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Chapter 14

Challenges and Perspectives of the Risk Assessment of the Genetic Susceptibility to Cancer in the Next-Generation Sequencing Era

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Additional information is available at the end of the chapter

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Abstract

The risk assessment of the genetic susceptibility to cancer is the process of addressing and communicating the genetic risks to individuals and families with cancer. The recent breakthroughs of the next-generation sequencing era are adding new challenges to the precision clinical care.

Keywords: susceptibility, next-generation sequencing, cancer genetics

1. Introduction

New molecular biology technologies, such as whole-exome and whole-genome sequencing have been shedding new light on the understanding of inherited cancer susceptibility. At the same time, translational oncology researches on somatic and germline mutations in actionable genes have been opening new dilemmas of the next-generation sequencing era. A critical issue of the so-called precision medicine is the genetic counseling of individuals with cancer susceptibility.

Susceptibility to cancer depends on the penetrance of germline variants or inherited alleles, which may be classified into three groups such as highly penetrant, moderately penetrant and lowly penetrant alleles.

Alleles with high penetrance have the highest lifetime risk of cancer, frequently more than 10 times the relative risk, dramatically affecting the quality of life and decreasing its expectancy. More than 50 rare Mendelian cancer syndromes are caused by germline mutations affecting either tumor suppressor genes, DNA repair genes or proto-oncogenes, mostly with autosomal dominant inheritance (**Table 1**).

Syndrome	Gene	Mutation status	Penetrance	Tumors
Hereditary breast and/or ovarian cancer	*BRCA1*	Heterozygous	High	Breast cancer
	BRCA2			Ovarian cancer
	RAD51 (B,C,D)		Moderate	Pancreatic cancer
	ATM		Moderate	Prostate cancer
	CHEK2		Moderate	Colorectal cancer
Lynch syndrome	*MLH1*	Heterozygous	High	Colorectal cancer
	MSH2			Endometrial cancer
	MSH6			Ovarian cancer
	PMS2			Gastric cancer
	EPCAM			Leukemia, lymphoma
MMR cancer syndrome	MMR genes	Homozygous	High	Rhabdomyosarcoma
Familial adenomatous polyposis	*APC*	Heterozygous	High	Gastrointestinal adenomas
				Colorectal cancer
				Duodenal cancer
MYH-associated polyposis	*MUTYH*	Homozygous	High	Colorectal cancer
Polymerase proofreading-associated polyposis	*POLE*	Heterozygous	high	Colorectal cancer
	POLD1			Endometrial cancer
Bloom syndrome	*BLM1*	Homozygous	High	Leukemia
				Colorectal cancer
				Wilms tumor
Nijmegen syndrome	*NBS1*	Homozygous	High	Lymphoma
				Medulloblastoma
				Rhabdomyosarcoma
Fanconi anemia	*FANC* genes (includes *BRCA2*, *PALB2*, *BRIP1*)	Homozygous	High	Leukemia
				Medulloblastoma
				Wilms tumor
Li-Fraumeni syndrome	*TP53*	Heterozygous	High	Breast cancer
Li-Fraumeni-like syndrome	*CHEK2*		Moderate	Sarcoma
				Adrenocortical cancer
				Brain tumor
Cowden syndrome	*PTEN*	Heterozygous	High	Hamartomatous polyps
				Skin tumors
				Breast cancer
				Thyroid cancer
				Endometrial cancer

Syndrome	Gene	Mutation status	Penetrance	Tumors
Hereditary diffuse gastric cancer	*CDH1*	Heterozygous	High	Gastric cancer (diffuse)
				Breast cancer (lobular)
Peutz-Jeghers syndrome	*STK11*	Heterozygous	High	Hamartomatous polyps
				Colorectal
				Small bowel
				Breast cancer
				Pancreatic cancer
Juvenile polyposis	*SMAD4*	Heterozygous	High	Hamartomatous polyps
	BMPR1A			Colorectal cancer
				Pancreatic cancer
Melanoma syndromes	*CDKN2A*	Heterozygous	High	Malignant melanoma
	CDK4			Pancreatic cancer
Neurofibromatosis	*NF1*	Heterozygous	High	Vestibular schwannoma
	NF2			Meningioma
				Neurofibroma
				Optic glioma
Tuberous sclerosis	*TSC1*	Heterozygous	High	Renal angiomyolipoma
	TSC2			Subependymoma
				Giant cell astrocytoma
Von Hippel-Lindau syndrome	*VHL*	Heterozygous	High	Hemangioblastomas
				Renal cell cancer
				Pheochromocytoma
Chuvash polycythemia		Homozygous	High	Vertebral angiomas
Birt-Hogg-Dubè syndrome	*FLCN*	Heterozygous	High	Renal cell cancer
				Skin tumors
Papillary renal cancer syndromes	*FH*	Heterozygous	High	Renal cell cancer
	MET			
Retinoblastoma	*RB1*	Heterozygous	High	Retinoblastoma
Hereditary Paraganglioma	*SDH (A, B, C, D)*	Heterozygous	High	Paraganglioma
				Pheochromocytoma
Multiple endocrine neoplasia 1	*MEN1*	Heterozygous	High	Pituitary adenoma
Multiple endocrine neoplasia 2	*RET*			Parathyroid adenoma
				Medullar thyroid cancer
				Pheochromocytoma

Table 1. Hereditary cancer syndromes.

Alleles with moderate or intermediate penetrance increase the relative risk of about two to five times. Although they are rare in most populations, they may be frequently found in populations with consanguineous families due to founder effects. Affected relatives can be often identified, but the reduced penetrance of the alleles may skip generations and jeopardizes the family history.

Lowly penetrant alleles were discovered by genome-wide association studies (GWAS) and may put individuals to risk of cancer at slightly higher rates than those of the general population. This is due to a polygenic model, in which several alleles, mainly single nucleotide polymorphisms (SNPs), each one carrying a low risk, combine additively or multiplicatively to confer a range of risks in the population. In this model, individuals with few alleles would be at a reduced risk, whereas those with many alleles might suffer a lifetime risk as high as 50% [1]. It is estimated that more than 100 common variants with low risk may contribute to cancer susceptibility. Actually, they explain part of the excess familial risk, and the so-called "missing heritability" remains largely unknown [2]. Thus, it is very important to identify lowly penetrant alleles responsible for cancer genetic susceptibility. Most of these alleles are intergenic—lie between genes—and many neighbor tumor suppressor genes and proto-oncogenes, possibly affecting their expression. Nowadays, with the advance of next-generation sequencing and genotyping assays, more variants have been identified, shedding new light on the genomic architecture of the inherited susceptibility of cancer.

2. Risk assessment of the genetic susceptibility to cancer

The risk assessment of the genetic susceptibility to cancer (RAGSC) is a process to evaluate a personal risk of carrying a germline variant that is associated to the cancer development. RAGSC may be performed through statistical models that incorporate factors such as personal and familial history of tumors, ethnic background, and so on [3]. The advent of new sequencing technologies and bioinformatics has led to improvements of estimating more precisely risks of germline variants in many genes and assessing empiric risks of cancer.

Being part of this dynamic process [4], genetic counseling involves the analysis of pedigrees and risk assessment models to determine whether a family history is suggestive of sporadic, familial or hereditary cancer [5]. The main goal of genetic counseling is to inform susceptible individuals about their chances of developing cancer, helping them to make decisions about genetic testing, screening, prevention and treatments. Pretest and posttest genetic counseling are essential for the efficacy of implementing evidence-based protocols, in terms of reducing mortality rates [6].

Table 2 summarizes the RAGSC process. Three main risk categories can be derived on the basis of patient and family genetic information. In the low-risk category (near-population risk), management is based on population screening, and genetic tests are generally not cost-effective; in the moderate-risk group, genetic counseling, genetic testing and management are individual-based; in the high-risk group, genetic counseling, testing and management are evidence-based and improve survival [7].

Average risk	High	Moderate/intermediate	Low/populational
Personal/family history	Mendelian syndromes	Familial aggregation	Sporadic
Genetic testing	Single gene sequencing/NGS panels/WGS/WES	NGS panels/WGS/WES	DTC[&]/WGS/SNP genotyping
Genetic counseling	Mandatory	Advisable	Available
Management	Evidence-based	Individual-based[1]	Not validated

DTC: direct-to-consumer tests; WGS: whole-genome sequencing; WES: whole-exome sequencing.
[1]Some evidence-based screening recommendations exist for breast and colorectal cancers.
[&]Restricted by the US Food and Drug Administration.

Table 2. Overview of the risk assessment of the genetic susceptibility to cancer.

3. Referrals for RAGSC

Besides sex and age, familial history is the main unmodifiable risk factor of developing cancer.

Assessing the risk factors of cancer in an individual or family is complex and raises psychological, social and ethical issues. It requires the understanding of areas of medical genetics

Personal history
Early onset of cancer diagnosis (e.g., breast cancer <45 years, colorectal cancer <50 years)
Multiple associated primary cancers: breast/ovary, colorectal/endometrium
Male breast cancer
Ovarian, fallopian tube, primary peritoneal cancer
Breast cancer and thyroid, sarcoma, adrenocortical carcinoma
Multiple colon polyps (>10 cumulative)
Colorectal or endometrial cancer with microsatellite instability and/or lack of expression of mismatch repair protein(s) by immunohistochemistry
Family history
Three close relatives (same side of family) with cancer of the same or syndromically related type (breast/ovary, colorectal/endometrium)
Two close relatives (same side of family) with cancer of the same or related type with at least one affected under 50 years
One first-degree relative with early onset cancer (breast <45 years, colorectal <50 years)
One fist-degree relative with multiple primary cancers
Two or more relatives with uncommon cancers (sarcoma, glioma, hemangioblastoma, etc.)
Relatives of patients with known *BRCA, APC, MYH*, Lynch syndrome mutations
Many relatives with cancer but no criteria for testing

Table 3. Referrals for hereditary cancer risk assessment.

and oncology, besides the ability of communication, and it demands more time than just a regular consultation. The American Society of Clinical Oncology (ASCO), the National Society of Genetic Counselors (NSGC) and the Oncology Nursing Society (ONS) have published guidelines for the practice of genetic counseling, risk assessment and genetic testing [6, 8]. Moreover, it includes management of at-risk individuals so that they can make informed choices about cancer screening, prevention and targeted therapies [9]. In **Table 3**, there are some indications of referral for RAGSC.

4. Next-generation sequencing

In 2013, at first, Roberts and Klein reported the use of next-generation sequencing (NGS) to identify a hereditary cancer syndrome. They found pathogenic germline variants in the *ATM* gene of six pancreatic cancer relatives from two different kindreds [10]. Jaeger et al. used whole-genome sequencing for the description of hereditary mixed polyposis syndrome [11].

More recently, multigene NGS panels have been used to analyze many highly and moderately penetrant variants. Although they use the same NGS technology, there is less information on predefined genes. In comparison with single-gene sequencing, panels are more time- and cost-efficient in many cases such as (1) when there is genetic or locus heterogeneity, (2) when there are actionable mutations in several genes and (3) when phenotype or family history is too unspecific or noninformative (e.g., adoption) [12].

One advantage of NGS is the possibility of including multiple genes in panels tailored to a certain familial aggregation of tumors such as breast or colon cancer. However, because of its economic viability, NGS has shifted the phenotype-driven hypothesis approach that is based on the characteristics of the syndrome. Slavin et al. found some interesting results about multigene panels. When they included only high-risk genes, the results were seldom positive, and there were more variants of unknown significance (VUS), probably because of the inclusion of more genes in the so-called "off-phenotype" pan-cancer panels [13]. Recently, evidence-based guidelines have included the utilization of multigene testing for hereditary breast and ovarian cancer risk assessment [14].

An important disadvantage of NGS is the probability of disclosing inconclusive or undetermined results. The interpretation of a VUS based on phenotype and genotype data is a difficult task and often jeopardizes the genetic counseling process. Choosing a panel with limited genes of high clinical utility specifically driven to the phenotype instead of pan-cancer panels with many low-risk genes can diminish the chances of finding variants with stressful interpretation [13]. Moreover, databases of variants with high and moderate risks are often not population-specific and may lead to misinterpretation of results.

Some ethical challenges are critical for implementing NGS in the clinics.

In March 2013, the American College of Medical Genetics and Genomics (ACMG) published recommendations on the reporting of incidental or secondary findings from NGS. The ACMG suggested the identification of 56 genes whose variants result in a high risk of developing a severe disease. Germline mutations of 16 of these genes cause hereditary cancer syndromes (**Table 4**) [15].

Syndrome	Gene
Li-Fraumeni	*TP53*
Peutz-Jeghers	*STK11*
Familial adenomatous polyposis	*APC*
Von-Hippel Lindau	*VHL*
Multiple endocrine neoplasia	*MEN1* (type 1); *RET* (type 2)
Hamartomatosis	*PTEN*
Retinoblastoma	*RB*
Paraganglioma-pheochromocytoma	*SDHAF2*, *SDHB*, *SDHC*, *SDHD*
Tuberous sclerosis complex	*TSC1*, *TSC2*
Neurofibromatosis type 2	*NF2*
WT1-related Wilms tumor	*WT1*

Table 4. ACMG list of hereditary cancer syndromes.

In 2015, the ACMG reviewed it based on the consensus that patients could opt out of the analysis of secondary findings. This decision must be made during the process of informed consent, before testing. As some of these cancer syndromes may have the onset during childhood, these guidelines may also be applied to children, whose parents should make the decision whether or not to opt out [16].

A recent review showed that following the recommendations of international human genetic societies, parents and their children must be previously informed by a written consent about which findings should be reported. The ordering clinician must discuss with the children´s parents all the possibilities of results, including the reporting of incidental findings, the "right not to know," the risks and the benefits, as well is responsible to obtain the informed consent and to provide pre- and posttest genetic counseling [17].

5. Conclusions

Inevitably, more challenges will arise with the application of NGS in RAGSC.

First, pretest counseling and informed consent models need to be redesigned to address the multiplex testing. Novel approaches must be developed to ensure that individuals understand the risks and benefits of choices regarding these tests. Second, the clinical management of carriers of moderately penetrant variants is still poorly defined, although some evidence-based guidelines may include them [14]. Third, finding VUS is always a potential risk, and such identification complicates data interpretation and often requires further investigation and variant reclassification. In addition, management of patients with VUS is unclear. Finally, many hereditary cancer syndromes have locus heterogeneity, incomplete penetrance and may represent phenocopies, adding difficulty in RAGSC.

In summary, the biggest challenge in counseling families with cancer is conferring precise information regarding genetic susceptibilities because it allows a better informed decision-making process about risk management, clinical surveillance, targeted therapies and preventive measures.

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