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Review Article

Mini review: Molecular pathology of personalized medicine in cancer susceptibility syndromes

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ABSTRACT

In current times, medical oncology is increasingly incorporating cancer genetics and genetic testing into its practice. About 5–10% of all cancers are caused due to inherited genetic mutation that increases susceptibility to a particular malignancy. There is an increasing practice of incorporation of genetic testing and results with potential benefits that have been seen in current-day oncology practice. The American College of Medical Genetics and Genomics highly advises conducting clinical molecular genetic testing within a laboratory that has received CLIA approval with results accurately interpreted by molecular geneticists. The patient is highly recommended to talk to a genetic specialist to explain about the risk, document the family history, and also explain the limitations and outcomes of the genetic testing. Nonetheless, significant discussions and ambiguity persist regarding the optimal approach for providing genetic testing services. These include considerations such as which tests should be employed, which patients should undergo testing, the order and timing of the tests, who should administer them, and the appropriate course of action for follow-up.

Keywords: Molecular pathology, Personalized medicine, Cancer susceptibility syndromes, Solid tumors, Hematological malignancies

INTRODUCTION

Familial cancers can occur in multiple individuals within the same family but are not caused due to single gene mutation.[1,2] These type of cancers cluster within families but are not hereditary in nature and result from a combination of various factors, such as multiple genes, and lifestyle factors such as diet and exercise, which collectively increases the risk of developing cancers.[3] Hereditary cancers are caused due to germline mutations in specific genes that are inherited from either one or both parents and are associated with susceptibility to particular cancers. Mostly autosomal dominant in nature, meaning the probability of 50% passing on this mutation or change to the next generation.[4] An individual who tested positive on a hereditary cancer test has more than one pathogenic variant in 3.1% of cases.[5] While germline mutations occur in all the cells of the body, cancers that are non-hereditary or sporadic are caused due to genetic mutations in the tumor cells or tissues concerned. These mutations are known as somatic mutations and are not inherited by the next generation.

A few of the cancers follow autosomal recessive patterns of inheritance, such as *MUTYH*-associated polyposis (MAP). MAP is associated with germline mutations in both the copies of

the *MUTYH* gene, one copy of each mutated allele inherited from the maternal and paternal sides. Patients developing colon cancer at an early age and having healthy parents and/or the presence of 15–20 colonic adenomas are indications of the possibility of MAP in an individual.[6]

Hereditary basis of breast cancer was first described by Broca more than a century ago in 1866 when he reported breast cancer in multiple family members.[7] Warthin and Henry Lynch reported distinct patterns of early age onset and multiple primary tumors in the same individual with colon cancer.[8,9] Li and Fraumeni described the clinical characteristics of families with p53 germline mutations as Li-Fraumeni syndrome (LFS) in the subsequent years.[10] In 1971 Knudson propound the two-hit hypothesis in Retinoblastoma (RB), where he suggested that the patients who had bilateral RB carried an inherited gene mutation along with an acquired second mutation.[11] Later, Friend SH *et al*. also confirmed the same hypothesis by and reported a high incidence of 2nd non-ocular tumor which was believed to be caused by the same mutation.[12]

There have been more than 100 distinct syndromes found, and the majority are rare.[13] About 5–10% of all cancers are caused due to inherited genetic mutation that increases susceptibility to a particular malignancy.[4,14] Being familiar with the more-prevalent syndromes, such as hereditary breast and ovarian cancer, Li-Fraumeni, Lynch Syndrome (HPNCC), familial adenomatous polyposis (FAP), RB, multiple endocrine neoplasia, and Von Hippel-Lindau (VHL) can help health-care professionals recognize different signs and symptoms in a patient as potentially having a genetic component, allowing for appropriate diagnostic testing and referrals.[4]

There has been a tremendous advancement in next-generation sequencing (NGS) technologies in the last 30 years. The application of massively parallel sequencing in germline and somatic cancers has become clinically important. Germline testing assists in identifying the risk of inherited cancer in an individual and at-risk family members and benefit in risk-reducing measures and cancer surveillance.[14] While somatic testing helps in therapeutic options for targeted therapies and immunotherapies.[15] Although germline and somatic testing are carried out independently oftentimes in diagnostic laboratories, integrating both approaches to provide optimal care for individuals affected with diverse forms of cancer.[16-18]

PENETRANCE AND EXPRESSIVITY

Penetrance is a measurement of the proportion of individuals in a population who carry a particular pathogenic mutation and exhibit the disease phenotype. For example, Mutations in the *RB1*, *APC*, *BRCA*1 and 2, *PTEN* genes as mentioned in [Table 1]. But in some syndromes, the association between the gene and its expressivity is reduced, like incomplete penetrance shown in Wilms tumor.

The degree to which a genotype manifests its phenotypic expression is measured by expressivity**.** Different levels of expression in different people may result from variations in the allelic makeup of the rest of the genome or from environmental influences. Thus, expressivity quantifies the degree to which a genotype is phenotypically expressed in individuals, as opposed to penetrance measurements that concentrate on whether or not a disease is expressed in a population.[19,20]

Understanding the penetrance and expressivity of cancer-predisposing genes is significant in understanding the

Table 1: Few examples of significant cancer susceptibility syndromes, their patterns of inheritance, and penetrance.[19]

Cancer syndrome	Gene	Main tumor type	Penetrance	Patterns of inheritance
FAP	*APC*	Colorectal carcinoma	70–100%	Autosomal dominant
Cowden's syndrome	*PTEN*	Breast, endometrium, follicular thyroid tumor	90–95%	Autosomal dominant
HBOC	*BRCA1* and *BRCA2*	Breast/ovary	Up to 85%	Autosomal dominant
LFS	*TP53*	AML, sarcoma, adrenocortical Carcinoma	90–100%	Autosomal dominant
Lynch syndrome/HNPCC	*MLH1, MSH2, MSH6, PMS1, PMS2*	Colorectal, endometrium, brain	90%	Autosomal dominant
RB	*RB*	Eye, bone	90%	Autosomal dominant
Wilms' tumor syndromes	*WT1*	Nephroblastoma	30% incomplete	Autosomal dominant
Gorlin syndrome/NBCC	*PTCH1*	Basal cell carcinoma/ medulloblastoma	90%	Autosomal dominant
ATS	*ATM*	Lymphomas, leukemia	100%	Autosomal recessive
FA	*FANCA*, *FANCB*, *FANCC*, *FANCD*, *FANCE*, *FANCF*, *FANCG*, *FANCL*	Acute myeloid leukemia	100%	Autosomal recessive
BS	*BLM*	Wilms tumor, colorectal cancers, Leukemia	100%	Autosomal recessive

FAP: Familial adenomatous polyposis, HBOC: Hereditary breast and ovarian cancer syndrome, LFS: Li-Fraumeni syndrome, HNPCC: Hereditary nonpolyposis colon cancer, NBCC: Nevoid basal cell carcinoma, ATS: Ataxia-telangiectasia syndrome, RB: Retinoblastoma, FA: Fanconi anemia, BS: Bloom syndrome

complexity of hereditary cancers and improving genetic counseling for patients as well as family members.[19]

INDICATIONS FOR GERMLINE CANCER TESTING INCLUDES

1. Breast cancer diagnosis in ≤50 years age: Triple negative subtype or Lobular Carcinoma; Male Bilateral/multiple primary, Ashkenazi Jewish Ancestry, Breast cancer and one additional tumor (LFS, ≥1 PJ polyp, Cowden syndrome).
2. Colorectal cancer (CRC) diagnosed at age <50: Mismatch repair deficient; multiple primary synchronous or metachronous CRC; ≥10 adenomatous or >5 hamartomatous gastrointestinal polyps; association with other cancers – endometrial, LFS, Cowden syndrome criteria.
3. All women are diagnosed with ovarian cancer whether it is a single case present in the patient or a first-degree relative. *BRCA1* and *BRCA2* pathogenic germline variants are detected in the vast majority of ovarian cancer patients, specifically with high-grade serous histology.
4. Prostate cancer diagnosed at any age: Intraductal/ cribriform histology, Gleason score ≥7; metastatic, regional (node-positive) or very-high-risk localized prostate; Ashkenanzi Jewish ancestry.
5. Pancreatic cancer diagnosed at any age: Intraductal papillary mucinous neoplasm histopathology.
6. Patients diagnosed with renal cancer, having age of diagnosis <50; Bilateral or multifocal tumors; ≥1 close relative renal cell carcinoma (RCC) with clear cell, papillary type 1, papillary type 2, collecting duct, tubulopapillary and Birt-Hogg-Dubé (BHD)-related histology, Fumarate hydratase (FH) associated RCC.
7. Thyroid cancers with Medullary subtype, a cribriform morular subtype of papillary thyroid cancer Papillary/ follicular thyroid cancer, and additional carney complex or Cowden syndrome.
8. Gastric cancers: Diffuse type, signet ring cell type, and mismatch repair deficient.
9. Melanoma: Melanoma and pancreatic cancer/ Astrocytoma in the same person.
10. Lynch syndrome-related cancer (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma) and the tumor shows evidence of mismatch repair (MMR) deficiency (either by microsatellite instability or loss of MMR protein expression).[21]

CATEGORIZATION OF GENETIC SYNDROMES BASED ON MOLECULAR PATHWAYS

The syndromes are supposed to be activate pathways that lead to uncontrolled proliferation, increased angiogenesis, or defective repair.

- Defect in PI3K/AKT/mTOR pathway: This is the most common pathway activated in cancer, which leads to the formation of hamartomas/overgrowth syndromes. Cowden syndrome (*PTEN* gene), Proteus syndrome (*AKT1*), Tuberous sclerosis complex (*TSC1/2*), Von Recklinghausen disease (*NF1* and *NF2*).[22]
- Defect in the RAS/RAF/MEK/ERK pathway: RASopathies, Von Recklinghausen disease (*NF1* and *NF2*).[23]
- Defect in angiogenesis: *VHL*
- Defects DNA repair mechanism: Hereditary breast and ovarian cancer syndrome, Lynch syndrome, LFS
- Defect in growth factor regulation: Gorlin syndrome (*PTCH1*)
- Others: FAP (*APC*).

TECHNIQUES

NGS-based methods are used to rapidly sequence known cancer-associated genes for identifying germline mutations at once or identify novel germline variants linked to cancer. NGS platforms allow researchers to sequence millions of DNA fragments in parallel, greatly accelerating the process and reducing the cost per base. The high-throughput data generated through NGS make them particularly valuable for understanding complex diseases, including cancers. Among different cancers, there is significant interest in studying those with a familial predisposition, as they offer opportunities to identify novel genes or gene variants that contribute to cancer development and can be detected at the germline level, thus playing a role in cancer pathogenesis.[24,25]

Multiplex-Ligation Dependent Probe Amplification is another technique that identifies large deletions/duplications in genes. It combines aspects of both polymerase chain reaction and hybridization techniques to analyze the copy number of specific DNA sequences.[26] Sanger sequencing chain termination sequencing technology is a method used to determine the nucleotide sequence of DNA.[27] It can be used for mutation confirmation among at-risk family members, siblings, and next generations. It has its limitations in sequencing a single gene as compared to massively parallel sequencing millions of fragments sequenced in NGS.

REPORTING OF VARIANTS ACCORDING TO AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS (ACMG) GUIDELINES

The ACMG guidelines assist in the evaluation and accurate interpretation of genetic variants and have laid down specific criteria for variant classification and reporting based on their association with genetic and clinical presentation. It outlines a systematic approach to evaluating genetic variants based on multiple lines of evidence, such as population frequency,

functional studies, computational, predictive, segregation data, clinical observations, and multiple databases [Table 2]. The guidelines also define standardized terms and criteria for variant interpretation, including pathogenic, likely pathogenic, uncertain significance, likely benign, and benign, based on the available evidence. The collective evidence from all the criteria evaluated, is then used to assign the appropriate variant classification.[28]

Table 2: American college of medical genetics and genomics evidences for classifying gene variants.

	Strong	Supporting	Supporting	Moderate	Strong	Very strong
Population data	MAF is too high for disorder BA1/BS1 OR observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affected statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene/gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7	Multiple lines of computational evidence support a deleterious effect on the gene/gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. Missenses common PP2	Mutational hotspot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Non-segregation with disease BS4		N≤1/8 if 1 family N≤1/4 if >1 family	N≤1/16 if 1 family N≤1/8 if >1 family	N≤1/32 if 1 family N≤1/16 if >1 family	
De novo data				De novo (without paternity and maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in trans with a dominant variant BP2 Observed in cis with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source without shared data=benign BP6	Reputable source=pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

GENETIC COUNSELING

Professional societies' consensus statements recommend pre-test and post-test genetic counseling to patients for Germline hereditary cancer genetic testing.[29] Taking into account the clinical and family history of the patient, informing the patient about indications of genetic testing, as well as addressing the patient's concerns is an important aspect to consider before ordering a genetic test.[30,31] Constructing a pedigree chart for 3 generations is the best way to visualize risk assessment among patients.[32,33]

The process of obtaining consent for germline testing should comprise an explanation of the test's rationale, potential outcomes, risks, and advantages. The results of a genetic test should be disclosed followed up with proper post-test genetic counseling.[31]

Post-test genetic counseling involves providing patients and their families with an in-depth summary of the genetic testing results, helping them to comprehend the test outcomes and associated risks; co-ordinating comprehensive follow-up care to plan for cancer prevention, timely surveillance, and

Table 3: Personalized therapy approvals by FDA and evidence-based studies in germline hereditary cancers.

Gene	Drug	Relationship	Study method
TSC1/2 (mTOR Pathway)	Estrogen-based medications, including oral contraceptives Everolimus, mTOR inhibitor	Shared risk outcome of progression to lymphangioleiomyomatosis TSC-associated Subependymal giant Astrocytoma and renal angiomyolipoma	Case Report[36] Case series[37] FDA Approved 2018[38]
VHL (Hypoxia induced factor-a)	WELIREG, HIF-2a inhibitors	Sensitivity VHL - RCC, CNS Hemangioblastomas, or pancreatic neuroendocrine tumors, not requiring immediate surgery.	FDA approval in 2021[39]
BRCA1/2 (HRR Pathway)	Oral Contraceptives Clomiphene Citrate Carboplatin, Cisplatin PARP inhibitors	Increased risk of breast cancer (Clinical context) Complete pathological response Increased sensitivity Disease free survival	Retrospective study[40] Case-control questionnaire[41] Hahnen *et al.* 2017[42] Caramelo *et al.* 2019[43] FDA 2018 (Breast), 2020 (Ovary), 2023 (Prostate)[44-46]
MLH1 *MSH2* *MSH6* *PMS2*	Aspirin and NSAIDs	Sensitivity	10-years follow-up of randomized controlled trial[47] Phase 1 clinical trial[48]
TP53	Genotoxic agents like etoposide and radiotherapy Carboplatin and Breast Cancer	Resistance Sensitivity	Review[49] *In vivo* models[50] Cohort Study[51]
APC (WNT Pathway)	Aspirin and NSAIDs	Shared risk outcome	FDA approved in 2018[52]
RET	Tyrosine Kinase Inhibitors Pralsetinib and selpercatinib	Sensitivity RET mutation-positive medullary thyroid cancer (MEN syndrome)	FDA approved in 2010[53]
SDHA	Tyrosine kinase inhibitors	Resistance (GISTs) Sensitivity (Metastatic PGG and PCC)	Observational study[54] Phase 2 clinical trial[55]
SDHB	Temozolomide Tyrosine Kinase Inhibitors	Sensitivity Resistance (GISTs) Sensitivity (Metastatic PGG and PCC)	Retrospective population study[56] Observational study[54] Case report[57] Phase 2 clinical trial[55]
SDHC	Tyrosine kinase inhibitors	Sensitivity (RCC)	Case Report[58]

MEN: Multiple endocrine neoplasia, VHL: Von hippel-lindau, TSC: Tuberous-sclerosis-complex, CNS: Central nervous system, FDA: Food and Drug Administration, NSAIDs: Non-steroidal anti-inflammatory drugs, MEN: Multiple endocrine neoplasia, GIST: Gastrointestinal stromal tumor, RCC: Renal cell carcinoma, PGC: Paraganglioma, PCC: Pheochromocytoma

offering individuals personalized treatment strategies. If an individual is tested "positive" for a germline variant associated with hereditary cancer, other at-risk family members should be encouraged to follow up for genetic counseling.[34]

MANAGEMENT

Personalized approaches to cancer genetic syndrome

Individuals who test positive for cancer-associated germline mutations require a comprehensive approach to cancer management. Compared to the general population, individuals with cancer germline mutations may necessitate preventive and specialized screening options tailored to the specific associated cancer risks. In certain cases [Table 3], risk reduction surgery options may be recommended to minimize the likelihood of cancer development. For instance, patients consider prophylactic surgeries like mastectomy/oophorectomy/colectomy to decrease the risk of respective cancer.[35]

Genetic risk predictions models

It has become increasingly common to use computational models in genetic risk prediction models in recent years. A number of risk assessment tools and models are available to evaluate the probability that an individual carries a genetic mutation or their risk to develop cancer. These tools assess the risk based on the presence or absence of gene mutations, personal or family history of cancer. BRCAPRO is an important risk model, developed based on the statistical R package, BayesMendel.[59] It calculates the individual's probability of carrying a pathogenic *BRCA1* or *BRCA2* gene mutation, the risk of developing contralateral breast cancer and ovarian cancer at different ages. Users can input clinical information such as age, tumor marker information, mastectomy, and oophorectomy information, family race, and ethnicity. BRCAPRO serves as a helpful tool for guiding individuals on whether to pursue genetic testing.[60]

Another breast cancer risk assessment tool is the Breast Cancer Risk Assessment Tool: Gail Model, named after Gail *et al*., is a statistical model that uses clinical information such as age, menstruation age, age at first live childbirth, and family history of cancer to estimate the risk of developing cancer.[61,62]

While these models may help in understanding the risk of an individual, this alone should not be used as a deciding factor to undergo genetic testing as they have certain limitations. Use of the tools might support decisions for a requirement for genetic testing, but it could also lead to stress and anxiety for patients and their family members if the patient is not guided and explained about the risk-assessment model and its implications.

CONCLUSION

Genetic testing for cancer may help in the estimation of an individual's lifetime risk of developing cancer by identifying specific genetic changes or mutations. Germline testing is a powerful tool for early detection and cancer prevention not only in proband cases but also in family members. Understanding the indications for germline testing is a responsibility for coordinating this care between the patient and clinician. Choosing the right test with the right technology will help in the correct interpretation of the results and guide the patient and their family in disease prognosis and awareness of preventative screening options, if available.

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Declaration of patient consent

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