

# GENETIC TESTING IN PATIENTS WITH HEREDITARY CANCER RISK: SOCIAL, ETHICAL AND LEGAL CONSIDERATIONS\*

M. MÁRQUEZ  
K. BELKIC  
S. NILSSON  
A. R. HOLMBERG\*\*

SUMMARY: I. *Introduction*. II. *Hereditary cancers*. III. *Genetic screening tests*. IV. *Options for carriers of gene mutations*. V. *Cancer prediction models*. VI. *Medical/psychological aspects and social/cultural implications of genetic testing*. VII. *Ethical considerations in genetic testing*. VIII. *Legal issues in genetic testing*. IX. *Conclusions*. X. *Appendix: acronyms used in this text*.

\* We gratefully acknowledge the review and advice by Associate Professor Kerstin Sandelin, Division of Surgery, Karolinska University Hospital & Karolinska Institute, Stockholm, Sweden. The article is dedicated to Counselor Flora E. Sanchez Ferrari, who is a member of the Panama Catholic Church Commission of Justice and Peace and is the author of the Inform Consent law 68/2003, Panama. This work was supported by grants from the Cancer Society in Stockholm, The King Gustav V Jubilee Fund, Stockholm, The Swedish Cancer Society, Stockholm's County Council through FoUU at the Karolinska Hospital and the Swedish Scientific Research Council (Vetenskapsrådet).

\*\* Dr. Márquez is PhD in Biotechnology, Senior Scientist, Scientific Coordinator Karolinska Institute, Department Oncology-Pathology, CCK, 17176, Stockholm, Sweden, and Universidad Autónoma de Nuevo León, Professor UANL.

Dr. Belkic is Adjunct Professor of Preventive Medicine, M. D., PhD, and a physician specialist in Internal Medicine, Karolinska Institute and Institute for Health Promotion & Disease Prevention Research, University of Southern California, U. S. A.

Dr. Nilsson is M. D., PhD. Professor of Oncology, Nuclear Medicine Specialist, Urologic Oncology Chief Karolinska Institute.

Dr. Holmberg is M.D., PhD, Senior Scientist and Applied Chemistry Manager in the Urologic Oncology Group, Karolinska Institute.

## I. INTRODUCTION

### 1. *Genetic and environmental mechanisms and risk*

Numerous genetic alterations underlie the development of cancer in a multi-step process. These genetic variants can be transmitted through the germline and result in susceptibility to cancer, or they can arise by somatic (sporadic) mutation. One of the major aims of cancer research has been to identify the mutated genes that are causally implicated in oncogenesis (cancer genes). Mutations in at least 291 such genes have been reported, more than 1% of all genes in the human genome.<sup>1</sup>

The etiology of cancer is multifactorial including endogenous factors (genetics, hormones, and the immune system), exogenous exposures (chemicals, viruses, radiation, possibly night-shift work), lifestyle factors (smoking, obesity, alcohol, nutrition, low levels of physical activity).<sup>2</sup> Most cancers are considered sporadic and multifactorial in etiology.

In terms of incidence, the most common malignancies worldwide (excluding non-melanoma skin cancers) are lung, colorectal, gastric and breast cancer. Incidence and mortality data show that among males, lung cancer is the most frequent and the leading cause of cancer death, followed by gastric, prostate cancer and colorectal cancer. Among females, breast cancer is the most commonly-occurring cancer and leading cause of cancer-related deaths, followed by lung, colorectal, and uterine cervical cancer.<sup>3</sup>

It has been estimated that 5 to 10% of e. g. breast, colon and ovarian cancers result from defects or mutations in specific genes inherited through the germline.<sup>4</sup> Since the cancer risk is greater for these persons than the general public, special early detection and prevention options for specific cancers need to be considered. More than 700 test methods for selected cancer genes

<sup>1</sup> Futreal, P. A. *et al.*, "A Census of Human Cancer Genes", *Nature Rev.*, 4, 2004, pp. 177-183.

<sup>2</sup> Belkic, K., *Molecular Imaging Through Magnetic Resonance for Clinical Oncology*, Cambridge, Cambridge International Science Publishing, 2004; Wee, CC. *et al.*, "Obesity and Breast Cancer Screening", *J Gen Intern Med*, 19, 2004, pp. 324-331.

<sup>3</sup> Ustum, C. y Ceber, E., "Ethical Issues for Cancer Screenings Five Countries Four Types of Cancer", *Prev Med*, 39, 2004, pp. 223-229; Adami, H. O. *et al.*, *Textbook of Cancer Epidemiology*, Oxford, Oxford University Press, 2002.

<sup>4</sup> Chew, H. K., "Genetic Evaluation of Cancer: the Importance of Family History", *Tex Med*, 97, 2, 2001, pp. 40-45.

are available commercially, and physicians need to determine which patients are appropriate candidates for such tests.<sup>5</sup>

For some hereditary disorders, such as Huntington disease and Alzheimer's disease, effective medical interventions are either minimal or just emerging. For other inherited diseases, there are proven means of prevention, as is the case of dietary modification to prevent the development of mental retardation from phenylketonuria. Pre-symptomatic interventions can significantly reduce the future harm caused by some common malignancies. For example, surgical removal of the ovaries and the fallopian tubes (salpingo-oophorectomy) has been shown to reduce the risk of breast cancer by nearly 50% in women with BRCA mutations.<sup>6</sup> Other studies have demonstrated the efficacy of screening and prevention in hereditary breast, colon, thyroid, and other cancers. However, for some cancer syndromes, genetic risk may be incompletely defined and interventions may be ineffective.<sup>7</sup>

*Breast and ovarian cancer.* Women with hereditary forms of BRCA mutations, on average develop breast cancer at a younger age compared to women who are afflicted with sporadic breast cancer.<sup>8</sup> Family history of breast or ovarian cancer at a relatively young age (below 50) is considered one of the major risk factors for testing positive for a BRCA1 or BRCA2 mutation.<sup>9</sup> This will often mean that women at risk have lost their mothers, sisters and/or aunts at an early age. The emotional impact of this loss upon family members must be borne in mind, and may well affect decisions related to counseling, testing and opting for risk-reducing surgical procedures.

As mentioned, breast cancer is the most frequently-occurring cancer among women, and the leading cause of cancer-related deaths. In 1990, there were an estimated 796 600 newly diagnosed cases of breast cancer worldwide.<sup>10</sup> In Mexico, the incidence rate has increased substantially in

<sup>5</sup> <http://www.GeneTest.com>.

<sup>6</sup> Frank, T. S., "Hereditary Cancer Syndromes", *Arch Pathol Lab Med*, 125, 2001, pp. 85-90.

<sup>7</sup> Offit, K. *et al.*, "The «Duty to Warn» a Patient's Family Members about Hereditary Disease Risk", *JAMA*, 292, 12, 2004, pp. 1469-1473.

<sup>8</sup> Kuhl, C. K. *et al.*, "Management of Women at High Risk for Breast Cancer: New Imaging Beyond Mammography", *The Breast*, 14, 2005, pp. 480-486.

<sup>9</sup> Peshkin, B. N. e Issacs, C., "Evaluation and Management of Women with BRCA1/2 Mutations", *Oncology*, 19, 2005, pp. 1451-1460.

<sup>10</sup> Hankinson, S. y Hunter, D., "Breast Cancer", en Adami, H. O. *et al.*, *Textbook of Cancer Epidemiology*, Nueva York, Oxford University Press, 2003, pp. 301-309.

the last several decades<sup>11</sup> such that breast cancer is now the second most common cause of cancer mortality among women after cervix cancer.

Among the known genes involved in hereditary breast and ovarian cancer are BRCA1 and BRCA2. But other gene mutations that appear to confer breast cancer risk, include p53 (Li Fraumeni syndrome), ataxia-telangiectasia (ATM) and CHK2. Their precise contribution to the incidence familial and hereditary breast cancer has yet to be fully elucidated.<sup>12</sup>

It should also be recalled that transmission of the mutated BRCA gene can occur through males. For that and other reasons, genetic risk may not always be apparent. Specific referral guidelines for the identification of high-risk patients have been developed.<sup>13</sup>

Because BRCA mutations occur overall at a frequency of about 1 in 250 women,<sup>14</sup> there are probably at least 100,000 women in Mexico who are carriers. Female carriers of BRCA1/2 mutations have a 50% to 85% lifetime risk of developing breast cancer and between a 15% to 60% lifetime risk of developing ovarian cancer.<sup>15</sup> The risk of ovarian cancer among carriers of BRCA1 mutations (about 40%) exceeds that for carriers BRCA2 mutations (about 20%). BRCA2 carriers who develop ovarian cancer typically do so at an older age. Male carriers of BRCA2 mutations have an increased risk of developing breast cancer and prostate cancer.<sup>16</sup>

*Colorectal cancer.* Colorectal cancer accounts for about 11% of all cancer cases in the western world.<sup>17</sup> In Mexico, it is the second most common

<sup>11</sup> Ruiz Flores, P. *et al.*, "Breast Cancer Genetics. BRCA1 and BRCA2: the Main Genes for Disease Predisposition", *Rev Invest Clin*, 53, 2001, pp. 46-64; López Ríos, O. *et al.*, "La epidemia de cáncer de mama en México. ¿Consecuencia de la transición demográfica?", *Salud Pública*, México, 39, 1997, pp. 1-7.

<sup>12</sup> American Cancer Society, *Cancer Fact and Figures 2005*, Atlanta, American cancer Society, 2005.

<sup>13</sup> Hampel, H. *et al.*, "Referral for Cancer Genetics Consultation: a Review and Compilation of Risk Assessment Criteria", *J Med Genet*, 41, 2004, pp. 81-91.

<sup>14</sup> Narod, S. A. y Foulkes, W. D., "BRCA1 and BRCA2: 1994 and beyond", *Nature Rev.*, 4, 2004, pp. 665-676.

<sup>15</sup> Matloff, E. T. *et al.*, "What would you do? Specialists' Perspectives on Cancer Genetic Testing, Prophylactic Surgery, and Insurance Discrimination", *J Clin Oncol*, 18, 2000, pp. 2484-2492.

<sup>16</sup> Narod, S. A. *et al.*, *op. cit.*, nota 14.

<sup>17</sup> Liljegren, A., *Hereditary Colorectal Cancer: Predisposition and Prevention*, Karolinska Institute Thesis, 2004.

cancer of the gastrointestinal tract,<sup>18</sup> after gastric cancer.<sup>19</sup> Hereditary colorectal cancer often affects young persons (25-45 years age). It has been said that colon cancer may be the most familial of all human cancers, with at least 10-15% of these malignancies estimated to be hereditary. Some authors suggest that 30% or more of colorectal cancers are due to, at least in part, to an inherited risk. In hereditary non-polyposis colorectal cancer, genes MLH1, MSH2, and MSH6 mutations are found in to a varying extent (MMR genes).<sup>20</sup> Carriers of HNPCC mutations have a 65% to 85% lifetime risk of developing colon cancer. Moreover, female HNPCC mutation carriers have 30% to 40% lifetime risk of developing uterine endometrial cancer and up to a 10% lifetime risk of developing ovarian cancer.<sup>21</sup>

*Thyroid cancer.* While quite rare, thyroid cancer is one of the most commonly diagnosed malignancies among persons below 40 years of age.<sup>22</sup> An estimated 10-20% of thyroid cancers are medullary carcinomas (MTC), and it is believed that 25% of all MTC are hereditary, i. e. multiple endocrine neoplasia (MEN 2). The incidence of MEN 2 is estimated to be 1 in 500 000 live births. The great majority of MEN 2 are hereditary. The exception is the clinical subtype known as MEN 2B, where up to 40% occur as isolated cases, the result of *de novo* mutations.<sup>23</sup>

Breast, colon and thyroid (MEN) cancers are excellent examples of how cancer prevention can be highly effective in reducing incidence and cancer mortality. These prevention programs comprise genetic counseling and, when possible, predictive genetic testing. If the identification of mutation carrier is coupled with interventions that reduce morbidity and mortality, and prevent emotional disturbances, genetic testing could contribute to enhanced cancer control and to improved health in breast, breast/ovarian, colon and thyroid cancer families.

<sup>18</sup> Luna Pérez, P. *et al.*, "Colorectal Cancer", *Rev Gastroenterol Mex*, 62, 1997, pp. 175-183.

<sup>19</sup> Tovar Guzmán, V. *et al.*, "Epidemiologic Panorama of Stomach Cancer Mortality in Mexico", *Arch Med Res.*, 32(4), 2001, pp. 312-317.

<sup>20</sup> Liljegren, A., *op. cit.*, nota 17.

<sup>21</sup> Matloff, E. T. *et al.*, *op. cit.*, nota 15.

<sup>22</sup> Adami, H. O. *et al.*, *op. cit.*, nota 3.

<sup>23</sup> Eng, C. y Ponder, B. A. J., "Multiple Endocrine Neoplasia type 2", en Eeles, R. A. *et al.*, *Genetic Predisposition to Cancer*, 2a. ed., Nueva York, Arnold Publishers, 2004, pp. 105-118.

This article is based on a review of the principal contributions to this field and will set forth the major interests at stake for patients considering predictive genetic testing, some legal bases for protecting patients, and general ethical principles that may guide to all the persons interest in this field offering resolutions of dilemmas that arise in genetic testing. Our aim is to provide background information which will contribute to the development of genetic testing programs in Mexico, and that such programs will be consistent with international ethical and legislative norms, as well as taking into account cultural and social specificities.

## II. HEREDITARY CANCERS

Hereditary cancers are usually inherited in an autosomal dominant fashion, affecting multiple individuals of a family, both male and female, through every generation. By definition, hereditary defects are present at birth and in all somatic cells.<sup>24</sup>

The history of cancer genetics began 30 years ago when Alfred Knudson<sup>25</sup> proposed a two-hit hypothesis to explain why some people are at an increased risk for cancer, having germline defects of cancer genes, such as tumor suppressors. He compared hereditary retinoblastoma, an ocular cancer of childhood, with sporadic retinoblastoma.

Most people are born with two functional copies of a tumor suppressor gene. Two separate somatic events would need to occur to inactivate both copies of the gene, a process that takes years. In contrast, persons with an inherited predisposition are born with one mutated, non-functional copy and one functional copy of the gene. Only one event is required to completely inactivate the gene. Thus these individuals are at an increased risk to develop cancer and to develop tumors at a younger age than is the general population.<sup>26</sup> Thus, hereditary tumors would be caused by an inherited mutation and a somatic mutation, while non hereditary tumors would be the result of two somatic mutations.<sup>27</sup>

The most common mutation class among the known cancer genes is a chromosomal translocation (80%), with a minority being non translocations

<sup>24</sup> Futreal, P. A. *et al.*, *op. cit.*, nota 1.

<sup>25</sup> Knudson, A. G. Jr., "Mutation an Cancer: Statistical Study of Retinoblastoma", *Proc Natl Acad Sci USA*, 68, 1971, pp. 820-823.

<sup>26</sup> Adami, H. O. *et al.*, *op. cit.*, nota 3.

<sup>27</sup> Narod, S. A. *et al.*, *op. cit.*, nota 14.

(20%). Most classes of mutations only affect a single gene, or, at most, two genes in the case of translocations. The gene amplification can affect several mega bases of DNA and encompass many genes. There is sometimes ambiguity in the identification of mutated genes that are responsible for high-penetrance (high risk) cancer-susceptibility syndromes or of mutated genes that are associated with characteristic “non-neoplastic” manifestations, in addition to cancer predisposition. Germline variants of many genes have been proposed as low-penetrance cancer susceptibility alleles without additional non-neoplastic features. These low-penetrance genes confer a relatively lower added cancer risk compared to the high-penetrance cancer-susceptibility syndromes (see further discussion in section III).<sup>28</sup>

### 1. *Clinical clues to hereditary cancers*

The terms familial and hereditary cancer are use often synonymously, but there are important differences between these two entities. Familial cancer is the more encompassing term, and may include not only genetic transmission but also other endogenous factors, exogenous exposures and life-style patterns. The observation that cancer can run in families had already been reported before the Mendelian laws of inheritance were discovered 100 years ago.

Clues for the presence of familial cancer are:

- Two or more first-degree family members affected.
- The possibility of joint exogenous exposures that are related to the disease.<sup>29</sup>

Hereditary cancers actually represent a minority of the familial cancers. Three typical findings help identify a family with hereditary cancer:

- A family history with multiple affected close relatives in several consecutive generations.
- An early age of diagnosis compared with sporadic cases of the same disease.
- Bilateral cancers in paired organs and multiple primary tumors in one person.

<sup>28</sup> Futreal, P. A. *et al.*, *op. cit.*, nota 1.

<sup>29</sup> Hill, A. D. *et al.*, “Hereditary Breast Cancer”, *Br J Surg*, 84(10) 1997, pp. 1334-1339.

These clinical findings reflect the effect of the mutant gene.

In table 1 we show the relative contribution of hereditary and family cancer with respect to malignancies of the colon and breast.

TABLE 1. PERCENTAGE OF HEREDITARY AND FAMILIAL CANCER FOR TWO COMMON MALIGNANCIES

Cancer type	Hereditary	Familial
Colon	5%	10%
Breast	3-10%	20%

2. Cancer genetics

As mentioned, most syndromes associated with an increased risk of cancer demonstrate an autosomal dominant mode of inheritance. This is shown in figure 1 for the mode of inheritance of breast and ovarian cancer.

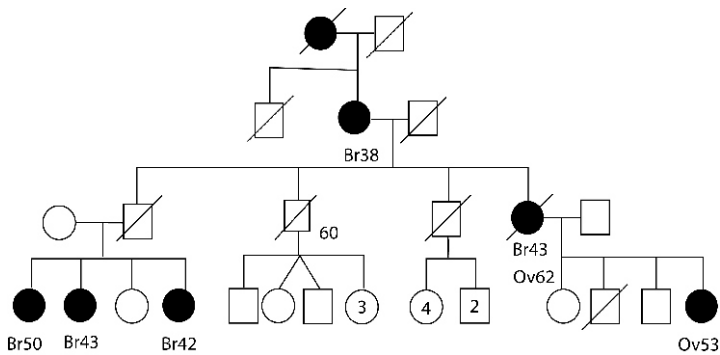


FIGURE 1. A typical cancer family with an autosomal dominant mode of inheritance of breast and ovarian cancer. Squares and circles denote males and females, respectively. Members afflicted with cancer are indicated by filled structures. Br 43=Breast cancer presenting at age 43 years; Ov 62 = ovarian cancer at age 62 years. A diagonal line indicates individuals who are deceased. Note the unaffected, deceased male (open square with diagonal line) gene carrier who had three daughters with breast cancer (After Lindblom, A. *et al.*, 2000).<sup>30</sup>

<sup>30</sup> Lindblom, A. y Nordeskjöld, M., “The biology of inherited cancer”, *Sem Cancer Biol*, 10, 2000, pp. 251-254.



In such kindred the affected members carry one mutant and one normal (wild-type) allele of the disease gene. The risk of each offspring inheriting the mutation is thus 50%. On average, one-half of the children of affected members will have the high cancer risk. The cancer risk for children of unaffected family members is low as on average that of the general population.

One of the most striking features of inherited cancer is that in one single family, different members may have different types of associated tumors. In breast cancer families, one patient may have both breast and ovarian cancer, while other relatives may have only breast or ovarian cancer. Some well-know syndromes like Li-Fraumeni syndrome or Lynch syndrome are associated with tumors in many organs.<sup>31</sup>

### 3. *Hereditary cancer syndromes*

#### *A. Hereditary breast and ovarian cancer. BRCA1 and BRCA2 genes*

In 1990, the first breast cancer susceptibility gene, designated BRCA1, was localized to chromosome 17 by a study of members of families with breast and ovarian cancer.<sup>32</sup> Since then, BRCA1 in 1994 and a second breast cancer gene, BRCA2 in 1995, have been cloned;<sup>33</sup> commercial testing for these two genes became available in 1997.

Both genes are believed to function as tumor suppressors possibly involved in DNA repair and transcriptional regulation; down-regulation of the estrogen receptor (BRCA1) and cell cycle control. Mutations in BRCA1/2 are associated with increased sensitivity to ionizing radiation.

BRCA1 and BRCA2 genes families are characterized by multiple cases of early onset breast and ovarian cancer. In the case of BRCA2, the otherwise rare, male breast cancer may be seen.<sup>34</sup>

<sup>31</sup> *Idem.*

<sup>32</sup> Hall, J. M. *et al.*, "Linkage of early-onset Familial Breast Cancer to Chromosome 17q21", *Science*, 250, 1990, pp. 1684-1689.

<sup>33</sup> Wooster, R. *et al.*, "Identification of the Breast Cancer Susceptibility Gene BRCA2", *Nature*, 378, 1995, pp. 789-792; Parthasarathy, S., "Architectures of Genetic Medicine: Comparing Genetic Testing for Breast Cancer in USA and the UK", *Social Studies Scien*, 35, 1, 2005, pp. 5-40.

<sup>34</sup> Adami, H. O. *et al.*, *op. cit.*, nota 3.

In contrast to most tumor suppressor genes, the breast and ovarian cancer genes (BRCA1/2) appear to be involved only in hereditary cancer and not in the corresponding sporadic forms.<sup>35</sup>

*B. Hereditary colorectal cancer: APC, MLH1, MSH2 or MSH6 genes*

Hereditary colorectal cancer has two syndromes. Familial adenomatous polyposis (FAP) is caused by a germline mutation in the APC gene that regulates  $\beta$ -catenins (proteins that bind to cell surface). FAP is characterized by hundreds to thousands of colonic polyps and almost inevitable colon cancer.<sup>36</sup> In hereditary nonpolyposis colon cancer (HNPCC), or Lynch syndrome, polyps are typically absent, whereas extra-colonic tumors including endometrial, ovarian, and genitourinary cancers are common. In contrast to FAP, HNPCC tumors result from the germline mutation in one of at least five mismatch DNA repair genes; MLH1, MSH2, PMS1, PMS2, MSH6.<sup>37</sup> Sequence analysis for mutations in APC and MLH1, MSH2 and MSH6, the mismatch repair genes mutated in most cases of HNPCC, is currently available. In addition, analysis for micro satellite instability, a hallmark of defects in mismatch repair genes, can be performed on suspected HNPCC-related tumors. These mutations can be detected in approximately 55% of the families, fulfilling the Amsterdam (AMS) criteria. These stipulate:<sup>38</sup>

- At least three relatives with colorectal cancer, or cancer of the endometrium, small bowel, urethra, or renal pelvis.
- One of whom is a first degree relative of the other two.
- At least two successive generations affected.
- At least one cancer diagnosed before the age of 50 years.

According to these criteria, investigations for MSH2 rearrangements should be included systematically in the routine diagnosis of HNPCC. The contribution of these alterations to HNPCC is higher than that of

<sup>35</sup> Lindblom, A., *op. cit.*, nota 30.

<sup>36</sup> Chew, H. K., *op. cit.*, nota 4.

<sup>37</sup> Akiyama, Y. *et al.*, "Germ-line Mutation of the hMSH6/GTBP Gene in an Atypical Hereditary Nonpolyposis Colorectal Cancer Kindred", *Cancer Res.*, 57, 1997, pp. 3920-3923.

<sup>38</sup> Di Fiore, F. *et al.*, "Screening for Genomic Rearrangements of the MMR Genes must be included in the Routine Diagnosis of HNPCC", *J Med Genet*, 41, 2004, pp. 18-20.

MSH6 mutations. Considering the lower frequency of MLH1 rearrangements, except in certain populations where they are associated with a small number of well-defined mutations. This is the so-called founder effect whereby a certain mutation is common to a specific population group and can theoretically be traced back to a common ancestor.<sup>39</sup> It is probably more efficient to search for HNPCC families when IHC staining of the tumors has revealed a selective loss of MLH1 expression.<sup>40</sup>

*C. Hereditary Multiple Endocrine Neoplasia type 2 (MEN2):  
RET proto-oncogene*

This gene, located on chromosomal sub-band 10q11.2, encodes a receptor tyrosine kinase expressed in neural and neuroendocrine organs and tumors. MEN 2A, which is the most common subtype, is characterized by a triad of MTC in virtually all cases, pheochromocytoma (PC) in 50% and hyperparathyroidism (HPT) 15-30% of cases. MEN 2B is similar to MEN 2A except that the age of tumor onset is before 10 years of age, and specific physical stigmata, such as mucosal neuromas, intestinal ganglioneuromatosis and marfanoid habitus, are seen. MEN 2 can present at any time from shortly after birth (MEN 2B) to over 70 years of age.

Since mutations of the RET proto-oncogene have been identified in more than 95% of all MEN 2 families, DNA-based testing is possible. All the relatives at 50% risk should undergo RET testing for the family-specific mutation prior to the age of 6 years. The exception is for MEN 2B. In MEN 2B families with a known mutation, at-risk relatives should be checked only for the family-specific mutation prior the age of 4 years. Routine RET testing in the management of MEN 2A, MEN 2B and all presentations of MTC is the standard of clinical care. This is because such genetic testing is sensitive and specific and the results alter medical management. It thus serves as a paradigm for the practice of molecular oncology.<sup>41</sup> While this is not a highly prevalent syndrome, it is an example of how genetic testing and clinical case profoundly impact upon health outcome.

<sup>39</sup> Lau, P. T. C. *et al.*, "Germ Line Mutations Associated with Breast Cancer Susceptibility", *Eur J Cancer*, 37, 2001, pp. 300-321.

<sup>40</sup> Di Fiore, F. *et al.*, *op. cit.*, nota 38.

<sup>41</sup> Eng, C. y Ponder, B. A. J., *op. cit.*, nota 23.

TABLE 2. SUMMARIZES SOME OF THE BETTER KNOWN HEREDITARY CANCER SYNDROMES

Cancer Type	Genes	Malignancies and Risk
Breast and ovarian	BRCA1, BRCA2, P53, CHK2, Ataxia telangiectasia (ATM), cowdens disease (PTEN)	Breast 50-97% (BRCA1/2), ovary 25-45% (BRCA1) 10-25% (BRCA2), male breast 6% (BRCA2), prostate carcinoma, pancreas and possible melanoma
Familial adenomatous polyposis (FAP)	APC	Colonic polyps and colorectal 100%; small intestinal adenomas and congenital hypertrophy of the retinal pigment epithelium, desmoid tumors and facial bone osteoma (Gardner syndrome) thyroid and brain (Turcot syndrome)
Hereditary non-polyposis colon cancer (HNPCC)	MLH1, MLH2, MSH6, PMS1, PMS2	Colorectal, endometrial 50-90%, gastrointestinal tract, biliary tract and renal pelvis
Multiple endocrine neoplasia type 2 (MEN 2)	RET proto-oncogene	Medullary thyroid carcinoma and pheochromocytoma 50%, hyperparathyroidism. (MEN2A); mucosal neuromas, ganglioneuromas, and characteristic facies (MEN 2B)
Li-Fraumeni syndrome	p53, CHK2	Breast 75-90%, soft tissue sarcomas, adrenocortical carcinomas, brain tumors, leukemias and others

Some common hereditary cancer syndromes, the implicated gene(s) and organs.<sup>42</sup>

<sup>42</sup> Bishop, D. T., "Genetic Predisposition to Cancer: an Introduction", en Eeles, R. A. *et al.*, *Genetic Predisposition to Cancer*, cit., nota 23, pp. 5-10.

### III. GENETIC SCREENING TESTS

The principal purposes of genetic testing are to diagnose disease, to identify inherited disease susceptibility, and to make possible the design of a prevention strategy and optimization of medical treatment.<sup>43</sup> Test procedures should be acceptable, safe, and relatively inexpensive.<sup>44</sup>

Genetic testing for cancer is still mainly used in North America, Europe, Australia and Israel. Some mutation surveys have been conducted in Asian countries. Africa and Latin America have not yet widely used this possibility, due mainly to scarce resources and attendant limitations in the development of health care services.

In the USA and the UK, *e. g.* the individuals is often directed to a test through the advice of a physician, but also this might occur by newspaper articles and direct marketing campaigns. Insofar as such market-driven efforts are undertaken with full implementation of all needed social, ethical and legal principles, especially genetic counselling, these commercial activities can have a positive effect by accelerating progress and disseminating these preventive measures.<sup>45</sup>

*Clinical management of those predisposed.* There are families in which a mutation can be found, although finding mutations in cancer-susceptibility genes remains technically challenging, with significant numbers of families having unrecognized mutations. Without an identified mutation, risk assessment is based on the 50:50 transmission of dominant inheritance. With identified mutations, risk assessment can be essentially certain with respect to mutation carrier status, whereas non-carriers have general population risk of cancer. In such circumstances, specific attention can be focused on those with the inherited predisposition.<sup>46</sup>

*Population screening.* In a population screening it is possible to identify a substantial number of new germline mutations, which occur in many cancer predisposition syndromes. The population screening until now is impractical because of the variety of mutations within any of the cancer-predisposition genes. There is no simple test, or small number of

<sup>43</sup> Burke, W. *et al.*, "Categorizing Genetic Test to Identify their Ethical, Legal, and Social Implications", *Am J Med Genet (Semin Med Genet)*, 106, 2001, pp. 233-240.

<sup>44</sup> Ustun, C. y Ceber, E., *op. cit.*, nota 3.

<sup>45</sup> Parthasarathy, S., *op. cit.*, nota 33.

<sup>46</sup> Bishop, D. T., *op. cit.*, nota 42.

tests, which could be performed on each gene on a population basis and it will be very expensive. There are nonetheless exceptions to this, such as approximately 2-2.5% of individuals of Ashkenazi Jewish origin carry one of three identified mutations (185delAG, 5382insC, 188del11) in the BRCA 1 and BRCA2 genes.<sup>47</sup> The success in a screening program depends on: identifying the type of cancer and the target population, selection of the proper technique, determination of the reduction of cancer mortality by a cancer screening program, evaluation and justification of the risk and benefits of the screening program.<sup>48</sup>

1. *Germ-line mutations leading to cancer susceptibility versus polymorphisms without major functional consequences*

As noted earlier, a mutation can be defined as any alteration in the primary DNA sequence, regardless of its consequences. Some mutations are lethal; others are harmful, while some can even be advantageous. Mutations which occur in the germline (i. e. in the sperm or oocytes) are then transmitted to the offspring. Other mutations occur during embryogenesis or in somatic tissues. Alternative forms of a given gene are termed "alleles". These alleles may be polymorphic variants without any apparent effect upon gene expression or function. Other variants may have only subtle effects upon gene expression, while yet other allelic variants may be the result of genetic mutations that lead to a clear change in protein function.<sup>49</sup> Polymorphisms can be defined as variations in alleles at a population frequency >1% and that have often been considered to be without major functional consequences, in and of themselves.<sup>50</sup> It should be noted, however, that polymorphisms especially in combination with other, possibly extrinsic factors may also be of substantial importance for cancer risk. In Mexico, e. g. it has been found that polymorphisms of certain cytokines may increase the risk of gastric cancer, in relation to

<sup>47</sup> Evans, D. G. R. y Morrison, P. J., "The Ethics of testing for Cancer-Predisposition Genes", en Eeles R. A. *et al.*, *Genetic Predisposition...., cit.*, nota 23, pp. 414-423.

<sup>48</sup> Ustun, C. y Ceber, E., *op. cit.*, nota 3.

<sup>49</sup> Jameson, J. L. y Koop, P., "Principles of Human Genetics", en Braunwald, E. *et al.* (eds.), *Harrison's Principles of Internal Medicine*, 15a. ed., Nueva York, McGraw-Hill, 2001, pp. 375-396.

<sup>50</sup> Adami, H. O. *et al.*, *op. cit.*, nota 3.

modification of the inflammatory response to *Helicobacter pylori*.<sup>51</sup> Another example is functional polymorphism of the progesterone receptor associated with a markedly increased risk of breast cancer among women with a body mass index > 30.<sup>52</sup> These two examples (and there are many more) underscore the fact that polymorphisms can indeed be of relevance if risk assessment for cancer is viewed within a multi-factorial framework. In contrast, genetic mutations that lead to changes in protein function of *e. g.* tumor suppressors, can lead more directly to marked susceptibility to cancer. These latter mutations have been the main focus of genetic testing for cancer.

With respect to *e. g.* the BRCA1 and BRCA2 mutations leading to a non-functional BRCA protein, approximately 80-90% lead to protein truncations. These are either small insertions or deletions, or are non-sense mutations that lead to the introduction of a stop codon. These mutations invariably generate a shortened and thereby non-functional BRCA protein.

## 2. Genetic screening test techniques

We now describe several of the most common techniques used for genetic screening tests.

*Reverse transcription-Polymerase Chain Reaction (RT-PCR).* In RT-PCR, the first step is to generate a DNA together with many copies of the messenger RNA of interest, using reverse transcriptase and the DNA is then used as a template for PCR reaction. The RT-PCR determines if a particular gene is expressed or not. As an internal control, co-amplification of an easily distinguishable control RNA template in the same reaction is often preferred.

*DNA sequencing.* Cycle sequencing (also called linear amplification sequencing) is built on a thermo cycling reaction, which employs one primer and includes dideoxynucleotide (ddNTP) chain terminator in the reaction. Generally, the primer or ddNTPs are attached with fluorophores.

<sup>51</sup> Garza González, E. *et al.*, "Role of Polymorphism of Certain Cytokines in Gastric Cancer in Mexico. Preliminary Results", *Revista Gastroenterología de México*, 68, 2003, pp. 107-112.

<sup>52</sup> Bradlow, H. L., "Steroids as Procarcinogenic Agents", *Ann NY Acad Sci*, 1028, 2004, pp. 216-232.

During electrophoresis, a monitor detects and record the fluorescent signals as the DNA passes through a fixed point in the gel.<sup>53</sup>

When sequencing is automatically performed, four separate fluorescent dyes are attached to a base-specific dideoxynucleotide. During the electrophoresis run a focused laser beam reads the fluorescence of the dyes, each having different wavelengths. The data are computer analyzed and are shown as curves with nucleotide-specific peaks.<sup>54</sup>

*Single Stranded Conformational Polymorphism analysis (SSCP).* This method is suitable for genomic fragments of up to 200 base pairs. The SSCP can detect different kinds of small aberrations like deletions, insertions and missense mutations. The detection rate is approximately 80%. Amplified denatured DNA products are forced to migrate electrophoretically in a polyacrylamide gel and visualized by radiolabeled primers or silver staining. The position of the mutation within the fragment is not revealed by SSCP.<sup>55</sup>

*Constant denaturant gel electrophoresis (CDGE).* The CDGE is suitable for screening fragments of up to 200 bases. The method is developed from the Denaturing Gradient Gel Electrophoresis (DGGE) and it is assumed to have a high detection rate (80-90%). A chain of GC bases is added to one of the primers in order to make strand heavier than the other. When the undenatured PCR fragment migrates through a denaturing gradient gel, it will melt because of the denaturing ability of the gel. If a mutation is introduced the conformation of the two strands will be different from un-mutated fragments. The GC chain is supposed to increase the sensitivity of the method. As in SSCP, the aberration found does not reveal the mutation position within the fragment.

*Protein Truncation Test (PTT).* Because of the preponderance of protein-truncating mutations, the research community quickly and widely adopted the *in vitro* translation technique also known as PTT. The test is rapid, inexpensive, allows detection of genomic deletions and reagents are available in kit form. It is an easily applicable method, suitable for large exons or for cDNA fragments of a length of 800 to 4000 base pairs. In the first step, PCR a T7 promoter and a eukaryotic translation initiating sequence are linked to a PCR primer. In a second step, the PCR product

<sup>53</sup> Lui, W. O., *Approaches for the Localization and Identification of Human Cancer Genes*, Karolinska Institute Thesis, 2002.

<sup>54</sup> Arver, B., *Hereditary Breast/Ovarian Cancer*, Karolinska Institute Thesis, 2001.

<sup>55</sup> *Idem*.



is used as a template in a coupled transcription-translation reaction in which radiolabeled amino acids are incorporated. The protein product is loaded on an electrophoresis gel and, if truncated, it will move faster than a protein of normal length. The method has a limitation, since it is not effective for screening short gene products and missense mutations.

Large rearrangements and big deletions will not be detected by any of these methods.

In contrast, DNA sequencing is able to identify rearranges and deletions that are large, and it is the ultimate method of choice to find most mutations with an accuracy near 98%. It is also used to finally identify the exact position of aberrations found with SSCP, CDGE or PTT.<sup>56</sup>

To ensure a comprehensive and sensitive “gold standard” some laboratories (Myriad Genetics) have developed a robotic sequencing technique to screen for mutations on a commercial basis.<sup>57</sup>

#### IV. OPTIONS FOR CARRIERS OF GENE MUTATIONS

The options for carriers of breast, FAB, HNPCC, MEN 2 mutations are: early and frequent surveillance, chemoprevention and prophylactic surgery.

##### 1. *Hereditary breast cancer*

###### *A. Surveillance*

There is no consensus about the actual time to enroll in control programs. However, many institutions offer women at increased risk to be followed at regular intervals where different image modalities are included, as well as frequent clinical breast examinations and training to perform self-examination of the breast on a very regular basis. The earliest age of onset in the family, can help indicate when this should be started (five years before the age of the youngest family member at the time of cancer detection). Currently, the recommended method is annual mammogram (notwithstanding its limitations) beginning at age 25.<sup>58</sup>

<sup>56</sup> *Idem*.

<sup>57</sup> Narod, S. A. y Foulkes, W. D., *op. cit.*, nota 14.

<sup>58</sup> Belkic, K., “Current Dilemmas and Future Perspectives for Breast Cancer Screening with a Focus on Optimization of Magnetic Resonance Spectroscopic Imaging by Advances in Signal Processing”, *Isr Med Assoc J*, 6, 2004 pp. 610-6118.

Mammography has less than optimal diagnostic accuracy plus entailing exposure to ionizing radiation. The problems with mammography are related to its poor specificity, the positive predictive value sometimes reported to be as low as 15-30%. The large numbers of false positive mammograms, lead to many biopsies of benign lesions. This is associated with considerable morbidity, not the least of which is anxiety, as well as rendering subsequent diagnostic evaluation difficult around the biopsy site. Moreover, the female breast is well recognized as a radio-sensitive organ. In addition, as mentioned, mutations in BRCA genes lead to impaired DNA repair, which further increased sensitivity to radiation. Also, mammography is less efficient in young women with dense breasts.<sup>59</sup>

Increasing interest is being generated by magnetic resonance (MR)-based methods for early detection and screening, especially for younger women at high risk for developing breast cancer.<sup>60</sup> One of the advantages of MR-based diagnostics is the lack of exposure to ionizing radiation for this radiosensitive tissue. This is especially important in view of the heightened radiosensitivity among those with genetic risk for developing breast cancer among women with BRCA germline mutations as well as for Li Fraumeni syndrome (p53 tumor suppressor gene mutations), and those who are heterozygous for ataxia-telangiectasia<sup>61</sup> and for whom screening should begin at a relatively early age and at frequent intervals.<sup>62</sup>

Contrast-enhanced MRI with fat-suppressed T1-weighting has a reported sensitivity between 95% and 100% for detection of breast cancer (Smith 2004).<sup>63</sup> It is especially useful for identifying cancers in dense breasts, as typically seen among younger women among whom cancers, unless calcified, are difficult to perceive using mammography.<sup>64</sup> Breast MRI is also considered superior to mammography for detecting multifocal or

<sup>59</sup> *Idem.*

<sup>60</sup> Smith, J. A. y Andreopoulou, E., "An Overview of the Status of Imaging Screening Technology for Breast Cancer", *Ann. Oncol.*, 15 (suppl. 1), 2004, pp. i18-i26.

<sup>61</sup> Kuni, H. *et al.*, "Mammography Screening-Neglected Aspects of Radiation Risks", *Gesundheitswesen*, 65, 2003, pp. 443-446; Laderoute, M. P., "Improved Safety and effectiveness of Imaging Predicted for MR Mammography", *Br. J. Cancer*, 90, 2004, pp. 278 y 279.

<sup>62</sup> Kuhl, C. K. *et al.*, *op. cit.*, nota 8.

<sup>63</sup> Smith, J. A. y Andreopoulou, E., *op. cit.*, nota 60.

<sup>64</sup> Kopans, D. B., *Breast Imaging*, 2a. ed., Philadelphia, Lippincott-Raven Publishers, 1998; Greendale, G. A. *et al.*, "Postmenopausal Hormone Therapy and Change in Mammographic Density", *J. Natl. Cancer Inst.*, 95, 2003, p. 30.

multi-centric cancers. However, false negative findings using MRI have been reported for small tumors, especially if they do not selectively take up the contrast agent. Furthermore, MRI cannot reveal microcalcifications,<sup>65</sup> and sometimes misses invasive ductal and lobular carcinomas, although non-detection with MRI occurs more frequently with *in situ* ductal carcinoma.<sup>66</sup> The major problem with MRI, however, is that despite excellent spatial resolution and generally superior sensitivity, it often has limited specificity, thus sharing with mammography a high false positive rate (overall, approximately 50%, with reports ranging from 37% to 97%).<sup>67</sup> In a recent prospective study among 1909 women with a genetic or familial predisposition to breast cancer, MRI showed better sensitivity for breast cancer, but lower specificity than mammography, i. e. MRI generated more uncertain findings, requiring follow-up or additional investigations.<sup>68</sup> Intensive surveillance programs with a large number of false positive findings may impact unfavorably upon quality of life.<sup>69</sup> Thus, questions still remain about the appropriateness of breast MRI as a screening tool in asymptomatic, high-risk patients, with the need to improve specificity particularly underscored.<sup>70</sup> Magnetic resonance spectroscopy (MRS) and spectroscopic imaging (MRSI) hold promise for improving the sensitivity of MRI by providing insights into molecular processes in addition to the morphologic information provided by MRI. However, both MRS and MRSI require further developmental work before they will be suitable for clinical practice. This developmental work is on-going, and

<sup>65</sup> Nass, S. J. *et al.* (eds.), *Mammography and Beyond: Developing Technologies for the Early Detection of Breast Cancers*, Washington, National Academy Press, 2001.

<sup>66</sup> Morris, E. A., "Breast cancer imaging with MRI", *Radiol Clin N Am*, 40, 2002, pp. 443-446.

<sup>67</sup> Katz-Brull, R. *et al.*, "Clinical Utility of Proton Magnetic Resonance Spectroscopy in Characterizing Breast Lesions", *J. Natl. Cancer Inst.*, 9, 2002, pp. 1197-1203; Kuhl, C. *et al.*, "Mammography, Breast Ultrasound and Magnetic Resonance Imaging for Surveillance of Women at High Familial Risk for Breast Cancer", *J Clin Oncol*, 23, 2005, pp. 8469-8476.

<sup>68</sup> Kriege, M. *et al.*, "Efficacy of MRI and Mammography for Breast-Cancer Screening in Women with a Familial or Genetic Predisposition", *N. Engl. J. Med.*, 351, 2004, pp. 427-437.

<sup>69</sup> Robson, M., "Breast Cancer Surveillance in Women with Hereditary Risk due to BRCA1 or BRCA2 Mutations", *Clin. Breast Cancer*, 5, 2004, p. 260.

<sup>70</sup> Smith, J. A. y Andreopoulou, E., *op. cit.*, nota 60.

includes optimization of data analytical techniques to enhance the acquisition of quantitative molecular information.<sup>71</sup>

At the present time, however, since none of the imaging modalities provides a clear advantage on its own, many clinicians find that a combination of these (including ultrasound) offers the best diagnostic strategy.

### B. Chemoprevention and risk reducing surgery

In a randomized trial NSABP P1 the use of Tamoxifen to high risk women was found to reduce the number of events, *i. e.* breast cancer.<sup>72</sup> However, another study could not demonstrate the same advantages.<sup>73</sup> Further trials are evaluating other compounds such as Raloxifene and Anastrozole, *e. g.* the STAR trial which may show favorable results with respect to chemoprevention).<sup>74</sup> It should be noted, that *e. g.* Tamoxifen is a synthetic anti-estrogen with a proven ability to reduce proliferation activity in estrogen-receptor positive breast cancers. Tamoxifen is, however, also associated with an increased risk of uterine endometrial cancer.

Prophylactic mastectomy and/or prophylactic oophorectomy are considered options for high-risk individuals in most European centers.<sup>75</sup> Bilateral prophylactic mastectomy reduces the risk of breast cancer in women with BRCA 1/2 mutations by approximately 90%.<sup>76</sup>

<sup>71</sup> Belkic, Dž y Belkic, K., "The fast Padé Transform in Magnetic Resonance Spectroscopy for Potential Improvements in early Cancer Diagnostics", *Phys Med Biol*, 50, 2005, pp. 4385-4408; Belkic, Dž y Belkic, K., "Mathematical optimization of *in vivo* NMR Chemistry through the fast Padé Transform: Potential relevance for early Breast Cancer Detection by Magnetic Resonance Spectroscopy", *J Math. Chem*, 2006, in press.

<sup>72</sup> King, M. C. *et al.*, "National Surgical Adjuvant Breast and Bowel Project. Tamoxifen and Breast Cancer Incidence among Women with Inherited Mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial", *JAMA*, *cit.*, nota 7, 14, 286, 18, 2001, pp. 2251-2256.

<sup>73</sup> Powles, T. J., "Anti-oestrogenic Chemoprevention of Breast Cancer-the Need to Progress", *Eur J Cancer*, 39, 5, 2003, pp. 572-579.

<sup>74</sup> Tobias, J. S., "Recent Advances in Endocrine Therapy for Postmenopausal Women with early Breast Cancer: Implications for Treatment and Prevention", *Ann Oncol*, 15(12), diciembre de 2004, pp. 1738-1747.

<sup>75</sup> Sandelin, K. *et al.*, "Oncological outcome after immediate Breast Reconstruction for Invasive Breast Cancer: a long-term Study", *Breast*, 13, 3, 2004, pp. 210-218.

<sup>76</sup> Rebbeck, T. R. *et al.*, "Bilateral Prophylactic Mastectomy Reduces Breast Cancer risk in BRCA1 and BRCA 2 Mutations Carriers: The PROSE Study Group", *J Clin Oncol*, 22, 2004, pp. 1055-1062; Hartmann, L. C. *et al.*, "Efficacy of Bilateral Prophylac-

The psychological consequences after risk-reducing surgery have been studied and show that the majority of women decrease their level of anxiety and are generally satisfied, but have problems in sexual relations and body image.<sup>77</sup>

## 2. Hereditary ovarian cancer

Compared to breast cancer, the situation with regard to ovarian cancer is more complex, because clinical manifestations appear in late stage of the disease. Recommendations for women with hereditary risk of ovarian cancer semi-annual or annual transvaginal sonography (TVS), in addition to clinical examination. The addition of Doppler flow imaging can improve the diagnostic accuracy of TVS, which alone has relatively low sensitivity. Some centers also begin measuring the tumor marker CA 125 at the age of 25 to 35 years. MRI is considered superior to CT for diagnosis of malignant ovarian masses and has been shown to increase the specificity for diagnosis of malignancy in adnexal masses considered suspicious by TVS. However, the distinction between benign and malignant ovarian masses is also difficult to make with MRI.<sup>78</sup>

Prophylactic oophorectomy has been shown to reduce the risk of breast cancer by nearly 50% in women with BRCA mutations and ovarian cancer risk by 85% to 95%, but it may be accompanied by menopausal symptoms, impaired quality of life, and accelerated bone loss.<sup>79</sup> The development of peritoneal carcinomatosis following oophorectomy has been documented in some instances to result from microscopic ovarian carcinoma present, but not diagnosed, at the time of the initial procedure.

Interventions to reduce the risk of a second cancer are considered to be as beneficial as chemotherapy with respect to life expectancy for a woman *e. g.*

tic Mastectomy in BRCA1 and BRCA2 Gene Mutation Carriers", *J Nat Can Inst*, 93, 21, 2001, pp. 1633-1637

<sup>77</sup> Hopwood, P. *et al.*, "Clinical follow-up after bilateral risk reducing (prophylactic) mastectomy: mental health and Body Image outcomes", *Psycho-oncol*, 9(6), 2000, pp. 462-472; Lostumbo, L. *et al.*, "Prophylactic Mastectomy for the Prevention of Breast Cancer", *Cochrane Database Syst Rev*, 4, 18 de octubre 2004, CD002748.

<sup>78</sup> Belkic, K., *op. cit.*, nota 2.

<sup>79</sup> Domchek, S. M., "Bilateral Risk-Reducing Oophorectomy in BRCA1 and BRCA2 Mutation Carriers", *J Natl Compr Canc Netw*, 4, 2, febrero de 2006, pp. 177-182; Olopade, O. I. y Artioli, G., "Efficacy of Risk-Reducing Salpingo-Oophorectomy in Women with BRCA-1 and BRCA-2 Mutations", *Breast J*, 10, 2004, pp. 5-9.

with BRCA-associated breast cancer.<sup>80</sup> Early detection of any recurrence is also of vital importance. For example, the disease-free survival of patients with a local recurrence of a small sized tumor (< 1 cm) after conservative surgery and radiotherapy was found to be substantially better than among those with larger local recurrences, according to a Dutch study. The authors<sup>81</sup> examined an unselected series of 266 patients with local recurrence after conservative surgery and radiotherapy for early breast cancer (BORST Group). They suggest that early detection of local recurrence can improve outcome. They also point to the need to examine biological behavior of breast cancers, as this may also affect the possibilities for early detection.

Oral contraceptives have been reported to reduce the risk of hereditary ovarian cancer. Longer duration of use appears to add to this reduction, and some reduction persists at least 15 years after cessation of use.<sup>82</sup>

However, there is some evidence, although not entirely consistent, that current or recent use of oral contraceptives confers a modestly increased risk of breast cancer.<sup>83</sup> The World Health Organization International Agency for Research and Cancer in June 2005 classified combination hormone contraception as carcinogenic to humans (Group 1), based upon evidence for risk of cervical and breast cancer as well as liver cancer, although confirming that there is "convincing evidence" of a protective effect against ovarian and endometrial cancer.<sup>84</sup> Bradlow and Sepkovic<sup>85</sup> point out that under certain circumstances (*e. g.* change in levels, metabolism as well as timing and interaction with other compounds) steroid compounds such as estrogen and progesterone can indeed act as pro-carcinogenic agents. There is, however, substantial debate and controversy about the WHO conclusions.<sup>86</sup>

<sup>80</sup> Frank, T. S., *op. cit.*, nota 6.

<sup>81</sup> Voogd, A. C. *et al.*, "Long-term Prognosis of Patient with Local Recurrence after Conservative Surgery and Radiotherapy for early Breast Cancer", *Eu J Cancer*, 41, 2005, pp. 2637-2644.

<sup>82</sup> Matloff, E. T. *et al.*, *op. cit.*, nota 15.

<sup>83</sup> Adami, H. O. *et al.*, *op. cit.*, nota 3.

<sup>84</sup> Cogliano, V. *et al.*, "Carcinogenicity of Combined Oestrogen-Progestagen Contraceptives and Menopausal Treatment", *Lancet Oncology*, 6, 2005, pp. 552 y 553.

<sup>85</sup> Bradlow y Sepkovic, "Steroids as Procarcinogenic Agents", *Ann N Y Acad Sci*, 1028, 2004, pp. 216-232.

<sup>86</sup> Schneider, H. P. G. *et al.*, "IARC Monographs Program on Carcinogenicity of Combined Hormonal contraceptives and Menopausal Therapy", *CLIMACTERIC*, 8, 2005, pp. 311-316.

### 3. *Hereditary colorectal and endometrial cancer*

The standard surveillance method in carriers of HNPCC mutations are fecal occult blood testing (FOBT) and full colonoscopy to the cecum every 1 to 3 years beginning between the ages of 20 and 25 years. The FOBT has a poor sensitivity and specificity and serial testing is recommended to increase sensitivity.<sup>87</sup> Virtual colonography with CT and MRI are potentially promising techniques that would be palatable to patients, however their diagnostic accuracy is still substantially lower than conventional colonoscopy which remains the gold standard.<sup>88</sup>

There are no agents approved to prevent colorectal cancer. Prophylactic subtotal colectomy with ileorectal anastomosis is an option for HNPCC carriers. This procedure may offer slightly greater gains in life expectancy for young HNPCC carriers than would surveillance alone.<sup>89</sup>

Endometrial cancer is also a risk for the HNPCC mutations carriers. Options for endometrial cancer surveillance include endometrial aspiration and transvaginal ultrasound procedures beginning between the ages of 25 and 35 years. MRI in screening for endometrial pathology, is not considered because the lack of specificity for early endometrial cancer.<sup>90</sup> Prophylactic hysterectomy is also an option.

### 4. *Thyroid cancer*

Relatives found not to carry the family-specific mutation are not at risk for ME 2 and can be spared unnecessary surgery, surveillance and psychological distress. Those relatives found to carry this mutation can then undergo surveillance and/or risk reducing surgery. Assessment for the RET mutation as a predictive test should be performed prior to age 6 for MEN 2A and FMTC (familial medullary thyroid carcinoma). When a RET mutation carrier is identified and has one or more tumors, then the

<sup>87</sup> Vilkin, A. *et al.*, "Performance Characteristics and Evaluation of an Automated-Developed and Quantitative, Immunochemical, Fecal Occult Blood Screening Test", *Am J Gastroenterol*, 100, 2005, pp. 1-7.

<sup>88</sup> Belkic, K., *op. cit.*, nota 2.

<sup>89</sup> Hodgson, S. V. y Murday, V., "Screening and Management of Familial Colon Cancer", en Eeles, R. A. *et al.*, *op. cit.*, nota 23, pp. 331-338.

<sup>90</sup> Belkic, K., *op. cit.*, nota 2.

tumors need to be removed. When a RET mutation carrier is identified and does not appear to have disease, risk reducing thyroidectomy should be performed, by removing three and a half or all four glands. Inheritance of this gene has enormous implications, since without surgery and removal of the thyroid the chances of developing medullary thyroid cancer are virtually 100%, and usually occurs in childhood. Medullary thyroid cancer appears even earlier in MEN 2B and is more aggressive. After the thyroidectomy the mutation carrier should be followed with annual serum calcitonin measurements, urine collection for catecholamines, vanillylmandelic acid (VMA) and serum chromogranin-A. A single pheochromocytoma screen should be performed prior to any surgery e. g. before risk reducing thyroidectomy.<sup>91</sup> Substitution for thyroid hormone exist so that this intervention is less controversial than for other hereditary cancer, although there are still major challenges involved due to the need to very early intervene in these children before they develop cancer. The long-term prognosis is excellent, with approximately 90% disease-free at 15 to 20 years post-thyroidectomy if performed before a palpable thyroid nodule appears.<sup>92</sup>

Some general screening guidelines for the population have been established for breast and colon cancer. These are summarized in table 3, where it should also be noted that some initial suggestions for breast cancer screening of women at high risk are included by the American Cancer Society.<sup>93</sup> These suggestions for women at high risk are considered to be preliminary and in need of further evaluation of their efficacy.

<sup>91</sup> Eng, C. y Ponder, B. A. J., *op. cit.*, nota 23.

<sup>92</sup> Sherman, S. I., "Disorders Affecting Multiple Endocrine Systems", en Braunwald, E. *et al.* (eds.), *Harrison's Principles of Internal Medicine*, 15a. ed., Nueva York, McGraw-Hill, 2001, pp. 2184-2191.

<sup>93</sup> Smith, R. A. *et al.*, "American Cancer Society Guidelines for Breast Cancer Screening: update 2003", *CA Cancer J Clin*, 53, 2003, pp. 141-169.



TABLE 3. NATIONAL SOCIETIES POPULATION SCREENING RECOMMENDATIONS FOR BREAST AND COLORECTAL CANCER IN THE USA, AUSTRALIA AND ENGLAND<sup>94</sup>

Cancer type	American Cancer Society/US Preventive Services Task Force (USPSTF)	Cancer Council Australia	National Health Service England.
Breast Cancer	<p><i>Women at Average Risk</i></p> <p>Mammography, age 40 to 69, every years Breast self-examination (BSE) over 20, monthly clinical breast examination age 20 to 39 every 3 years; over age 40 every year</p> <p><i>Women at Increased Risk</i></p> <p>No specific recommendations—suggestions that earlier initiation, shorter screening intervals, additional screening modalities such as MRI may be beneficial</p>	Mammography, 40 and over, every 2 years	Mammography, age 50 to 64 every 3 years Breast self-examination, all women, monthly
Colorectal Cancer	Flexible sigmoidoscopy, beginning at age 50 (people who are not at high risk have), every 5 years colonoscopy, beginning at age 50 (people who are not at high risk have), every 10 years	Fecal occult blood test (FOBT), age 50 and over, every 1-2 years	Fecal occult blood test (FOBT), age 50-69 (English colorectal screen pilot study)

## V. CANCER PREDICTION MODELS

Cancer researchers and clinicians are increasingly interested in statistical models designed to predict the occurrence of cancer. Strengths and

<sup>94</sup> Adapted after Ustum, C. y Ceber, E., *op. cit.*, nota 3; *idem*.

limitations of cancer/genetic, susceptibility/prediction models, present and future, need to be carefully evaluated.<sup>95</sup>

Accurate assessment of these probabilities is important given the potential implications for medical decision-making including the identification of patients who might benefit from preventive measures, genetic counseling or from entry into clinical trials.<sup>96</sup>

An important part of risk modeling is to obtain accurate relative risk estimates for etiologic factors, such as demographics, reproductive history, smoking, dietary patterns, medications, genetic factors (family history) and clinical and biologic markers (*e. g.* CA-125, alpha-fetoprotein, etcétera).

### 1. *Gail model*

The Gail model of absolute risk of cancer is based on information of 2,852 women with breast cancer and 3,146 controls selected from a population of 280,000 prospectively followed women. The model is appropriate to estimate risk of breast cancer in individuals not suspected of carrying a germline mutated breast/ovarian cancer gene. Factors such as current age, age at menarche, age at first live birth, family history, and number of breast biopsies were included when calculating the lifetime risk of breast cancer. Once a single gene trait is ruled out the tables and figures permit an estimation of a woman's risk to develop breast cancer in the next decade. A graph shown the woman's 10, 20 or 30 year absolute risk could be used.<sup>97</sup>

### 2. *Claus model*

This model is based on data set including 4,730 patients and 8,688 control subjects. The model considers one or two affected relatives,

<sup>95</sup> Freedman, A. N. *et al.*, "Cancer Risk Prediction Models: a Workshop on Development, Evaluation, and Application", *J Natl Cancer Inst.*, 97, 10, 18 de mayo de 2005, pp. 715-723.

<sup>96</sup> Claus, E. B., "Risk Models Used to Counsel Women for Breast and Ovarian Cancer: a Guide for Clinicians", *Fam Cancer*, 1, 3-4, 2001, pp. 197-206.

<sup>97</sup> Freedman, A. N. *et al.*, *op. cit.*, nota 95; Gail, M. H. *et al.*, "Projecting individualized Probabilities of Developing Breast Cancer For White Females who Are Being Examined Annually", *J Natl Cancer Inst.*, 81, 1989, pp. 879-886.

proximity of the relation, age at onset in relatives and the age of the person being counseled into account. The genotype effect is in function with the age. It includes tables that can be used for genetic counseling of women with a family history<sup>98</sup> There are other cancer risk prediction models such as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation (BOADICEA) susceptibility model by Antoniou and colleagues,<sup>99</sup> and the Colorectal Cancer Analysis Program (CRCAPRO) software statistical model use family history of colorectal and endometrial cancer to assess the probability that an individual carries a mutation of the MLH1 and MSH2 genes.<sup>100</sup> Both prediction models use a Mendelian approach that assumes autosomal dominant inheritance.

## VI. MEDICAL/PSYCHOLOGICAL ASPECTS AND SOCIAL/CULTURAL IMPLICATIONS OF GENETIC TESTING

### 1. *Medical and psychological aspects*

Genetic tests can be categorized according to two principal characteristics: their clinical validity (*i. e.* the accuracy with which a test predicts a particular clinical outcome) and the availability of effective treatment for the condition or risk status identified by testing. Those two characteristics will affect the ethical, social and legal implications of different genetic testing. It will also affect the mode of the non-directive counseling and informed consent procedures for different genetic tests.

#### A. *Testing*

A diagnostic test is performed, detecting DNA sequence alteration(s) known to be at high frequency in individuals affected with the disorder

<sup>98</sup> Claus, E. B., *op. cit.*, nota 96.

<sup>99</sup> Antoniou, A. C. *et al.*, "The BOADICEA model of genetic susceptibility to breast and ovarian cancer", *Br J Cancer*, 91, 2004, pp. 1580-1590.

<sup>100</sup> Bayes Mendel Laboratory. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University. Available at: <http://astor.som.jhmi.edu/BayesMEndel/crcapro.HTML/> [last accessed: december 1, 2004].

in question. Also, biochemical testing may be done on cells or specimens directly. A diagnostic test is undertaken involving the study of several family members, in order to determine the segregation pattern of the “at risk” locus. Markers are used, either flank or intragenic to the disease gene locus, providing accurate prediction of disease risk. In certain disorders, linkage studies provide the most accurate and cost-effective diagnostic testing if the disorder has significant mutation heterogeneity.<sup>101</sup>

### *B. Investigation procedures*

- The actual investigation usually proceeds as follows:
- Pedigree design.
- Preliminary analysis.
- Patient data journals or death certificate (with permission).
- Analysis.
- Determine whether or not there is hereditary high-risk for the specific cancer in the family.
- Genetic testing.

### *C. Categorization of genetic tests*

When an effective treatment exists and a genetic test identifies individuals who would benefit from such treatment, genetic testing seems highly justified. When an effective treatment is available and the risk for not performing such treatment is grave, health care providers may have an obligation to provide both testing and associated treatment to those who test positive.

The genetic test can be categorized in clinical validity and in the effectiveness of treatment available to people with positive results.

a) *High clinical validity: effective treatment.* The principal concern is to ensure that eligible persons are tested and have access to treatment. When the treatment is highly effective, it reduces the stigma of the condition. For example when a RET mutation carrier is identified and does not appear to have disease, the mutation carrier should undergo risk-re-

<sup>101</sup> Chew, H. K., *op. cit.*, nota 4.

ducing thyroidectomy, an effective treatment with thyroid replacement therapy following the intervention.

b) *High clinical validity: lack of effective treatment.* Here, psychological distress and potential for discrimination become very important. This category demands careful counseling which allows the individual to determine whether or not to proceed with testing. An example is Huntington's disease.

c) *Limited clinical validity (or low penetrance): relatively effective intervention.* A test with low predictive value may be acceptable when the label carries little emotional weight. It has to be a balance between the potential stigma and the effectiveness of the treatment. For example, there is a considerable uncertainty about BRCA1/2 mutations, depending on the nature of mutations, environmental factors and the setting of high risk-families (*i. e.* defined populations with the founder effect versus the general population). Interventions for BRCA 1/2 mutations, *i. e.* surveillance screening and risk reducing surgery are quite effective, although, as discussed, there is still need for further improvement.

d) *Low clinical validity: lack of effective treatment.* "When a test has poor ability to predict clinical outcome and there is no associated treatment, testing is difficult to justify on either medical or social grounds". It is reasonable to consider that testing in this category should not be offered, as illustrated in the strong consensus against ApoE genotyping to identify asymptomatic persons with risk of Alzheimer disease.<sup>102</sup>

#### D. Counselling. Counselling should be non-directive

Non-directive counselling is considered "a cornerstone of medical genetics practice, the counsellor provides information about genetic risk and explains choices regarding testing or management, but does not provide recommendations about the appropriate course of action".<sup>103</sup> The counselling will assist the patient to determine the best course of action consistent with his/her own personal values and preferences, rather than exclusively by medical indications. This will have implication for important decisions such as: terminating a pregnancy, childbearing and other life planning. The recommendations related to reproduction are particu-

<sup>102</sup> Burke, W. *et al.*, *op. cit.*, nota 43.

<sup>103</sup> American Society of Human Genetics, "Genetic Counseling", *Am J Hum Genet*, 27, 1975, pp. 240-242.

larly important, given the tainted history of genetics and eugenics in United States.<sup>104</sup>

The decision to be tested is rarely an autonomous decision based solely on the needs and preferences of the individual being tested. Rather, it is a socially situated decision, one that is often based on feelings of responsibility and commitment to other family members.<sup>105</sup> Because of the emotional impact in the family members, a professional genetic counselor is most often necessary.

Genetic counseling involves assessment of the accuracy of the diagnosis, discussion of the medical consequences of the disorder, the probability of developing or transmitting disease, and the ways in which it can be prevented or ameliorated. Genetic counseling also provides support to families, offering them patient-oriented literature, and helping them find ways to cope with the genetic condition.

#### *E. The procedure*

The genetic counsellor meets with the patient and/or family to gather pertinent data regarding the patient's genetic condition and the pedigree. She/he then applies genetic counselling to the specific diagnosis and family situation to render an explanation of the disorder and its recurrence risks. The counsellor also outlines appropriate genetic follow-up and provides support.

#### *F. Psychological consequences*

Genetic testing can have a major impact upon family relationships and psychological and social well being. Fear of genetic testing is largely due to the uncertainty that still surrounds its repercussions, in particular the fear that genetic information will cause harm (*e. g.*, denial of employment, education, financial loans, etcétera).<sup>106</sup> Overall, the option of risk-reduc-

<sup>104</sup> Eugenics Archive, 2001. Available at: [http:// vector.cshl.org/eugenics/](http://vector.cshl.org/eugenics/). American Society of Clinical Oncology, "Genetic Testing for Cancer Susceptibility", *J Clin Oncol*, 14, 1996, pp. 1730-1736 (commentary, pp. 1737-1740).

<sup>105</sup> Van Riper, M., "Genetic testing and the family", *J. Midwifery Womens Health*, 50, 2005, pp. 227-33.

<sup>106</sup> Lowrey, K. M., "Legal and Ethical Issues in Cancer Genetics Nursing", *Sem Oncol Nursing*, 20, 2004, pp. 203-208.

ing surgery should only be considered if the family or personal history of cancer has been verified. It should never be performed while a genetic test result is pending. The risk-reducing surgery must be the woman's own choice. Factors that need to be taken into consideration are that family communications may be poor, emotional distress is often high, such that worry about cancer can interfere with good decision-making. The long-term psychological impact of genetic testing is still not fully known both for carriers as well as for non-carriers of gene mutations. Psychological evaluation is essential prior to any risk-reducing surgery.<sup>107</sup>

A study of adolescent daughters of mothers with breast cancer, *e. g.*, revealed a high prevalence of concern about future health, underscoring the need for comprehensive programs entailing genetic and health risk assessment together with bolstering coping mechanisms and communication.<sup>108</sup>

Genetic counseling among women at increased risk for developing hereditary breast cancer has been demonstrated to reduce women's anxiety levels and improve the overall accuracy of perceived risk.<sup>109</sup> Moreover, a recent study of 519 women at high risk for breast cancer indicated that the intensive surveillance did not have an unfavorable impact upon health-related quality of life and general levels of distress. In fact, the women at high risk who chose regular breast cancer screening were found to have a better health status than women from the general population.<sup>110</sup>

## 2. Social/cultural implications of genetic testing

The social and cultural implications of genetic testing for Latin American countries such as Mexico are, in fact, an uncharted territory. We have very little direct empirical data from which to draw conclusions.

<sup>107</sup> Kash, K. M. *et al.*, "Psychological Issues in Cancer Genetics", en Eeles, R. A. *et al.*, *Genetic...*, *cit.*, nota 23, pp. 404-411.

<sup>108</sup> Cappelli, M. *et al.*, "Psychological and Genetic Counseling Implications for Adolescent Daughters of Mothers with Breast Cancer", *Clin Genet*, 67, 2005, pp. 481-491.

<sup>109</sup> Meiser, B. y Halliday, J. L., "What is the Impact of genetic counseling in women at increased risk of developing hereditary breast cancer?" *A Meta-Analytic Review. Soc Sci Med*, 2002, 54, pp. 1463-70.

<sup>110</sup> Rihnsburger, A. J. *et al.*, "Impact of Screening for Breast Cancer in High-Risk Women on Health-Related quality of Life", *Br J Cancer*, 91, 2004, pp. 69-76.

Some inferences, however, can possibly be suggested from the general experience of compliance with cancer screening guidelines of Latina populations, in *e. g.* the U. S., where this topic has been studied extensively. Perhaps one of the most important insights is that indeed cultural factors, particularly familism and fatalism can play a decisive role. Specifically, fatalism is seen as a critical barrier to compliance. On the other hand, familism, defined as the immediate and extended family as a source of support, belonging, identity, and purpose, can potentially be a promoter of compliance with cancer screening guidelines. It is vital that community health programmes explain that early breast cancer detection increases chances for survival dramatically, which would allow women to take better care of their family, *i. e.* by complying with cancer screening women are truly putting their families first. Seen in this light, familism has been suggested as a potential leverage point for helping Latina families at high risk for breast cancer to cope with this difficult situation and accept the need for additional surveillance and other measures.<sup>111</sup>

The importance of direct and personal communication is also emphasized. For example, among women of Mexican descent living in Southern California, *personalismo* defined as a warm and personal way of relating to an individual<sup>112</sup> has been found to improve participation in health-related studies and programs.<sup>113</sup>

A key message is that one cannot assume that the cancer screening behaviors are the same for Latin American peoples, as in the U. S. and Europe. Particular care should be taken to ensure that efforts in this area do not engender fear, but rather are friendly and inviting to promote maximum participation. Future work in implementing genetic testing programs for cancer risk in Mexico will need to pay very close attention to these social and cultural issues.

<sup>111</sup> Terán, L. M., "Correlates of Compliance with Mammography Screening Guidelines among low-income Latinas: an Exploratory Study", *Doctoral Dissertation*, Los Angeles, University of Southern California, 2004.

<sup>112</sup> Choca, P. R., "Dysfunctional Mexican-American family Patterns and Strategies for Intervention", en Marín, P. P. (ed.), *La Frontera Perspective, Providing Mental Health Services for Mexican Americans*, Tucson, La Frontera Center Inc., 1979, pp. 63-72.

<sup>113</sup> Terán, L. *et al.*, "An exploration of psychosocial determinants of obesity among Hispanic women", *Hisp J Behav Sci*, 24, 2002, pp. 92-103.



## VII. ETHICAL CONSIDERATIONS IN GENETIC TESTING

Several countries United States of America, Canada, Australia, England and Turkey have worked together to develop a common approach to screening programs with well-defined ethical principles. The latter include: informed consent, decisional capacity, decision-making, and confidentiality.<sup>114</sup>

Advances in molecular genetics have created bioethical dilemmas that confront today's physicians. Debates over research and screening ethics have until recently revolved around two related questions: the voluntary informed consent of subjects, and appropriate relationship between risk and benefit to the subjects.

Every patient has a right to full and accurate information about his or her medical condition. This legal principle took place primarily through court decisions concerning informed consent. Over time, physicians have recognized that most patients prefer to learn the truth about their condition and use the information well.<sup>115</sup>

The obligation, if any, to warn a family members of the identification of a cancer gene mutation has generated concerns regarding the conflict between the physician's ethical obligations to respect the privacy of genetic information *vs.* the potential liabilities resulting from the physician's failure to notify at-risk relatives.

### 1. *Major ethical principles*

Ethical decisions should be discussed in each country, as it would be impossible to impose a single international policy. Four of the basic principles of biomedical ethics are: 1) beneficence, 2) non-malevolence, 3) respect for individual autonomy and 4) justice. In simple terms, these principles mean that physicians should do good (beneficence), do no harm (non-malevolence), respect patients' wishes even if the medical professional disagree with an individual's decision (autonomy) and the right to be treated the same as others (justice, particularly vulnerable groups *e. g.* children, and the mentally ill).<sup>116</sup> When a physician's notion

<sup>114</sup> Ustun, C. y Ceber, E., *op. cit.*, nota 3.

<sup>115</sup> *Idem.*

<sup>116</sup> *Idem*; Marshall, K. G., "Prevention. How much Harm?, how much Benefit?, The Ethics of Informed Consent for Preventive Screening Programs", *Can Med Assoc J.*, 155, 1996, pp. 377-383.

of “beneficence” (an act done for the benefit of others) and the patient’s autonomy come into conflict, an ethical imperative may compel the physician to override the patient’s autonomy.

## 2. *Ethical rules in cancer genetics*

To protect the patients’ interest in genetic testing, the most salient ethical considerations are not principles, but rules that have been developed in light of these principles *i. e.* informed consent and confidentiality. Health providers should become familiar with laws regarding genetic information, confidentiality, genetic discrimination and informed consent.

## 3. *Full informed consent*

It is vital that the patient understands the nature of genetic testing and all of its potential implications (false-positive, false-negative, and inconclusive). The patient is free to apply his own value in deciding whether to follow the provider’s advice and how to use the information provided to resolve his or her own health problems. The moral aspects of informed consent ensure that the patient’s autonomy is respected, that the patient has an understanding of pertinent information and is free of controlling influences. “Legally effective informed consent” is essentially the right to self-determination: to decide what will be done to one’s own body.<sup>117</sup>

## 4. *The right not to know*

Just as important as an individual’s legal right to informed consent is the right to “informed refusal”: the legal right to obtain all pertinent information before refusing genetic testing. If the recommended test or treatment is itself risky, then the physician should always explain the potential consequences of declining to follow the recommended course of action. A patient must be informed of all physical, social, relational and psychological risk to oneself and loved ones, as well as all benefits of genetic testing.<sup>118</sup>

<sup>117</sup> Lowrey, K. M., *op. cit.*, nota 106.

<sup>118</sup> *Idem.*

There are potential areas of conflict in families, when the right of one individual to know may conflict with the right of a relative not to know. This conflict has been described with regard to testing children, and also when an offspring reveals a parent's genotype. Some reasons why a gene test may be refused are: because the test does not predict when the disease will appear, a positive result would impose too great a burden on partner/family, a negative test would generate guilt feelings in sibling relationships. It should also be mentioned that some individuals may even be reluctant to give up further screening, even though no mutation has been found. All of these reasons are applicable to a predictive gene test for cancer predisposition, although, unlike syndromes such as Huntington's chorea, screening and risk reducing surgery may prevent the disease. A decision to opt for a predictive test for Huntington and Li-Fraumeni should preceded by counseling.<sup>119</sup>

### 5. Confidentiality

Confidentiality in genetic information is an important ethical consideration especially in families with disease history, for whom genetic information may be viewed as a threat or a stigma. All family members are implicated when an individual reproductive function is affected and there is a risk that future generations are affected. For these reasons, autonomy, the patient's right to privacy, and confidentiality of the genetic testing results are generally accepted as the principal ethical considerations. The "duty to warn" of a cancer risk is by the individual with the cancer disease. But if the patient does not want to disclose information about cancer risk, the physician must do this. The American Society of Human Genetics<sup>120</sup> and the Commission for the study of ethical problems in medical, biomedical and behavioral research in United States of America.<sup>121</sup> suggest that genetic information could be released to relatives under certain conditions: a) unsuccessful obtaining consent for the

<sup>119</sup> Evans, D. G. R. y Morrison, P. J., *op. cit.*, nota 47.

<sup>120</sup> ASHG statement, "Professional Disclosure of Familial Genetic Information", *Am J Hum Genet*, 62, 1998, pp. 474-483.

<sup>121</sup> United States President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Screening and counseling for genetic conditions, a report on the ethical, social, and legal implications of genetic screening, counseling and education programs. Washington, US Government Printing Office, 1983, p. 53.

release, *b*) high probability of irreversible harm to a relative, *c*) the release has a high probability of preventing the harm and *d*) only the information necessary to prevent harm is released.<sup>122</sup>

A key assumption underlying the ethical justification for a “duty to warn” is the availability of medical interventions to reduce the risk of developing a disease or to lessen the ensuing harm. For hereditary disorders, such as some cancer forms (colon and breast), there are proven means of prevention. Presymptomatic interventions can significantly reduce the future harm caused by some common malignancies. However, for some cancer syndromes, genetic risk may be incompletely defined and interventions may be ineffective, and the impact of failing to warn relatives of their hereditary risk for cancer is less clear.<sup>123</sup>

#### *6. Testing in childhood, cancer predisposition genes*

Genetic testing is appropriate in a child if he/she will receive an immediate medical benefit, such as an early surveillance and treatment of early onset of cancer. Genetic testing in adopted children is justified only if it provides immediate medical benefit.<sup>124</sup>

There are some cancers that appear in childhood like familial adenomatous polyposis (FAP) (since the first year old children are 80% cases), MEN 2B, neurofibromatosis type 2 (NF2) and von Hippel Lindau disease (vHL), the phenotype is variable and diagnostic features may not be present until well into adult life. These individuals are at 50% prior risk and are usually screened for signs that may require mild (indirect ophthalmoscopy, “benign” disease markers, MRI (in older children)) to considerable invasiveness (sigmoidoscopy/colonoscopy). For children with risk of FAP, the DNA test would be offered in conjunction with ophthalmoscopy and dental screening. Insofar as an APC mutation of a given family has been identified, with DNA testing only the mutation-positive children would need endoscopic and other surveillance.<sup>125</sup>

<sup>122</sup> Lowrey, K. M., *op. cit.*, nota 106.

<sup>123</sup> Offit, K., *op. cit.*, nota 7.

<sup>124</sup> Lowrey, K. M., *op. cit.*, nota 106.

<sup>125</sup> Jarvinen, H. J., “Hereditary Cancer: Guidelines in Clinical Practice. Colorectal Cancer Genetics 2004”, *Annals of Oncology* 2004, 15, 4, pp. iv127-131.

In general DNA tests can be delayed until 16 years of age, with the exception of cancers that can appear during childhood. Table 4 provides some suggested guidelines for the timing of DNA-predictive test and screening of some of the most common hereditary cancers.

TABLE 4. GUIDELINES FOR TIMING OF DNA-PREDICTIVE TEST AND SCREENING SOME OF THE MOST COMMON HEREDITARY CANCERS<sup>126</sup>

Disease	Probable earliest tumor	Risk in childhood	Recommended start screening	Recommended start DNA test
FAP	First year	80%	10-16years	10-16 years
BRCA1 breast cancer	>16 years	<0.1%	Before 30 years	>18 years
BRCA2 breast cancer	>16 years	<0.1%	Before 30 years	>18 years
HNPCC	>16 years	<0.1%	25-30 years	>18 years
Multiple endocrine neoplasia (Men 2A)	3 years	2.5%	3-4 years	3-4 or 18+
Multiple endocrine neoplasia (Men 2B)	1 year	<50%	Birth	Birth

## VIII. LEGAL ISSUES IN GENETIC TESTING

Legislation should balance between the interest of the individual, the society, and the determination of who can obtain, use, and disclose genetic information. There are two principal areas of concern in genetic testing namely employment and insurance.

<sup>126</sup> Evans y Morrison, *op. cit.*, nota 47.

### 1. *Employment discrimination*

A reason for avoiding genetic testing is the fear of employment discrimination (*i. e.*, employers' use of genetic information in hiring, promotion, and salary decisions). Whether a genetic defect would constitute a "disability" or not has been disputed in the United States of America (Employment and Opportunities Commission and Americans with Disabilities Act, ADA, 1991). In the United States, it is prohibited to discriminate employees on the basis of genetic testing results, or information about a request for genetic testing services.

### 2. *Insurance discrimination*

Fear of losing health insurance is a major reason for avoiding genetic testing in many countries where private insurance is a major means of obtaining health care services. In the United States the Health Insurance Portability and Accountability Act (HIPAA) of 1996 provides some protection for those tested for a genetic predisposition to disease. HIPAA established strict confidentiality for the storage and transmission of health information and places narrow and precise conditions under which a covered entity may disclose such personal health information. It also prohibits the classification of genetic predisposition to disease as a pre-existing condition, which can be used to deny insurance coverage, unless the individual already has been diagnosed with that condition. The genetic information non-discrimination Act of 2003 (S. 1053) prohibits insurance or employment discrimination on the basis of genetic information.<sup>127</sup> However, if the cost of the test is covered by the insurer, there will be a strong conflict of interest that will deter truly confidential handling of this information so that it will not be used for other purposes by that insurer.

Legal and ethical considerations during a test for cancer-predisposition genes are given by the American Society of Human Genetics<sup>128</sup> and the American Society of Clinical Oncology<sup>129</sup> examples as follows:

1. Every patient has to have the right to full and accurate information about his or her medical condition. There are various reasons why some-

<sup>127</sup> <http://www.genome.gov/711510231>.

<sup>128</sup> ASHG statement, *op. cit.*, nota 120.

<sup>129</sup> American Society of Clinical Oncology Policy Statement Update, "Genetic Testing for Cancer susceptibility", *J Clin Oncol*, 21, 2003, pp. 2397-2406.

one may want to know if he or she has inherited the family gene fault: to have certainty; to plan having children; to plan appropriate action (risk reducing surgery); to inform children and/or partner; to plan future projects; to help clinical science.

2. As mentioned, the patients need to be aware of the limitations, potential risk, benefits and implications of gene testing.<sup>130</sup> The argument for giving patients relatively little information is based on benevolent paternalism or beneficence. This paternalistic approach is ethically unacceptable in most Western cultures, and it is generally accepted that patient should receive enough information to allow informed decisions or as much information as the patient freely chooses to have. The data should be provided in language that the patient can understand and that fosters independent thought, questions and decisions. Comprehension is as essential as disclosure.<sup>131</sup>

3. Full informed consent. Implies that patients assert their autonomy by playing an active role in decision-making, not merely agreeing to someone else's recommendations.

4. The general rule of confidentiality. Genetic information, like all medical information, should be protected by the legal and ethical principle of confidentiality. This principle is not absolute, and in exceptional cases, ethical, legal and statutory obligations may permit health professionals to disclose otherwise confidential information. A duty to warn could override the health professional's duty to maintain confidentiality, if disclosure of genetic information could foreseeable prevent serious harm.

The obligation to warn family members of the identification of a cancer gene mutation is a contentious area, when the affected individual specifically does not want to disclose information in a family who is at risk. It is the duty of people in this situation to inform their relatives

5. The right not to know might be applicable *e. g.* in genetic medical cases where it may take many years before any intervention is necessary (*e. g.* in childhood or in cases where no treatment is possible). Other examples include: when a positive result would be "too difficult to live with", expressed preference to live in uncertainty, problems at work and with insurance and when a positive result would impose too great a burden on partner/family.

<sup>130</sup> Chew, H. K., *op. cit.*, nota 4.

<sup>131</sup> Marshall, K. G., *op. cit.*, nota 116.

6. Prohibits discrimination or denial of health insurance or employment based on genetic testing.

7. Research samples. Individuals must be fully aware of the possible outcome of testing for research purposes. Informed consent must always be obtained. The samples should be anonymously coded and used for research purposes only.

8. Predictive DNA testing is not appropriate without informed consent and appropriate genetic counseling.

9. Regulations of the “analytic validity” have to exist for genetic testing services, to provide access to laboratory facilities in order to ensure proper procedure is carried out, with regard to the use of expertise, as well as the use of reagents and equipment.<sup>132</sup>

10. Clinical research protocols at academic medical centers must be approved by an Institutional Review Board. An ethical board must consist of physicians, scientists, and ethical experts. The Board must examine the research protocols in order to ensure that they are ethically and scientifically valid.<sup>133</sup>

### 3. *International positions regarding genetic confidentiality*

The majority of countries agree on permitting only limited disclosure of genetic test results (without the consent of the patient), if the potential harm to at-risk relatives is grave and imminent. Limited disclosure has been recognized at international and regional /national levels in United States of America. Internationally, both the World Medical Association (in its “Declaration on the Human Genome Project” [44th World Medical Assembly WMA 1992]) and experts advising the World Health Organization (WHO). Regarding these proposed guidelines on medical genetics and genetic services, the WMA and WHO recommend that confidentiality of genetic information should be maintained, except when family members are at high risk of serious harm and where disclosure could avert this harm.

At the regional level, the Council of Europe (1992), maintained that confidentiality of genetic information must be ensured at all times. It must be protected by the rules governing medical data. However, they make an

<sup>132</sup> Parthasarathy, S., *op. cit.*, nota 33.

<sup>133</sup> *Idem.*



allowance for disclosure in the case of severe genetic risk affecting the health of family members and their future children. The genetic data of a member of a couple cannot be communicated without the free and informed consent of the other member (Council of Europe 1990). In 1997 The Convention on Human Rights and Biomedicine allowed for the communication of genetic test results when necessary, *inter alia*, for the interest of public safety, the protection of public health or the protection of the rights and freedoms of others (Council of Europe 1997).

In the United Kingdom, the Nuffield Council on Bioethics (1993) accepted the confidentiality of medical information. It also recommended that if a patient refuses to disclose test results to family members, and if the physician has stressed the importance of sharing such information and has attempted to persuade the individual to allow disclosure, the patient's desire for confidentiality may be overridden, but only in exceptional circumstances. In Netherlands (1989) the Health Council holds the view that unauthorized disclosure may be permissible, under limited circumstances when serious harm can be avoided.

In Australia (1996) the Privacy commissioner recommends that an individual's right to privacy give way to the imperative to prevent harm, where the risk is serious, real, and imminent and "where there is a possibility of effective intervention and the consequences of non-intervention are serious for affected relatives".

In Japan (1996) the Society of Human Genetics, in its "Guidelines for Genetic Testing", recommends that where necessary to avoid serious injury, confidentiality can be broken, even in the absence of (subject) consent.

Norway and Sweden take the stand of protecting personal privacy, with no exceptions made for disclosure, even under extreme circumstances. Switzerland (1993) and France (1991) have established guidelines not permitting disclosure without the patient's consent. In a reiteration of this principle in 1995, the French National Ethics Committee stipulates that the principle of assistance to persons in danger, in the event of a subject's refusal, the physician is confronted with an ethical dilemma that must be resolved, particularly where children are involved.<sup>134</sup>

In Mexico, as in most of the above-mentioned nations, the harm of non-disclosure to relatives or spouse is considered to outweigh the po-

<sup>134</sup> Lowrey, K. M., *op. cit.*, nota 106.

tential harm of overriding patient confidentiality. In most of the nations, the “patient” is regarded as the family rather than the individual.<sup>135</sup>

## IX. CONCLUSIONS

Genetic testing can be a powerful tool in the struggle to reduce cancer morbidity and mortality. Genetic research is based upon scientific, ethical, social, and legal principles. Physicians need to be “up to date” and aware of a large and increasing amount of related information. The primary care physician must recognize individuals from hereditary cancer families and offer appropriate gene testing, plan risk-reduction strategies, and identify high-risk family members.

Regarding various genetic test categories, some have become routine within medical care, while others generate serious and legitimate concerns. For tests with high clinical validity leading to effective intervention, research needs to determine the best strategies to ensure access to testing and treatment. When the tests have limited predictive value, careful considerations are needed to provide clinicians and policymakers with pertinent information to determine appropriate test use. In the case of BRCA 1/2 mutation testing, the value of testing may vary according to different testing contexts.<sup>136</sup>

There are two principal clinical questions in this area: is this hereditary cancer due to a high penetrance genetic mutation versus familial but not recognizably hereditary cancer? Is the individual at risk of developing cancer?

The fact is that having close relatives with cancer (*e. g.* breast, colon, thyroid) generally increases one’s own risk. The risk is usually higher if cancer occurs at a young age in a family member.

Since breast and colorectal cancer are common and the tests involved are laborious and expensive, a strong family history or pedigree must exist before diagnostic testing, except in well-defined high-risk popula-

<sup>135</sup> Lisker, R. *et al.*, “Mexican Geneticist’s Opinions on Disclosure Issues”, *Clin Genet*, 54, 1998, pp. 321-329.

<sup>136</sup> Burke, W., *op. cit.*, nota 43.

tions. Criteria should be set at the clinical level for deciding which individuals should be tested.<sup>137</sup>

Limitations of assessing risk from family history of cancer need to be considered. For example, adoption, small family size, and inaccurate history may lead to erroneous conclusions about risk.<sup>138</sup>

Routine RET testing in management of MEN 2A/B is the standard of clinical care. This is because such genetic testing is sensitive and specific and the result alters medical management; it thus serves as a paradigm for the practice of molecular oncology.

For clinical decision-making it is important to incorporate biomarker data (*e. g.* p53 and Her-1), as well as imaging and genetic studies. These technologies can help clinicians and patients to decide which intervention to pursue and to help assess the impact of the interventions.

Regarding the treatment options for hereditary cancer *i. e.* surveillance, chemoprevention and risk-reducing surgery, each one of them may be the optimal strategy depending on the specific situation. Unlike preventive oophorectomy, preventive mastectomy is usually not propagated as “first-line” option for the management of women with familial breast cancer. If intensified surveillance is chosen, the starting recommendation of screening at age of 30 (at the latest), or 5 years prior to the youngest family member with the disease. Accordingly, screening intervals will have to be kept short compared with women at average risk. Mammography screening and magnetic resonance imaging (MRI), ultrasound-if integrated is usually recommended semi-annually usually accompanied by clinical breast examination and/or breast self-examination.<sup>139</sup> Magnetic resonance spectroscopy (MRS) and spectroscopic imaging (MRSI) are being explored in the research setting with the aim of optimizing breast cancer surveillance via molecular imaging without exposure to ionizing radiation. However, MRS and MRSI are not yet part of routine clinical practice.

General protective measures against cancer are also important for the gene mutations carriers. These include avoiding exposure to chemical carcinogens and radiation, maintaining a normal body weight and physical activity with healthy dietary intake and minimal alcohol intake. Decisions about the use of exogenous estrogens, progesterones, as well as

<sup>137</sup> Clinical Molecular Genetics Society, “Familial Breast Cancer”, 2003, [http://www.cmgs.org/BPG/Guidelines/1\\_ed/bc.htm](http://www.cmgs.org/BPG/Guidelines/1_ed/bc.htm).

<sup>138</sup> Freedman, A. N. *et al.*, *op. cit.*, nota 95.

<sup>139</sup> Kuhl, C. K. *et al.*, *op. cit.*, nota 8.

tamoxifen must be weighed particularly carefully. Needless to say, avoidance of smoking as the leading preventable cause of cancer deaths is always of high priority. Emerging evidence about risks such as extended periods of work on the night shift warrant careful attention as well.

Screening for breast and colorectal cancer reduce the risk of death by approximately 25% in breast and 20% in colorectal cancer in Western countries (Canada, Britain and United States of America). A further potential benefit of screening is a reduction in the trauma associated with the treatment of the disease. Tumors diagnosed at an earlier stage and smaller size needs less extensive surgery and chemotherapy. Each country has developed screening programs fitting to its own conditions. Ethical principles should be taken into consideration during the process (benefits, no harm).<sup>140</sup>

This genetic information has interpersonal and emotional implications and health professionals must provide a good support via genetic counseling during the process of genetic testing.<sup>141</sup>

Genetic testing for hereditary cancer has been a subject of intensive debate. The patient must have full and accurate information: limitations, risks, benefits and implications. With the right to be informed, the individual has to do his/her own life-altering decisions based on the risk of contracting hereditary cancer. The full-informed consent gives autonomy and active role decision-making. Here the genetic information should be individual as well as for his/her family. Individual self-determination, privacy and confidentiality of genetic information (medical and research) must be respected. Just as important as an individual's legal right to informed consent is his or her right to inform refusal (right "not to know") the legal right to obtain all pertinent information before refusing genetic testing.<sup>142</sup>

Ethical, legal and statutory exceptions limit the principle of confidentiality and in specific and very limited circumstances, may permit disclosure. The genetic test results are family information, and the patients who are diagnosed have the duty to inform to the family. If the patient refuses to inform, the physician has a positive duty to inform an individual about the potential risk for his/her relatives, if the risk is serious, imminent, likely and if prevention or treatment is available. If the physician refused to inform to the family, this can be considered medical negligence.

<sup>140</sup> Ustum, C. and Ceber, E., *op. cit.*, nota 3.

<sup>141</sup> Lowrey, K. M., *op. cit.*, nota 106.

<sup>142</sup> *Idem.*

Genetic testing is commercially available, and the priorities now are: quality control to assure optimal sensitivity, specificity, efficacy of the test and psychological support as genetic counseling. Now that tests are widely available, protection of confidentiality becomes a critical issue. It must be decided who first receives the results: each tested subject or the physician or the laboratory? Then we need to insure that this entity (hopefully a person) will not disclose the information. It is vital that only the person tested receives the information. Only with the consent of that person can any other person(s) receive this information.

Educational programs are needed both for the public and the medical community to understand the limitations of such screening tests and to recognize of the magnitude of the ethical, psychological and legal considerations.

We consider that these special preventive services which include the diagnostic evaluations/surveillance, all the psychosocial support services, especially genetic counseling, as well as any needed medical treatment should be provided within the framework of public health services.

The clinicians must be aware of the laws that govern genetic information, insurance discrimination, confidentiality, duty to warn, employment discrimination and most importantly, to ensure that the patient decision is fully informed.

We suggest that priorities in this area should be to:

- Create national standard and apply laws to respect social, moral, ethical, religious, values affecting the procurement and use of genetic information.
- Prohibit misuse of genetic information by employers (hiring, promotion, salary), by insurance companies, educational institutions or other kind of institutions.
- Communicate genetic screening research results (anonymously coded) to the appropriate scientific bodies, and support educational activities in the area of genetics.
- Create a genetic test counsel from an independent scientific and ethics advisory group, with experts from the fields of biology, ethics, sociology, law, together with community representatives.
- Establish health laws in Mexico to protect and limit the patient-medical doctor roles in the issue of genetic testing.

- To develop within the public health sector special preventive services for hereditary cancer, which include the diagnostic evaluations/surveillance, all the psychosocial support services, especially genetic counseling, as well as any needed medical treatment. These services should be part of a broader cancer prevention and early detection program for the entire population. Moreover, successful programs to protect those at high genetic risk can also inform and bolster the broader efforts to protect the entire population against the scourge of cancer.

#### X. APPENDIX: ACRONYMS USED IN THIS TEXT<sup>143</sup>

AMS	Amsterdam.
ATM	Ataxia-Telangiectasia.
BOADICEA	Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation.
CRCAPRO	Colorectal Cancer Analysis Program.
CDGE	Constant Denaturant Gel Electrophoresis.
ddNTP	dideoxynucleotide.
FAP	Familial Adenomatous Polyposis.
FOBT	Fecal Occult Blood Testing.
GC	guanine and cytosine.
HIPAA	Health Insurance Portability and Accountability Act.
HNPCC	Hereditary Non-Polyposis Colon Cancer.
MEN	Multiple Endocrine Neoplasia.
MR	Magnetic Resonance.
MRI	Magnetic Resonance Imaging.
MRS	Magnetic Resonance Spectroscopy.
MRSI	Magnetic Resonance Spectroscopic Imaging.
MTC	medullary carcinoma of the thyroid.
PTT	Protein Truncation Test.
NSAB BP1	National Surgical Adjuvant Breast and Bowel Project.
RT-PCR	Reverse Transcription-Polymerase Chain Reaction.
SSCP	Single Stranded Conformational Polymorphism Analysis.
TVS	Transvaginal Sonography.

<sup>143</sup> The common name of genes are also denoted by capital letters, which are not acronyms.