

Cancer Genetics Research Literatures

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports in the cancer genetics related studies as references.

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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports in the cancer genetics related studies as references.

The following introduces recent reports as references in the related studies.

Aldea, M., L. Craciun, et al. "Repositioning metformin in cancer: genetics, drug targets, and new ways of delivery." *Tumour Biol.* 2014 Jun;35(6):5101-10. doi: 10.1007/s13277-014-1676-8. Epub 2014 Feb 7.

After sitting many years on the shelves of drug stores as a harmless antidiabetic drug, metformin comes back in the spotlight of the scientific community as a surprisingly effective antineoplastic drug. Metformin targets multiple pathways that play pivotal roles in cancer progression, impacting various cellular processes, such as proliferation, cell death, metabolism, and even the cancer stemness features. The biomolecular characteristics of tumors, such as appropriate expression of organic cation transporters or genetic alterations including p53, K-ras, LKB1, and PI3K may impact metformin's anticancer efficiency. This could indicate a need for tumor genetic profiling in order to identify patients most likely to benefit from metformin treatment. Considering that the majority of

experimental models suggest that higher, supra-clinical doses of metformin should be used in order to obtain an antineoplastic effect, new ways of drug delivery could be developed, such as metformin-loaded nanoparticles or incorporation of metformin into microparticles used in transarterial chemoembolization, with the aim of obtaining higher intratumoral drug concentrations and a targeted therapy which will ultimately maximize metformin's efficacy.

Allford, A., N. Qureshi, et al. "What hinders minority ethnic access to cancer genetics services and what may help?" *Eur J Hum Genet.* 2014 Jul;22(7):866-74. doi: 10.1038/ejhg.2013.257. Epub 2013 Nov 20.

Ethnic disparities in use of cancer genetics services raise concerns about equitable opportunity to benefit from familial cancer risk assessment, improved survival and quality of life. This paper considers available research to explore what may hinder or facilitate minority ethnic access to cancer genetics services. We sought to inform service development for people of South Asian, African or Irish origin at risk of familial breast, ovarian, colorectal and prostate cancers in the UK. Relevant studies from the UK, North America and Australasia were identified from six electronic research databases. Current evidence is limited but suggests low awareness and understanding of familial cancer risk among minority ethnic communities studied. Socio-cultural variations in beliefs, notably stigma about cancer or inherited risk of cancer, are identified. These factors may affect seeking of advice from providers and disparities in referral. Achieving effective cross-cultural communication in the complex contexts of both cancer and genetics counselling, whether between individuals and providers, when mediated by third party interpreters, or within families, pose further

challenges. Some promising experience of facilitating minority ethnic access has been gained by introduction of culturally sensitive provider and counselling initiatives, and by enabling patient self-referral. However, further research to inform and assess these interventions, and others that address the range of challenges identified for cancer genetics services are needed. This should be based on a more comprehensive understanding of what happens at differing points of access and interaction at community, cancer care and genetic service levels.

August, E. M., G. P. Quinn, et al. "Important considerations for recruiting women to cancer genetics studies in Puerto Rico." *J Cancer Educ.* 2012 Mar;27(1):105-11. doi: [10.1007/s13187-011-0265-4](https://doi.org/10.1007/s13187-011-0265-4).

A goal of the Minority Institution/Cancer Center Partnership between the Ponce School of Medicine in Puerto Rico and the H. Lee Moffitt Cancer Center & Research Institute in Florida is to provide cross-cultural training in cancer research. This is achieved through a collaborative summer exchange program, which provides US students with an opportunity to conduct research in Puerto Rico. As part of this program, students recruited participants and collected data for a study to enhance the understanding of sociocultural factors among Puerto Rican women regarding genetic testing for hereditary breast/ovarian cancer. Limited studies have examined cancer genetics issues among Latinos, particularly those specific to the various Latino subgroups, such as Puerto Ricans. As a result of the student training experience, culturally appropriate strategies for the recruitment of women in Puerto Rico have been identified. These recommendations can inform the design of cancer research projects and interventions targeting the Puerto Rican population.

Bailey-Wilson, J. E., E. J. Childs, et al. "Analysis of Xq27-28 linkage in the international consortium for prostate cancer genetics (ICPCG) families." *BMC Med Genet.* 2012 Jun 19;13:46. doi: [10.1186/1471-2350-13-46](https://doi.org/10.1186/1471-2350-13-46).

BACKGROUND: Genetic variants are likely to contribute to a portion of prostate cancer risk. Full elucidation of the genetic etiology of prostate cancer is difficult because of incomplete penetrance and genetic and phenotypic heterogeneity. Current evidence suggests that genetic linkage to prostate cancer has been found on several chromosomes including the X; however, identification of causative genes has been elusive. **METHODS:** Parametric and non-parametric linkage analyses were performed using 26 microsatellite markers in each of 11 groups of multiple-case prostate cancer families from the International Consortium for Prostate Cancer Genetics

(ICPCG). Meta-analyses of the resultant family-specific linkage statistics across the entire 1,323 families and in several predefined subsets were then performed. **RESULTS:** Meta-analyses of linkage statistics resulted in a maximum parametric heterogeneity lod score (HLOD) of 1.28, and an allele-sharing lod score (LOD) of 2.0 in favor of linkage to Xq27-q28 at 138 cM. In subset analyses, families with average age at onset less than 65 years exhibited a maximum HLOD of 1.8 (at 138 cM) versus a maximum regional HLOD of only 0.32 in families with average age at onset of 65 years or older. Surprisingly, the subset of families with only 2-3 affected men and some evidence of male-to-male transmission of prostate cancer gave the strongest evidence of linkage to the region (HLOD = 3.24, 134 cM). For this subset, the HLOD was slightly increased (HLOD = 3.47 at 134 cM) when families used in the original published report of linkage to Xq27-28 were excluded. **CONCLUSIONS:** Although there was not strong support for linkage to the Xq27-28 region in the complete set of families, the subset of families with earlier age at onset exhibited more evidence of linkage than families with later onset of disease. A subset of families with 2-3 affected individuals and with some evidence of male to male disease transmission showed stronger linkage signals. Our results suggest that the genetic basis for prostate cancer in our families is much more complex than a single susceptibility locus on the X chromosome, and that future explorations of the Xq27-28 region should focus on the subset of families identified here with the strongest evidence of linkage to this region.

Beeghly-Fadiel, A., X. O. Shu, et al. "Genetic variation in VEGF family genes and breast cancer risk: a report from the Shanghai Breast Cancer Genetics Study." *Cancer Epidemiol Biomarkers Prev.* 2011 Jan;20(1):33-41. doi: [10.1158/1055-9965.EPI-10-0793](https://doi.org/10.1158/1055-9965.EPI-10-0793). Epub 2010 Nov 30.

BACKGROUND: In addition to mediating aspects of physiologic and pathologic angiogenesis, the VEGF family also contributes to carcinogenesis. **METHODS:** We comprehensively characterized genetic variation across four VEGF family genes and evaluated associations with breast cancer risk with odds ratios (OR) and 95% CIs for participants of the two-stage case-control Shanghai Breast Cancer Genetics Study (SBCGS). Stage 1 evaluated 200 single nucleotide polymorphisms (SNP) across two VEGF ligands (VEGFA and VEGFC) and two VEGF receptors (FLT1/VEGFR1 and KDR/VEGFR2) among 2,079 cases and 2,148 controls. Five SNPs with promising associations were assessed in stage 2 among 4,419 cases and 1,851 controls. **RESULTS:** Two SNPs were consistently associated with breast

cancer risk across our two study stages and were significant in combined analyses. Compared with FLT1 rs9551471 major allele homozygotes (AA), reduced risks were associated with AG (OR = 0.92, 95% CI: 0.84-1.00) and GG (OR = 0.78, 95% CI: 0.64-0.95) genotypes (P(trend) = 0.005). Compared with VEGFA rs833070 major allele carriers (CC or CT), increased risk was associated with TT genotypes (OR = 1.26, 95% CI: 1.05-1.52, P = 0.016). CONCLUSION: Results from our study indicate that common genetic variation in VEGFA and FLT1 (VEGFR1) may contribute to breast cancer susceptibility. IMPACT: Our findings provide clues for future studies on VEGF family genes in relation to cancer susceptibility and survival.

Blair, V. R. "Familial gastric cancer: genetics, diagnosis, and management." *Surg Oncol Clin N Am*. 2012 Jan;21(1):35-56. doi: 10.1016/j.soc.2011.09.003.

This article focuses on the diagnosis and management of familial gastric cancer, particularly hereditary diffuse gastric cancer (HDGC). First, existing consensus guidelines are discussed and then the pathology and genetics of HDGC are reviewed. Second, patient management is covered, including surveillance gastroscopy, prophylactic total gastrectomy, and management of the risk of breast cancer.

Blazer, K. R., C. Christie, et al. "Impact of web-based case conferencing on cancer genetics training outcomes for community-based clinicians." *J Cancer Educ*. 2012 Jun;27(2):217-25. doi: 10.1007/s13187-012-0313-8.

INTRODUCTION: Technology and market forces are driving the demand for cancer risk assessment services in the community setting, where few clinicians are trained to order and interpret predictive genetic tests. City of Hope conducts a three-phase course in genetic cancer risk assessment (GCRA) for community-based clinicians, comprised of distance didactics, face-to-face workshops, and 12 months of professional development. As designed, the course cannot meet increasing demands for GCRA training. Action research identified face-to-face workshops as a barrier to increasing course capacity. This study compared the learning effectiveness of Web-based case conferencing to face-to-face training. METHODS: A quasi-experimental design compared pre- to post-knowledge, skills, and professional self-efficacy outcomes from 2009 to 2010 course cohorts (n = 96). The intervention group (n = 52) engaged in Web-based case conferences during distance learning; the comparison group (n = 44) participated in the course as originally designed. RESULTS: Both groups and all practice disciplines demonstrated significant

pre- to post-increases on all measures. Knowledge increases were higher for the intervention group (p < 0.015); skills and self-efficacy increases were comparable between groups (p < 0.33 and p < 0.30, respectively). DISCUSSION: Findings support the learning utility of Web-based case conferencing. Further studies may inform the development of tools to assess the impact of Web-based case conferencing on practice change and patient outcomes, in alignment with the highest standards of continuing professional development.

Blazer, K. R., D. J. Macdonald, et al. "Personalized cancer genetics training for personalized medicine: improving community-based healthcare through a genetically literate workforce." *Genet Med*. 2011 Sep;13(9):832-40. doi: 10.1097/GIM.0b013e31821882b7.

PURPOSE: To assess the impact of a multimodal interdisciplinary course on genetic cancer risk assessment and research collaboration for community-based clinicians. Clinicians are increasingly requested to conduct genetic cancer risk assessment, but many are inadequately prepared to provide these services. METHODS: A prospective analysis of 131 participants (48 physicians, 41 advanced-practice nurses, and 42 genetic counselors) from community settings across the United States. The course was delivered in three phases: distance didactic learning, face-to-face training, and 12 months of web-based professional development activities to support integration of skills into practice. Cancer genetics knowledge, skills, professional self-efficacy, and practice changes were measured at baseline, immediate, and 14 months postcourse. RESULTS: Knowledge, skills, and self-efficacy scores were significantly different between practice disciplines; however, postscores increased significantly overall and for each discipline (P < 0.001). Fourteen-month practice outcomes reflect significant increases in provision of genetic cancer risk assessment services (P = 0.018), dissemination of cancer prevention information (P = 0.005) and high-risk screening recommendations (P = 0.004) to patients, patient enrollment in research (P = 0.013), and educational outreach about genetic cancer risk assessment (P = 0.003). CONCLUSIONS: Results support the efficacy of the multimodal course as a tool to develop a genetically literate workforce. Sustained alumni participation in web-based professional development activities has evolved into a distance-mediated community of practice in clinical cancer genetics, modeling the lifelong learning goals envisioned by leading continuing medical education stakeholders.

Bonaiti, B., F. Alarcon, et al. "A new scoring system in cancer genetics: application to criteria for BRCA1 and BRCA2 mutation screening." J Med Genet. 2014 Feb;51(2):114-21. doi: 10.1136/jmedgenet-2013-101674. Epub 2013 Dec 16.

BACKGROUND: In hereditary forms of cancer due to mutations of genes such as BRCA1 and BRCA2, methods have been proposed to predict the presence of a mutation in a family. **METHODS:** Relying on carriage probability computation is the most predictive, but scores are a good proxy and avoid using computer software. An empirical method, the Manchester scoring system, has been elaborated for BRCA1 and BRCA2 mutation identification. We propose a general scoring system based on a transformation of the carriage probability. Up to an approximation, the transformed carriage probability becomes an additive score. We applied this new scoring system to the diagnosis of BRCA1-associated and BRCA2-associated breast-ovarian cancer predisposition. Using simulations, its performance was evaluated and compared with that of the Manchester scoring system and of the exact probability. Finally, the score system was used on a sample of 4563 families screened for BRCA1 and BRCA2 mutations. **RESULTS:** The performance of the new scoring system was superior to the Manchester scoring system, but the probability computation remained the most predictive. The better performance of the new scoring system was attributed to accounting for unaffected family members and for the degree of kinship of relatives with the proband. **CONCLUSIONS:** The new scoring system has a theoretical basis and may be applied to any cancer family syndrome and, more generally, to any disease with monogenic subentities, in which the causal gene mutations have been identified. It will be easily modified when additional predictive factors are found.

Boucher, J., K. Habin, et al. "Cancer genetics and genomics: essentials for oncology nurses." Clin J Oncol Nurs. 2014 Jun;18(3):355-9. doi: 10.1188/14.CJON.355-359.

Cancer genetics and genomics are rapidly evolving, with new discoveries emerging in genetic mutations, variants, genomic sequencing, risk-reduction methods, and targeted therapies. To educate patients and families, state-of-the-art care requires nurses to understand terminology, scientific and technological advances, and pharmacogenomics. Clinical application of cancer genetics and genomics involves working in interdisciplinary teams to properly identify patient risk through assessing family history, facilitating genetic testing and counseling services, applying risk-reduction methods, and administering and monitoring targeted therapies.

Brennan, P. "Breast cancer risk in MEN1 - a cancer genetics perspective." Clin Endocrinol (Oxf). 2015 Mar;82(3):327-229. doi: 10.1111/cen.12614. Epub 2014 Nov 5.

The tumour spectrum associated with multiple endocrine neoplasia type 1 (MEN1) has been known for many years. New data suggest that females with MEN1 may face an additional, hitherto unrecognized, risk of early-onset breast cancer. The menin protein is certainly known to have a role in regulating oestrogen receptor activity; but how robust are the data linking MEN1 to breast cancer? This article examines the published data from the viewpoint of a cancer geneticist and considers whether there really is a justifiable indication for enhanced breast surveillance in women with MEN1.

Brierley, K. L., D. Campfield, et al. "Errors in delivery of cancer genetics services: implications for practice." Conn Med. 2010 Aug;74(7):413-23.

Advances in genetics have prompted recommendations that all healthcare providers perform genetic counseling and testing. Some experts are concerned about potential negative outcomes from cancer genetic testing performed without genetic counseling by certified genetics professionals. We report a national series of cases illustrating negative outcomes of cancer genetic testing performed without counseling by a qualified provider. Three major patterns emerged from analysis of these cases: 1) Wrong genetic test ordered, 2) Genetic test results misinterpreted, and 3) Inadequate genetic counseling. Negative outcomes included unnecessary prophylactic surgeries, unnecessary testing, psychosocial distress, and false reassurance resulting in inappropriate medical management. **CONCLUSION:** With the complexities of cancer genetic counseling and testing, it may be unrealistic to expect all clinicians to provide these services. A more realistic approach is better provider education and a framework in which healthcare providers identify patients who would benefit from a referral to a certified genetic counselor or experienced cancer genetics professional.

Catalona, W. J., J. E. Bailey-Wilson, et al. National Cancer Institute Prostate Cancer Genetics Workshop. Cancer Res. 2011 May 15;71(10):3442-6. doi: 10.1158/0008-5472.CAN-11-0314. Epub 2011 May 10.

Compelling evidence supports a genetic component to prostate cancer susceptibility and aggressiveness. Recent genome-wide association studies have identified more than 30 single-nucleotide polymorphisms associated with prostate cancer susceptibility. It remains unclear, however, whether

such genetic variants are associated with disease aggressiveness--one of the most important questions in prostate cancer research today. To help clarify this and substantially expand research in the genetic determinants of prostate cancer aggressiveness, the first National Cancer Institute Prostate Cancer Genetics Workshop assembled researchers to develop plans for a large new research consortium and patient cohort. The workshop reviewed the prior work in this area and addressed the practical issues in planning future studies. With new DNA sequencing technology, the potential application of sequencing information to patient care is emerging. The workshop, therefore, included state-of-the-art presentations by experts on new genotyping technologies, including sequencing and associated bioinformatics issues, which are just beginning to be applied to cancer genetics.

Ciccarelli, F. D. "The (r)evolution of cancer genetics." BMC Biol. 2010 Jun 11;8:74. doi: 10.1186/1741-7007-8-74.

The identification of an increasing number of cancer genes is opening up unexpected scenarios in cancer genetics. When analyzed for their systemic properties, these genes show a general fragility towards perturbation. A recent paper published in BMC Biology shows how the founder domains of known cancer genes emerged at two macroevolutionary transitions - the advent of the first cell and the transition to metazoan multicellularity. See <http://www.biomedcentral.com/1741-7007/8/66>.

Cima, I., R. Schiess, et al. "Cancer genetics-guided discovery of serum biomarker signatures for diagnosis and prognosis of prostate cancer." Proc Natl Acad Sci U S A. 2011 Feb 22;108(8):3342-7. doi: 10.1073/pnas.1013699108. Epub 2011 Feb 7.

A key barrier to the realization of personalized medicine for cancer is the identification of biomarkers. Here we describe a two-stage strategy for the discovery of serum biomarker signatures corresponding to specific cancer-causing mutations and its application to prostate cancer (PCa) in the context of the commonly occurring phosphatase and tensin homolog (PTEN) tumor-suppressor gene inactivation. In the first stage of our approach, we identified 775 N-linked glycoproteins from sera and prostate tissue of wild-type and Pten-null mice. Using label-free quantitative proteomics, we showed that Pten inactivation leads to measurable perturbations in the murine prostate and serum glycoproteome. Following bioinformatic prioritization, in a second stage we applied targeted proteomics to detect and quantify 39 human ortholog candidate biomarkers in the sera of PCa patients and control individuals. The

resulting proteomic profiles were analyzed by machine learning to build predictive regression models for tissue PTEN status and diagnosis and grading of PCa. Our approach suggests a general path to rational cancer biomarker discovery and initial validation guided by cancer genetics and based on the integration of experimental mouse models, proteomics-based technologies, and computational modeling.

Crowley, E., F. Di Nicolantonio, et al. "Liquid biopsy: monitoring cancer-genetics in the blood." Nat Rev Clin Oncol. 2013 Aug;10(8):472-84. doi: 10.1038/nrclinonc.2013.110. Epub 2013 Jul 9.

Cancer is associated with mutated genes, and analysis of tumour-linked genetic alterations is increasingly used for diagnostic, prognostic and treatment purposes. The genetic profile of solid tumours is currently obtained from surgical or biopsy specimens; however, the latter procedure cannot always be performed routinely owing to its invasive nature. Information acquired from a single biopsy provides a spatially and temporally limited snap-shot of a tumour and might fail to reflect its heterogeneity. Tumour cells release circulating free DNA (cfDNA) into the blood, but the majority of circulating DNA is often not of cancerous origin, and detection of cancer-associated alleles in the blood has long been impossible to achieve. Technological advances have overcome these restrictions, making it possible to identify both genetic and epigenetic aberrations. A liquid biopsy, or blood sample, can provide the genetic landscape of all cancerous lesions (primary and metastases) as well as offering the opportunity to systematically track genomic evolution. This Review will explore how tumour-associated mutations detectable in the blood can be used in the clinic after diagnosis, including the assessment of prognosis, early detection of disease recurrence, and as surrogates for traditional biopsies with the purpose of predicting response to treatments and the development of acquired resistance.

Delahanty, R. J., A. Beeghly-Fadiel, et al. "Association of obesity-related genetic variants with endometrial cancer risk: a report from the Shanghai Endometrial Cancer Genetics Study." Am J Epidemiol. 2011 Nov 15;174(10):1115-26. doi: 10.1093/aje/kwr233. Epub 2011 Oct 5.

Obesity is a well-established risk factor for endometrial cancer, the most common gynecologic malignancy. Recent genome-wide association studies (GWAS) have identified multiple genetic markers for obesity. The authors evaluated the association of obesity-related single nucleotide polymorphisms (SNPs) with endometrial cancer using GWAS data

from their recently completed study, the Shanghai Endometrial Cancer Genetics Study, which comprised 832 endometrial cancer cases and 2,049 controls (1996-2005). Thirty-five SNPs previously associated with obesity or body mass index (BMI; weight (kg)/height (m)²) at a minimum significance level of $\leq 5 \times 10^{-7}$ in the US National Human Genome Research Institute's GWAS catalog (<http://genome.gov/gwastudies>) and representing 26 unique loci were evaluated by either direct genotyping or imputation. The authors found that for 22 of the 26 unique loci tested (84.6%), the BMI-associated risk variants were present at a higher frequency in cases than in population controls ($P = 0.0003$). Multiple regression analysis showed that 9 of 35 BMI-associated variants, representing 7 loci, were significantly associated ($P \leq 0.05$) with the risk of endometrial cancer; for all but 1 SNP, the direction of association was consistent with that found for BMI. For consistent SNPs, the allelic odds ratios ranged from 1.15 to 1.29. These 7 loci are in the SEC16B/RASAL, TMEM18, MSRA, SOX6, MTCH2, FTO, and MC4R genes. The associations persisted after adjustment for BMI, suggesting that genetic markers of obesity provide value in addition to BMI in predicting endometrial cancer risk.

Doherty, J., D. C. Bonadies, et al. "Testing for Hereditary Breast Cancer: Panel or Targeted Testing? Experience from a Clinical Cancer Genetics Practice." *J Genet Couns.* 2014 Dec 5.

Approaches to hereditary breast cancer testing are shifting as multi-gene panels become more widely available. This paper describes our center's experience and outcomes of a 6-gene panel test as a first-tier approach in patients who were candidates for BRCA testing. Between July and December 2013, a 6-gene panel test was ordered for patients meeting criteria for BRCA testing. A retrospective review detailed the mutation and variant of uncertain significance (VUS) rates for the genes analyzed. The mutation rate was 5.2 % ($n = 7$) and the VUS rate was 6.7 % ($n = 9$). A subsequent review determined the number of BRCA-negative patients who would have been offered additional single gene testing had BRCA, only, been their first-tier test. Applying consensus criteria revealed 7.1 % ($n = 9$) cases that met criteria for additional testing. Pedigree analysis by a certified genetic counselor revealed 26.8 % ($n = 34$) cases that would have been offered additional testing based on personal and/or family history. Our results suggest that this panel may be warranted as a first-tier test for a small subset of patients, but likely represents over testing for the majority of patients who are candidates for BRCA testing. The genes selected for panels, the extra costs per patient and the chance of VUS must be

considered before we uniformly switch from BRCA to full panel testing on all patients.

Eijzena, W., E. M. Bleiker, et al. "Psychosocial aspects of hereditary cancer (PAHC) questionnaire: development and testing of a screening questionnaire for use in clinical cancer genetics." *Psychooncology.* 2014 Aug;23(8):862-9. doi: 10.1002/pon.3485. Epub 2014 Jan 20.

BACKGROUND: Up to three-quarters of individuals who undergo cancer genetic counseling and testing report psychosocial problems specifically related to that setting. The objectives of this study were to develop and evaluate the screening properties of a questionnaire designed to assess specific psychosocial problems related to cancer genetic counseling. **METHODS:** We adopted the European Organisation for Research and Treatment of Cancer Quality of Life Group guidelines to develop the Psychosocial Aspects of Hereditary Cancer (PAHC) questionnaire, a 26-item questionnaire organized into six problem domains: genetics, practical issues, family, living with cancer, emotions, and children. The Distress Thermometer and a question per domain on the perceived need for extra psychosocial services were included as well. We administered the questionnaire and the Hospital Anxiety and Depression Scale to 127 counselees at the time of genetic counseling and 3 weeks after DNA test disclosure. As a gold standard to evaluate the screening properties of the questionnaire, participants underwent a semi-structured interview with an experienced social worker who assessed the presence and severity of problems per domain. **RESULTS:** A cutoff score representing responses of 'quite a bit' or 'very much' to one or more items within a given problem domain yielded moderate to high sensitivity across domains. A cutoff of 4 on the Distress Thermometer yielded high sensitivity. The questions regarding the perceived need for extra psychosocial services yielded high specificity and negative predictive values. **CONCLUSION:** The Psychosocial Aspects of Hereditary Cancer questionnaire in combination with the Distress Thermometer can be used as a first-line screener for psychosocial problems within the cancer genetic counseling setting.

Etchegary, H., B. Potter, et al. "Cultural differences in family communication about inherited cancer: implications for cancer genetics research." *J Cult Divers.* 2013 Winter;20(4):195-201.

It is widely accepted that clinical genetic services should provide culturally competent service to clients. However, systematic research is needed on the cultural meanings of heredity, family cancer, and family communication about inherited risk in order to

move towards culturally competent cancer genetic services. Cultural differences in how families communicate about inherited risk is a particularly important, but neglected, research focus. The purpose of this paper is to: (1) review extant literature on cultural differences in family communication about inherited cancer risk; and (2) provide suggestions for cancer genetics research that will ultimately help furnish the evidence base for the training and provision of culturally competent cancer genetics services.

Foley, S. B., J. J. Rios, et al. "Use of Whole Genome Sequencing for Diagnosis and Discovery in the Cancer Genetics Clinic." *EBioMedicine*. 2015 Jan;2(1):74-81.

Despite the potential of whole-genome sequencing (WGS) to improve patient diagnosis and care, the empirical value of WGS in the cancer genetics clinic is unknown. We performed WGS on members of two cohorts of cancer genetics patients: those with BRCA1/2 mutations (n = 176) and those without (n = 82). Initial analysis of potentially pathogenic variants (PPVs, defined as nonsynonymous variants with allele frequency < 1% in ESP6500) in 163 clinically-relevant genes suggested that WGS will provide useful clinical results. This is despite the fact that a majority of PPVs were novel missense variants likely to be classified as variants of unknown significance (VUS). Furthermore, previously reported pathogenic missense variants did not always associate with their predicted diseases in our patients. This suggests that the clinical use of WGS will require large-scale efforts to consolidate WGS and patient data to improve accuracy of interpretation of rare variants. While loss-of-function (LoF) variants represented only a small fraction of PPVs, WGS identified additional cancer risk LoF PPVs in patients with known BRCA1/2 mutations and led to cancer risk diagnoses in 21% of non-BRCA cancer genetics patients after expanding our analysis to 3209 ClinVar genes. These data illustrate how WGS can be used to improve our ability to discover patients' cancer genetic risks.

Gibbon, S. "Ancestry, Temporality, and Potentiality: Engaging Cancer Genetics in Southern Brazil." *Curr Anthropol*. 2013 Oct;54(Suppl 7):S107-S117.

In this paper I examine the variety of ways potential is articulated, entailed, and produced in how the field of cancer genetics is being constituted as a domain of transnational research and an emerging site of health-care intervention in southern Brazil. Drawing on analysis of fieldwork in Brazilian cancer-genetics clinics, I explore how different expressions of potential come to inform dynamically the pursuit of

prevention, care, and research as diversely scaled investments for those working and living with cancer-genetics knowledge and technologies. It illustrates how specific temporalities help to constitute and "abductively" frame the meaning of these different potentials particularly as this relates to a focus on ancestry. Colonial histories of migration, the embodied effects of dietary habits, or the moral failings of near and distant ancestors as well as promissory futures and the contingency of lived lives become at different times templates for identifying, materializing, and transforming how the potential of cancer genetics in Brazil is articulated. Potential is also expressed through an idiom of "choice" in different efforts to situate participation in cancer-genetics research as prevention or to negotiate access to basic public health. I explore how these expressions of cancer genetics as potential powerfully yet unevenly work to sustain knowledge practices as well as propel patients and their families into fledgling domains of clinical practice and scientific research. At the same time there is always an "excess of meaning" in these endeavors that make visible lines of fracture and disjuncture in collective efforts to make future histories of and from the pursuit of cancer genetics in southern Brazil.

Goldim, J. R. and S. Gibbon "Between personal and relational privacy: understanding the work of informed consent in cancer genetics in Brazil." *J Community Genet*. 2015 May 22.

Drawing from perspectives of both bioethics and anthropology, this article explores how the boundaries between personal and relational privacy are negotiated by patients and practitioners in the context of an emerging domain of cancer genetics in Brazil. It reflects on the place of informed consent in the history of bioethics in North America in contrast to the development of bioethics in Brazil and the particular social cultural context in which consent is sought in Brazilian public health care. Making use of empirical research with families and individuals receiving genetic counselling related to increased genetic risk for cancer, in genetic clinics in southern Brazil, it examines how informed consent is linked to the necessary movement between personal and relational privacy. The paper illustrates the value of a particular tool known as a 'sociogram' to examine the complex interpersonal dynamics that arise in negotiating informed consent at the interface between the family and the individual in Brazil. The paper, therefore, points to the scope of further interdisciplinary exchanges between anthropology and bioethics, confronting the new challenges that arise in the context of medical genetics in developing country.

Hall, T. O., A. D. Renz, et al. "Awareness and uptake of direct-to-consumer genetic testing among cancer cases, their relatives, and controls: the Northwest Cancer Genetics Network." Genet Test Mol Biomarkers. 2012 Jul;16(7):744-8. doi: 10.1089/gtmb.2011.0235. Epub 2012 Jun 25.

AIMS: To determine if awareness of, interest in, and use of direct-to-consumer (DTC) genetic testing is greater in a sample of high-risk individuals (cancer cases and their relatives), compared to controls. METHODS: Participants were recruited from the Northwest Cancer Genetics Network. A follow-up survey was mailed to participants to assess DTC genetic testing awareness, interest, and use. RESULTS: One thousand two hundred sixty-seven participants responded to the survey. Forty-nine percent of respondents were aware of DTC genetic testing. Of those aware, 19% indicated interest in obtaining and <1% reported having used DTC genetic testing. Additional information supplied by respondents who reported use of DTC genetic tests indicated that 55% of these respondents likely engaged in clinical genetic testing, rather than DTC genetic testing. CONCLUSION: Awareness of DTC genetic testing was greater in our sample of high-risk individuals than in controls and population-based studies. Although interest in and use of these tests among cases in our sample were equivalent to other population-based studies, interest in testing was higher among relatives and people who self-referred for a registry focused on cancer than among cases and controls. Additionally, our results suggest that there may be some confusion about what constitutes DTC genetic testing.

Hanning, K. A., M. Steel, et al. "Why do women not return family history forms when referred to breast cancer genetics services? A mixed-method study." Health Expect. 2014 Jan 5. doi: 10.1111/hex.12166.

BACKGROUND: Personal and family data forms, completed by women referred to breast cancer genetics clinics, are valuable tools for verification and extension of family history, crucial steps in accurate risk evaluation. A significant minority of women do not complete and return these forms, despite reminders, even when completion is a pre-requisite for a clinic appointment. OBJECTIVE: To facilitate access of women at increased familial risk of breast cancer to screening and counselling services by investigating reasons for non-return of the forms. PARTICIPANTS AND DESIGN: Based on a single regional 'breast cancer family' service in the UK, Analysis of quantitative data comparing women who did not return forms (n = 55) with those who had done so (n = 59), together with qualitative evaluation of potential barriers to form-completion through semi-

structured telephone interviews with a random subset of 'non-returners' (n = 23). RESULTS: Non-returners have higher proportions of the very young (below the age at which surveillance could be offered) and of women from lower social deprivation categories. Interviews revealed that the majority of non-returners are anxious, rather than unconcerned about their breast cancer risk and circumstances and attitudes contributed to non-compliance. Twenty-one participants confirmed that they would welcome an appointment at a 'breast cancer family' clinic, but nine did not attend for the appointment. They were significantly younger than those who attend, but were not at lower familial risk. DISCUSSION AND CONCLUSIONS: Many women who fail to complete and return a family history form would benefit from risk assessment and genetic counselling. Several steps are suggested that might help them access the relevant services.

Hilgart, J., J. A. Hayward, et al. "E-genetics: exploring the acceptability and feasibility of using technology in cancer genetics services." Clin Genet. 2012 Jun;81(6):514-20. doi: 10.1111/j.1399-0004.2011.01813.x. Epub 2011 Dec 13.

The use of information and communication technologies (ICTs) in the delivery of cancer genetics services could improve equality of access in rural areas and help meet the increasing demand for specialist genetics services. An online patient survey and focus groups with patients and staff from the Cancer Genetics Service for Wales (CGSW) were used to explore the acceptability and feasibility of utilizing ICTs within genetics services, which we have termed e-genetics. A total of 225 patients completed the online survey. Many aspects of e-genetics proposed in the survey were highly acceptable to patients, including an electronic version of the family history questionnaire, an email facility for cancer genetic queries, and a computerized decision-aid. Participants in the focus groups emphasized the importance of patient choice when developing new models of service delivery. For example, the use of genetic counselling via telemedicine was not considered to be preferable to face-to-face clinic appointments but could benefit those unable to travel. This article highlights the fact that e-genetics initiatives may not be appropriate for all cancer genetics service users. However, user-friendly developments that can be easily implemented and attend to individual needs could improve efficiency and cost-effectiveness, whilst providing high-quality services to remote areas.

Hill, J. A., S. Y. Lee, et al. "Cancer genetics education in a low- to middle-income country: evaluation of an

interactive workshop for clinicians in Kenya." PLoS One. 2015 Jun 2;10(6):e0129852. doi: 10.1371/journal.pone.0129852. eCollection 2015.

BACKGROUND: Clinical genetic testing is becoming an integral part of medical care for inherited disorders. While genetic testing and counseling are readily available in high-income countries, in low- and middle-income countries like Kenya genetic testing is limited and genetic counseling is virtually non-existent. Genetic testing is likely to become widespread in Kenya within the next decade, yet there has not been a concomitant increase in genetic counseling resources. To address this gap, we designed an interactive workshop for clinicians in Kenya focused on the genetics of the childhood eye cancer retinoblastoma. The objectives were to increase retinoblastoma genetics knowledge, build genetic counseling skills and increase confidence in those skills. **METHODS:** The workshop was conducted at the 2013 Kenyan National Retinoblastoma Strategy meeting. It included a retinoblastoma genetics presentation, small group discussion of case studies and genetic counseling role-play. Knowledge was assessed by standardized test, and genetic counseling skills and confidence by questionnaire. **RESULTS:** Knowledge increased significantly post-workshop, driven by increased knowledge of retinoblastoma causative genetics. One-year post-workshop, participant knowledge had returned to baseline, indicating that knowledge retention requires more frequent reinforcement. Participants reported feeling more confident discussing genetics with patients, and had integrated more genetic counseling into patient interactions. **CONCLUSION:** A comprehensive retinoblastoma genetics workshop can increase the knowledge and skills necessary for effective retinoblastoma genetic counseling.

Houlston, R. S. "COGENT (COlorectal cancer GENEtics) revisited." Mutagenesis. 2012 Mar;27(2):143-51. doi: 10.1093/mutage/ger059.

Many colorectal cancers (CRCs) develop in genetically susceptible individuals most of whom are not carriers of germ line mismatch repair or APC gene mutations and much of the heritable risk of CRC appears to be attributable to the co-inheritance of multiple low-risk variants. The accumulated experience to date in identifying this class of susceptibility allele has highlighted the need to conduct statistically and methodologically rigorous studies and the need for the multi-centre collaboration. This has been the motivation for establishing the COGENT (COlorectal cancer GENEtics) consortium which now includes over 20 research groups in Europe, Australia, the Americas, China and Japan actively working on CRC genetics. Here, we review

the rationale for identifying low-penetrance variants for CRC and the current and future challenges for COGENT.

Iredale, R. and K. Madden "Let's talk about genes, and I don't mean trousers: encouraging cancer genetics literacy amongst children." Ecancermedicalscience. 2014 Feb 27;8:408. doi: 10.3332/ecancer.2014.408. eCollection 2014.

Acquiring genetic literacy is one of the most important things a person can do to promote their own and their family's health. Family history-genetics and the shared environment is a significant risk factor for cancer as well as other common diseases, such as cardiovascular disease and diabetes. A good understanding of family health history should increasingly be used to personalise health messages and promote healthy lifestyles. The Let's Talk About Genes project explored whether it was feasible and acceptable to engage young children in Wales with family history as it relates specifically to cancer, so they increase their cancer genetics literacy over time and become more aware of general health issues that relate to cancer.

Katoh, M., M. Igarashi, et al. "Cancer genetics and genomics of human FOX family genes." Cancer Lett. 2013 Jan 28;328(2):198-206. doi: 10.1016/j.canlet.2012.09.017. Epub 2012 Sep 27.

Forkhead-box (FOX) family proteins, involved in cell growth and differentiation as well as embryogenesis and longevity, are DNA-binding proteins regulating transcription and DNA repair. The focus of this review is on the mechanisms of FOX-related human carcinogenesis. FOXA1 is overexpressed as a result of gene amplification in lung cancer, esophageal cancer, ER-positive breast cancer and anaplastic thyroid cancer and is point-mutated in prostate cancer. FOXA1 overexpression in breast cancer and prostate cancer is associated with good or poor prognosis, respectively. Single nucleotide polymorphism (SNP) within the 5'-UTR of the FOXE1 (TTF2) gene is associated with thyroid cancer risk. FOXF1 overexpression in breast cancer is associated with epithelial-to-mesenchymal transition (EMT). FOXM1 is overexpressed owing to gene amplification in basal-type breast cancer and diffuse large B-cell lymphoma (DLBCL), and it is transcriptionally upregulated owing to Hedgehog-GLI, hypoxia-HIF1alpha or YAP-TEAD signaling activation. FOXM1 overexpression leads to malignant phenotypes by directly upregulating CCNB1, AURKB, MYC and SKP2 and indirectly upregulating ZEB1 and ZEB2 via miR-200b downregulation. Tumor suppressor functions of FOXO transcription factors are lost in cancer cells as a result of

chromosomal translocation, deletion, miRNA-mediated repression, AKT-mediated cytoplasmic sequestration or ubiquitination-mediated proteasomal degradation. FOXP1 is upregulated as a result of gene fusion or amplification in DLBCL and MALT lymphoma and also repression of miRNAs, such as miR-1, miR-34a and miR-504. FOXP1 overexpression is associated with poor prognosis in DLBCL, gastric MALT lymphoma and hepatocellular carcinoma but with good prognosis in breast cancer. In neuroblastoma, the entire coding region of the FOXR1 (FOXN5) gene is fused to the MLL or the PAFAH1B gene owing to interstitial deletions. FOXR1 fusion genes function as oncogenes that repress transcription of FOXO target genes. Whole-genome sequencing data from tens of thousands of human cancers will uncover the mutational landscape of FOX family genes themselves as well as FOX-binding sites, which will be ultimately applied for cancer diagnostics, prognostics, and therapeutics.

Kohut, K., L. D'Mello, et al. "Implications for cancer genetics practice of pro-actively assessing family history in a General Practice cohort in North West London." *Fam Cancer*. 2012 Mar;11(1):107-13. doi: [10.1007/s10689-011-9482-6](https://doi.org/10.1007/s10689-011-9482-6).

At present cancer genetics referrals are reactive to individuals asking for a referral and providing a family history thereafter. A previous pilot study in a single General Practice (GP) catchment area in North London showed a 1.5-fold increase in breast cancer risk in the Ashkenazi Jewish population compared with the non-Ashkenazi mixed population. The breast cancer incidence was equal in the Ashkenazim in both pre- and postmenopausal groups. We wanted to investigate the effect of proactively seeking family history data from the entire female population of the practice to determine the effect on cancer genetics referral. Objectives To determine the need for cancer genetics intervention for women in a single GP catchment area. (1) to determine the incidence and strength of family history of cancer in women aged over 18 in the practice, (2) to offer cancer genetics advice and determine the uptake of counselling in those with a positive family history, (3) to identify potential BRCA1/BRCA2 gene mutation carriers who can be offered clinical follow up with appropriate translational research studies. Design Population-based cohort study of one General Practice female population. Participants Three hundred and eighty-three women over the age of 18 from one General Practice who responded to a questionnaire about family history of cancer. The whole female adult GP population was the target and the total number sampled was 3,820. Results 10% of patients completed the questionnaire (n = 383). A family

history of cancer was present in 338 cases, 95 went on to have genetic counselling or had previously had counselling and 47 were genetically tested. We identified three carriers of an Ashkenazi Jewish founder mutation in BRCA1. Conclusions Response rate to a family history questionnaire such as that used in genetics centres was low (10%) and other approaches will be needed to proactively assess family history. Although the Ashkenazim are present in 39% of the GP catchment area, 62% of those who returned a family history questionnaire were from this ethnic group and of those returned, 44% warranted referral to a cancer genetics unit. In the non Ashkenazim, the questionnaire return rate was 38% and 18% of those warranted referral to cancer genetics.

Lal, H., K. L. Kolaja, et al. "Cancer genetics and the cardiotoxicity of the therapeutics." *J Am Coll Cardiol*. 2013 Jan 22;61(3):267-74. doi: [10.1016/j.jacc.2012.05.066](https://doi.org/10.1016/j.jacc.2012.05.066).

Cancer genomics has focused on the discovery of mutations and chromosomal structural rearrangements that either increase susceptibility to cancer or support the cancer phenotype. Protein kinases are the most frequently mutated genes in the cancer genome, making them attractive therapeutic targets for drug design. However, the use of some of the kinase inhibitors (KIs) has been associated with toxicities to the heart and vasculature, including acute coronary syndromes and heart failure. Herein we discuss the genetic basis of cancer, focusing on mutations in the kinase genome (kinome) that lead to tumorigenesis. This will allow an understanding of the real and potential power of modern cancer therapeutics. The underlying mechanisms that drive the cardiotoxicity of the KIs are also examined. The preclinical models for predicting cardiotoxicity, including induced pluripotent stem cells and zebrafish, are reviewed, with the hope of eventually being able to identify problematic agents before their use in patients. Finally, the use of biomarkers in the clinic is discussed, and newer strategies (i.e., metabolomics and enhanced imaging strategies) that may allow earlier and more accurate detection of cardiotoxicity are reviewed.

Lowery, J. T., N. Horick, et al. "A randomized trial to increase colonoscopy screening in members of high-risk families in the colorectal cancer family registry and cancer genetics network." *Cancer Epidemiol Biomarkers Prev*. 2014 Apr;23(4):601-10. doi: [10.1158/1055-9965.EPI-13-1085](https://doi.org/10.1158/1055-9965.EPI-13-1085). Epub 2014 Feb 5.

BACKGROUND: Individuals with a strong family history of colorectal cancer have significant risk for colorectal cancer, although adherence to colonoscopy screening in these groups remains low.

This study assessed whether a tailored telephone counseling intervention can increase adherence to colonoscopy in members of high-risk families in a randomized, controlled trial. **METHODS:** Eligible participants were recruited from two national cancer registries if they had a first-degree relative with colorectal cancer under age 60 or multiple affected family members, which included families that met the Amsterdam criteria for hereditary non-polyposis colon cancer (HNPCC), and if they were due for colonoscopy within 24 months. Participants were randomized to receive a tailored telephone intervention grounded in behavioral theory or a mailed packet with general information about screening. Colonoscopy status was assessed through follow-up surveys and endoscopy reports. Cox proportional hazards models were used to assess intervention effect. **RESULTS:** Of the 632 participants (ages 25-80), 60% were female, the majority were White, non-Hispanic, educated, and had health insurance. Colonoscopy adherence increased 11 percentage points in the tailored telephone intervention group, compared with no significant change in the mailed group. The telephone intervention was associated with a 32% increase in screening adherence compared with the mailed intervention (HR, 1.32; P = 0.01). **CONCLUSIONS:** A tailored telephone intervention can effectively increase colonoscopy adherence in high-risk persons. This intervention has the potential for broad dissemination to healthcare organizations or other high-risk populations. **IMPACT:** Increasing adherence to colonoscopy among persons with increased colorectal cancer risk could effectively reduce incidence and mortality from this disease.

Mahon, S. M. "Allocation of work activities in a comprehensive cancer genetics program." Clin J Oncol Nurs. 2013 Aug 1;17(4):397-404. doi: 10.1188/13.CJON.397-404.

Hereditary cancer programs that provide risk assessment, genetic education, and counseling services are becoming increasingly common. This article describes one possible approach to providing comprehensive cancer genetics care by a credentialed genetics advanced practice nurse. In addition to the description of the program, data from a recently conducted time study are included to provide insight into work allocation of different program components. Findings from the study indicate that about 41% of the time is spent in direct clinical time with patients and families, including initial visit counseling, phone consultation, and follow-up visits. The rest of the time is spent in other indirect care activities, including previsit activities, risk calculation, clinical trials enrollment, correspondence, teaching, and administrative duties. For those developing or

expanding a cancer genetics program, considering all activities that will occur and the time allocated to each activity is important.

Mauer, C. B., S. M. Pirzadeh-Miller, et al. "The integration of next-generation sequencing panels in the clinical cancer genetics practice: an institutional experience." Genet Med. 2014 May;16(5):407-12. doi: 10.1038/gim.2013.160. Epub 2013 Oct 10.

PURPOSE: The advent of next-generation sequencing for cancer susceptibility genes holds promise for clinical genetics application, but the practical issues surrounding integration of this testing into the clinical setting have not been well addressed. This article describes the clinical experience of genetic counselors in an academic and community setting with next-generation sequencing cancer panels. **METHODS:** Between April 2012 and January 2013, 60 next-generation sequencing panels were ordered. A retrospective review was conducted to determine the indication for ordering the results of the tests and the patient management based on the results. **RESULTS:** Ten tests were canceled due to out-of-pocket costs or previously identified mutations. Among the 50 tests, 5 (10%) showed a positive result. Moreover, 15 of the 50 (30%) panels detected variant(s) of uncertain significance or variant(s) suspected benign. **CONCLUSION:** We propose clinical guidelines for identifying high-risk patients who should be offered this testing. Our data support the National Comprehensive Cancer Network recommendations that next-generation sequencing be ordered as a second-tier test for high-risk individuals with cancer by trained cancer genetics providers. Literature review and expert knowledge should be used to create management plans for the identification of both positive and variants of uncertain significance results. Providers should be aware of limitations regarding reimbursement for testing and recommended management strategies.

McDonald, J. A., F. K. Barg, et al. "Understanding participation by African Americans in cancer genetics research." J Natl Med Assoc. 2012 Jul-Aug;104(7-8):324-30.

PURPOSE: Understanding genetic factors that contribute to racial differences in cancer outcomes may reduce racial disparities in cancer morbidity and mortality. Achieving this goal will be limited by low rates of African American participation in cancer genetics research. **METHOD:** We conducted a qualitative study with African American adults (n = 91) to understand attitudes about participating in cancer genetics research and to identify factors that are considered when making a decision about participating in this type of research. **RESULTS:**

Participants would consider the potential benefits to themselves, family members, and their community when making a decision to participate in cancer genetics research. However, concerns about exploitation, distrust of researchers, and investigators' motives were also important to participation decisions. Individuals would also consider who has access to their personal information and what would happen to these data. Side effects, logistical issues, and the potential to gain knowledge about health issues were also described as important factors in decision making. CONCLUSION: African Americans may consider a number of ethical, legal, and social issues when making a decision to participate in cancer genetics research. These issues should be addressed as part of recruitment efforts.

Mukherjee, A. and E. A. Rakha "Integrating breast cancer genetics into clinical practice." Womens Health (Lond Engl). 2012 Jan;8(1):99-112. doi: [10.2217/whe.11.81](https://doi.org/10.2217/whe.11.81).

Breast cancer prognosis and treatment is guided by traditional clinicopathological parameters and individual molecular markers. Despite the remarkable advances in our scientific understanding of breast cancer genetics, the impact of such information on medical care has, to date, been modest. Although the use of simple genetics is already in vogue in clinical practice, the concept of molecular profiling and multiparameter gene classifiers was raised after the introduction of the high-throughput gene expression microarrays. This technology, in addition to highlighting the molecular heterogeneity of breast cancer, has led to the development of prognostic and predictive gene signatures. Studies are underway to assess the clinical validity and clinical utility of these multigene assays and their incorporation into clinical practice. This article reviews the current status and projected future use of genetics and genomics in breast cancer management and their impact on the refinement of risk stratification to permit individualized and patient-tailored therapy. Limitations based on our current scientific understanding and realistic expectations are also explored.

Narod, S. A. "Testing for CHEK2 in the cancer genetics clinic: ready for prime time?" Clin Genet. 2010 Jul;78(1):1-7. doi: [10.1111/j.1399-0004.2010.01402.x](https://doi.org/10.1111/j.1399-0004.2010.01402.x).

The 1100delC mutation of the CHEK2 gene was found to be a cause of breast cancer in 2002. The lifetime risk of breast cancer among women with a mutation and with a family history of breast cancer is approximately 25%. These women are good candidates for screening with MRI and for

chemoprevention with tamoxifen. It is reasonable to test for this single mutation when women undergo testing for BRCA1 and BRCA2.

Nelson-Moseke, A. C., J. M. Jeter, et al. "An unusual BRCA mutation distribution in a high risk cancer genetics clinic." Fam Cancer. 2013 Mar;12(1):83-7. doi: [10.1007/s10689-012-9581-z](https://doi.org/10.1007/s10689-012-9581-z).

The Database of Individuals at High Risk for Breast, Ovarian, or Other Hereditary Cancers at the Arizona Cancer Center in Tucson, Arizona assesses cancer risk factors and outcomes in patients with a family history of cancer or a known genetic mutation. We analyzed the subset of clinic probands who carry deleterious BRCA gene mutations to identify factors that could explain why mutations in BRCA2 outnumber those in BRCA1. Medical, family, social, ethnic and genetic mutation histories were collected from consenting patients' electronic medical records. Differences between BRCA1 and BRCA2 probands from this database were analyzed for statistical significance and compared to published analyses. A significantly higher proportion of our clinic probands carry mutations in BRCA2 than BRCA1, compared with previous reports of mutation prevalence. This also holds true for the Hispanic sub-group. Probands with BRCA2 mutations were significantly more likely than their BRCA1 counterparts to present to the high risk clinic without a diagnosis of cancer. Other differences between the groups were not significant. Six previously unreported BRCA2 mutations appear in our clinic population. The increased proportion of probands carrying deleterious BRCA2 mutations is likely multifactorial, but may reflect aspects of Southern Arizona's unique ethnic heritage.

Pollock, J. and J. S. Welsh "Clinical cancer genetics. Part 2: Breast." Am J Clin Oncol. 2014 Feb;37(1):86-9. doi: [10.1097/COC.0b013e31823fe657](https://doi.org/10.1097/COC.0b013e31823fe657).

Since the discovery of proven genetic mutations which predispose people to breast cancer along with the routine availability of genetic testing for such mutations, a number of issues have surfaced regarding potential methods of breast cancer diagnosis, surveillance, treatment, and risk reduction. Many of these issues pertain to the practice of radiation oncology and can affect decisions on management. This article aims to describe some of the more salient features of individuals at high genetic risk for breast developing cancer along with aspects of their tumor biology, clinical natural history, and how the radiation oncologist may address these challenges.

Pollock, J. and J. S. Welsh "Clinical cancer genetics: Part I: Gastrointestinal." Am J Clin Oncol. 2011

Jun;34(3):332-6. doi:
10.1097/COC.0b013e3181dea432.

There is an increasing recognition of the importance of genetic and familial cancer syndromes in routine clinical practice. Although most of gastrointestinal cancers are sporadic, a number of important cancer predisposition syndromes are now recognized and well characterized. In this review, we discuss some of the basic principles of clinical cancer genetics and clinically relevant aspects of the more common gastrointestinal cancer syndromes from the perspective of practicing radiation oncologists.

Prochniak, C. F., L. J. Martin, et al. "Barriers to and motivations for physician referral of patients to cancer genetics clinics." *J Genet Couns.* 2012 Apr;21(2):305-25. doi: 10.1007/s10897-011-9401-x. Epub 2011 Aug 13.

Although it is well known that under-referral of colon cancer patients to cancer genetics clinics is a chronic problem, no study has yet examined why physicians may be ordering testing independently rather than referring patients to cancer genetics clinics. The current study explored variables which may impact a physician's preference for ordering testing independently or referring patients to outside cancer genetics experts. An online questionnaire, distributed to the membership of the American College of Gastroenterology and the American Society of Colorectal Surgeons, yielded responses from 298 physicians. Motivations to refer to cancer genetics clinics rather than order testing independently included fear of genetic discrimination and a belief that patients benefit from genetic counseling about the risks, benefits and consequences of testing. These results suggest that in order to increase referrals, genetic counselors must educate physicians about the unique benefits patients receive from participating in genetic counseling.

Quinn, G. P., J. Q. McIntyre, et al. "Challenges in recruiting Mexican women for cancer genetics research." *J Community Genet.* 2011 Mar;2(1):43-7. doi: 10.1007/s12687-010-0032-y. Epub 2010 Dec 1.

Hispanic women often have low participation rates in cancer genetics research. Additionally, Hispanic sub-ethnicities may have varying accrual rates based on unique cultural factors. Hispanic women were recruited through flyers placed in the Tampa Bay Community to participate in an interview about knowledge of hereditary breast and ovarian cancer. The study goal was to recruit 20 women from each Hispanic sub-ethnicity: Puerto Rican, Mexican, and Cuban. This article reports on the difficulty in recruiting Mexican women. One hundred forty-three women called the study hotline to inquire about

participation. Seventy-six callers were ineligible for the study. Thirty-four percent (n = 26) of ineligible were Mexican women; within this group, 62% (n = 16) were unable to participate because they did not know the cancer site of their first degree relative. Inclusion criteria requiring knowledge of family history of cancer for behavioral research may be too stringent. The socio-cultural norms of Mexican families may not include discussions of cancer specifics. This study demonstrates Mexican women may have limited knowledge about their family history of cancer. Considerations of these knowledge limitations should be built into cancer genetics-related research. Referral criteria to assess the risk of hereditary breast and ovarian cancer by cancer genetics professionals are predicated on the patient providing details about cancer within multiple generations of family members, thus, posing a barrier for Mexican women who may have limited knowledge of their family history of cancer.

Rizzolo, P., V. Silvestri, et al. "Male breast cancer: genetics, epigenetics, and ethical aspects." *Ann Oncol.* 2013 Nov;24 Suppl 8:viii75-viii82. doi: 10.1093/annonc/mdt316.

BACKGROUND AND STUDY DESIGN: Male breast cancer (MBC) is a rare disease compared with female BC and our current understanding regarding breast carcinogenesis in men has been largely extrapolated from the female counterpart. We focus on differences between the ethical issues related to male and female BC patients. A systematic literature search by using PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>), was carried out to provide a synopsis of the current research in the field of MBC genetics, epigenetics and ethics. Original articles and reviews published up to September 2012 were selected by using the following search key words to query the PubMed website: 'male breast cancer', 'male breast cancer and genetic susceptibility', 'male breast cancer and epigenetics', 'male breast cancer and methylation', 'male breast cancer and miRNA', 'male breast cancer and ethics'. **RESULTS AND CONCLUSIONS:** As in women, three classes of breast cancer genetic susceptibility (high, moderate, and low penetrance) are recognized in men. However, genes involved and their impact do not exactly overlap in female and male BC. Epigenetic alterations are currently scarcely investigated in MBC, however, the different methylation and miRNA expression profiles identified to date in female and male BCs suggest a potential role for epigenetic alterations as diagnostic biomarkers. Overall, much still needs to be learned about MBC and, because of its rarity, the main effort is to develop large consortia for moving forward in understanding MBC and

improving the management of MBC patients on a perspective of gender medicine.

Roberts, J. S., D. I. Shalowitz, et al. "Returning individual research results: development of a cancer genetics education and risk communication protocol." *J Empir Res Hum Res Ethics*. 2010 Sep;5(3):17-30. doi: 10.1525/jer.2010.5.3.17.

The obligations of researchers to disclose clinically and/or personally significant individual research results are highly debated, but few empirical studies have addressed this topic. We describe the development of a protocol for returning research results to participants at one site of a multicenter study of the genetic epidemiology of melanoma. Protocol development involved numerous challenges: (1) deciding whether genotype results merited disclosure; (2) achieving an appropriate format for communicating results; (3) developing education materials; (4) deciding whether to retest samples for additional laboratory validation; (5) identifying and notifying selected participants; and (6) assessing the impact of disclosure. Our experience suggests potential obstacles depending on researcher resources and the design of the parent study, but offers a process by which researchers can responsibly return individual study results and evaluate the impact of disclosure.

Scheuner, M. T., A. B. Hamilton, et al. "A cancer genetics toolkit improves access to genetic services through documentation and use of the family history by primary-care clinicians." *Genet Med*. 2014 Jan;16(1):60-9. doi: 10.1038/gim.2013.75. Epub 2013 Jun 13.

PURPOSE: We developed, implemented, and evaluated a multicomponent cancer genetics toolkit designed to improve recognition and appropriate referral of individuals at risk for hereditary cancer syndromes. **METHODS:** We evaluated toolkit implementation in the women's clinics at a large Veterans Administration medical center using mixed methods, including pre-post semistructured interviews, clinician surveys, and chart reviews, and during implementation, monthly tracking of genetic consultation requests and use of a reminder in the electronic health record. We randomly sampled 10% of progress notes 6 months before (n = 139) and 18 months during implementation (n = 677). **RESULTS:** The toolkit increased cancer family history documentation by almost 10% (26.6% pre- and 36.3% postimplementation). The reminder was a key component of the toolkit; when used, it was associated with a twofold increase in cancer family history documentation (odds ratio = 2.09; 95% confidence interval: 1.39-3.15), and the history was more complete. Patients whose clinicians completed the

reminder were twice as likely to be referred for genetic consultation (4.1-9.6%, $P < 0.0001$). **CONCLUSION:** A multicomponent approach to the systematic collection and use of family history by primary-care clinicians increased access to genetic services.

Schluskel, A. T., R. A. Gagliano, Jr., et al. "The evolution of colorectal cancer genetics-Part 2: clinical implications and applications." *J Gastrointest Oncol*. 2014 Oct;5(5):336-44. doi: 10.3978/j.issn.2078-6891.2014.068.

The genetic understanding of colorectal cancer (CRC) continues to grow, and it is now estimated that 10% of the population has a known hereditary CRC syndrome. This article will examine the evolving surgical and medical management of hereditary CRC syndromes, and the impact of tumor genetics on therapy. This review will focus on the most common hereditary CRC-prone diseases seen in clinical practice, which include Lynch syndrome (LS), familial adenomatous polyposis (FAP) & attenuated FAP (AFAP), MutYH-associated polyposis (MAP), and serrated polyposis syndrome (SPS). Each section will review the current recommendations in the evaluation and treatment of these syndromes, as well as review surgical management and operative planning. A highly detailed multigeneration cancer family history with verified genealogy and pathology documentation whenever possible, coupled with germline mutation testing when indicated, is critically important to management decisions. Although caring for patients with these syndromes remains complex, the application of this knowledge facilitates better treatment of both individuals and their affected family members for generations to come.

Teerlink, C. C., S. N. Thibodeau, et al. "Association analysis of 9,560 prostate cancer cases from the International Consortium of Prostate Cancer Genetics confirms the role of reported prostate cancer associated SNPs for familial disease." *Hum Genet*. 2014 Mar;133(3):347-56. doi: 10.1007/s00439-013-1384-2. Epub 2013 Oct 26.

Previous GWAS studies have reported significant associations between various common SNPs and prostate cancer risk using cases unselected for family history. How these variants influence risk in familial prostate cancer is not well studied. Here, we analyzed 25 previously reported SNPs across 14 loci from prior prostate cancer GWAS. The International Consortium for Prostate Cancer Genetics (ICPCG) previously validated some of these using a family-based association method (FBAT). However, this approach suffered reduced power due to the conditional statistics implemented in FBAT. Here, we

use a case-control design with an empirical analysis strategy to analyze the ICPCG resource for association between these 25 SNPs and familial prostate cancer risk. Fourteen sites contributed 12,506 samples (9,560 prostate cancer cases, 3,368 with aggressive disease, and 2,946 controls from 2,283 pedigrees). We performed association analysis with Genie software which accounts for relationships. We analyzed all familial prostate cancer cases and the subset of aggressive cases. For the familial prostate cancer phenotype, 20 of the 25 SNPs were at least nominally associated with prostate cancer and 16 remained significant after multiple testing correction ($p \leq 1E(-3)$) occurring on chromosomal bands 6q25, 7p15, 8q24, 10q11, 11q13, 17q12, 17q24, and Xp11. For aggressive disease, 16 of the SNPs had at least nominal evidence and 8 were statistically significant including 2p15. The results indicate that the majority of common, low-risk alleles identified in GWAS studies for all prostate cancer also contribute risk for familial prostate cancer, and that some may contribute risk to aggressive disease.

Varesco, L., V. Viassolo, et al. "Performance of BOADICEA and BRCAPRO genetic models and of empirical criteria based on cancer family history for predicting BRCA mutation carrier probabilities: a retrospective study in a sample of Italian cancer genetics clinics." *Breast*. 2013 Dec;22(6):1130-5. doi: [10.1016/j.breast.2013.07.053](https://doi.org/10.1016/j.breast.2013.07.053). Epub 2013 Sep 5.

PURPOSE: To evaluate in current practice the performance of BOADICEA and BRCAPRO risk models and empirical criteria based on cancer family history for the selection of individuals for BRCA genetic testing. **PATIENTS AND METHODS:** The probability of BRCA mutation according to the three tools was retrospectively estimated in 918 index cases consecutively undergone BRCA testing at 15 Italian cancer genetics clinics between 2006 and 2008. **RESULTS:** 179 of 918 cases (19.5%) carried BRCA mutations. With the strict use of the criteria based on cancer family history 173 BRCA (21.9%) mutations would have been detected in 789 individuals. At the commonly used 10% threshold of BRCA mutation carrier probability, the genetic models showed a similar performance [PPV (38% and 37%), sensitivity (76% and 77%) and specificity (70% and 69%)]. Their strict use would have avoided around 60% of the tests but would have missed approximately 1 every 4 carriers. **CONCLUSION:** Our data highlight the complexity of BRCA testing referral in routine practice and question the strict use of genetic models for BRCA risk assessment.

Weitzel, J. N., J. Clague, et al. "Prevalence and type of BRCA mutations in Hispanics undergoing genetic

cancer risk assessment in the southwestern United States: a report from the Clinical Cancer Genetics Community Research Network." *J Clin Oncol*. 2013 Jan 10;31(2):210-6. doi: [10.1200/JCO.2011.41.0027](https://doi.org/10.1200/JCO.2011.41.0027). Epub 2012 Dec 10.

PURPOSE: To determine the prevalence and type of BRCA1 and BRCA2 (BRCA) mutations among Hispanics in the Southwestern United States and their potential impact on genetic cancer risk assessment (GCRA). **PATIENTS AND METHODS:** Hispanics (n = 746) with a personal or family history of breast and/or ovarian cancer were enrolled in an institutional review board-approved registry and received GCRA and BRCA testing within a consortium of 14 clinics. Population-based Hispanic breast cancer cases (n = 492) enrolled in the Northern California Breast Cancer Family Registry, negative by sequencing for BRCA mutations, were analyzed for the presence of the BRCA1 ex9-12del large rearrangement. **RESULTS:** Deleterious BRCA mutations were detected in 189 (25%) of 746 familial clinic patients (124 BRCA1, 65 BRCA2); 21 (11%) of 189 were large rearrangement mutations, of which 62% (13 of 21) were BRCA1 ex9-12del. Nine recurrent mutations accounted for 53% of the total. Among these, BRCA1 ex9-12del seems to be a Mexican founder mutation and represents 10% to 12% of all BRCA1 mutations in clinic- and population-based cohorts in the United States. **CONCLUSION:** BRCA mutations were prevalent in the largest study of Hispanic breast and/or ovarian cancer families in the United States to date, and a significant proportion were large rearrangement mutations. The high frequency of large rearrangement mutations warrants screening in every case. We document the first Mexican founder mutation (BRCA1 ex9-12del), which, along with other recurrent mutations, suggests the potential for a cost-effective panel approach to ancestry-informed GCRA.

Yorczyk, A., L. S. Robinson, et al. "Use of panel tests in place of single gene tests in the cancer genetics clinic." *Clin Genet*. 2014 Oct 16. doi: [10.1111/cge.12488](https://doi.org/10.1111/cge.12488).

Improved technology has made it possible to test for mutations within multiple genes simultaneously. It is not clear when these gene 'panels' should be used in the hereditary cancer setting. These analyses were intended to guide panel testing criteria. Offering hereditary panel testing as a first and final, 'single-tier', option was explored. A 'two-tiered' approach, in which panel testing is offered reflexively following stricter criteria, was then applied to the same data. Within our cohort of 105 patients, the single-tier approach was associated with a higher mutation detection rate (6.7% vs 3.8%) and variant of

uncertain significance (VUS) rate (0.94 vs 0.23 average per person) compared to a two-tiered approach. Of the VUSs also identified in other patients by another lab, 53% were classified differently between laboratories. Individuals reporting African American race had more VUSs compared to other ancestry groups ($p = 0.001$). The test cost for a single-tier test was 21% more than a two-tiered approach. Single-tier panel testing was associated with higher mutation and VUS rates, and there is inconsistent classification of the VUS/low penetrant genes between laboratories.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

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