academic setting. In addition, licensure for genetic counselors (currently available in some states) is likely to help facilitate insurer/counselor contracting.

Thus, continued translational research and regulatory protection, as well as professional efforts to educate both providers and consumers, will be required to most effectively apply recent advances in genomic research to personalized cancer care and prevention.

For additional information, Table 8[91] provides a glossary of terms. ■

TABLE 8. Glossary of Terms

Alleles: Alternate forms of the same gene. Humans typically inherit one copy of each gene (allele) from each parent. Different alleles produce variations in inherited characteristics such as eye color or blood type.

De novo: A mutation present for the first time in a family member. De novo mutations result from a mutation in a germ cell (egg or sperm) of one parent, or a mutation that occurs early in embryogenesis.

Epigenetic: A modification in gene expression that is not due to a change in the DNA sequence of a gene (eg, DNA methylation).

Exome: The 1% of the human genome that is the most functionally relevant and most likely to cause noticeable phenotypes (physical, biochemical, or physiological expression). Comprised of short segments of DNA called exons. The exome provides the genetic blueprint for proteins.

Expressivity: Refers to the variation in phenotype (expression) of one's genotype (genetic makeup). For example, 2 individuals may be affected by the same condition with one expressing the condition more severely than the other, due to genetic, epigenetic, environmental, aging, or other factors. Differs from penetrance, defined below.

Genetic heterogeneity: Variation in expression of a specific condition due to either different alleles (allelic heterogeneity [eg, different mutations in *BRCA1* confer high risk for breast and ovarian cancer]) or mutations in different genes (locus heterogeneity [eg, risk for breast and ovarian cancer with either a *BRCA1* or *BRCA2* mutation).

Genetic isolates: A population that has a similar genetic background because of common ancestry, often due to geographical isolation, cultural selection, or other mechanisms. This sometimes leads to "founder" mutations (mutations common in a specific population, such as the 3 specific *BRCA* gene mutations that account for most *BRCA*-related breast and ovarian cancer in persons of Ashkenazi Jewish heritage).

Genome: An organism's entire set of genetic material (instructions) containing all information necessary to build and maintain the organism.

Genomics: The study of whole-genome structure and function, including the characterization and architecture of genes and their mRNA and protein products, the relationships between genes and proteins of different species, epigenomic mechanisms, and pharmacogenetics.

Genome-wide association studies (GWAS): An approach that examines genetic markers across the entire human genome, with the aim of developing strategies to detect, treat, and prevent disease.

Genotype-phenotype correlations: The association between a specific genetic trait (genotype) and the resulting physical trait, abnormality, or pattern of abnormalities (phenotype).

Germline (also known as constitutional) DNA: Technically refers to the DNA sequence in germ cells (egg and sperm). However, in practice also refers to DNA extracted from nucleated blood cells as germline DNA is the source of DNA for all other cells in the body. Germline DNA is heritable and becomes incorporated into the DNA of every cell in the body of offspring.

Heterozygous: Two different alleles of a particular gene occupying the gene's position on the homologous (similar) chromosomes.

HL7: Abbreviated from Health Level 7 (available at: http://www.hl7.org/), is the global authority for developing a standardized framework for the exchange, integration, sharing, and retrieval of electronic health information.

Homologues: The chromosome of a particular pair, one inherited from the mother and one from the father, containing the same genetic loci in the same order.

Imprinting: The process by which maternally and paternally derived chromosomes are chemically modified, leading to different expression of a certain gene or genes on a chromosome, depending on whether the chromosome is of maternal or paternal origin.

Locus: The position of a gene or copy of a gene (allele) on a chromosome. Plural is loci.

Mendelian: Referring to the Austrian biologist Gregor Mendel (1822-1884), who is credited with the basic laws of classical genetic inheritance. The modes of Mendelian inheritance are autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive.

Metabolomics: The study of the complete collection of metabolites present in a cell or tissue under a particular set of conditions that generate a biochemical profile.

MicroRNA (miRNA): A short piece of RNA (approximately 22 bases in length) that binds to complementary sequences on target messenger RNA pieces and generally suppresses production of the corresponding protein.

Pedigree: A diagram representing the genetic relationships and relevant health history of members of a family. Pedigree symbols and nomenclature have been standardized[91] to allow clinicians and researchers to readily identify pertinent details about inherited traits and patterns of disease.

Penetrance: The proportion of individuals with a genetic trait who will exhibit the associated trait or phenotype (eg, *Ret* gene mutations are nearly 100% penetrant, so nearly all mutation carriers will develop thyroid cancer without prophylactic intervention [thyroidectomy]).

Pharmacogenetics/genomics: Genetically/genomically informed approach to designing drugs and vaccines.

Promoter methylation: An epigenetic modification of a DNA sequence that results from disruption in gene expression by attachment of a methyl group to the DNA at cytosine bases upstream from the gene coding region. For example, nonexpression of *MLH1* (MutL homolog 1, colon cancer, nonpolyposis type 2) on immunohistochemistry staining may be a result of methylation rather than a mutation in the DNA sequence. Methylation is also considered the main mechanism in imprinting.

Single-nucleotide polymorphisms (SNPs; pronounced "snips"): A DNA variation occurring when a single nucleotide (A, T, C, or G) in the genome sequence differs from the usual nucleotide at that position. Some SNPs are associated with disease, whereas many others are normal variations of the genome.

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