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Genetic Testing and Counselling for Cancer: Evolution, Future and Psychological Impact

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ABSTRACT

Background: Genetic counsellors are uniquely qualified to address cancer risk, interpretation of genetic results, and the inevitable complications of the subsequent ethical, legal and psychosocial issues that are encountered by individuals dealing with cancer and with the evolution of technology that can aid in screening and testing, it has become increasingly important for a country like India to evolve its healthcare policies accordingly.

Main Body: Entry into and the timing of the first genetic counsellor's referral hold importance as they are based on family history, ethnicity, phenotypic expressions, high-risk tumour types, non-oncological findings and incidental findings, and ensure that all prophylactic measures, possible tests, therapies and management options are considered. Testing procedures on the gene-level is based on examination of entire genomes and of specific genes in order to estimate the pathogenicity of the variant. Moreover, risk stratification is an important tenet of genetic counselling that has enormous implications on the psychosocial well-being of the patient and their families. In India, the burden of cancer varies in accordance with gender, religion, socio-economic status and the resolution of this adversity seems to lie in the development of nation-wide policies aimed at improving access to healthcare including evolving technologies for screening and management.

Conclusion: Cancer screening, testing, management are all aspects of genetic counselling that should evolve in accordance contemporary developments in the respective fields. Personalised medicine, e-health interventions and population-based screening are some examples of the aforementioned development.

Background

The field of cancer screening and testing has come a long way; its evolution from basic biochemical tests screening for particular analytes [1] to the use of gene-based testing and screening models is a definitive example of the evolution of our understanding of cancer syndromes and their underlying genetic basis. Identification of people with cancer predisposition syndromes and germ line pathogenic variants [2] has become easier with the advent and utilization of genome-wide gene sequencing panels [3,4] chromosomal arrays, and whole exome/genome sequencing and, somatic tumor testing (especially for childhood cancers), emphasizing the increasing necessity for both cancer predisposition testing and genetic counselling programs specializing in the testing, management and care of cancer [5].

Genetic counsellors are uniquely qualified to address cancer risk, interpretation of genetic results, and the inevitable complications of the subsequent ethical [6], legal and psychosocial issues that are encountered by individuals dealing with this malady [7,8]. Obtaining informed consent [5,6] from both minors and adults, ascertaining the timing for a genetics referral, providing periodic counselling and the associated aid overtime (especially in the smooth transition of younger patients to adult/ geriatric care) [8,9] and the dearth of childhood cancer predisposition syndromes are some of the unique challenges that plague us today [10]. Incidental findings due to the prevalence of genetic testing are associated with their own set of psychological implications [11].

In countries like India, where there is enormous disparity between socio-economic classes, a genetic counsellor will encounter additional problems including the lack of awareness and education amongst the under-privileged classes, gender- and religion-associated disparity in terms of cancer treatment, management and the reality of the influence of political agendas over government health policies.

Entry to Genetic Counselling

Referral to a genetic counselling clinic for cancer evaluation can occur due to the prevalence of cancer syndromes within the family (family history) [12], ethnicity [13,14], phenotypic expressions, high-risk tumour types, non-oncological findings, like the lip-pigmentation and greater the characteristic macules associated with Peutz-Jeghers syndrome and neurofibromatosis type1 (and bi-allelic mismatch repair) respectively and incidental findings (variances in predisposition genes on chromosomal microarrays and secondary findings detected by exome sequencing) [9]. Family history alone, however, is not a reliable factor when accounting for the necessity of a referral as cancer predisposition has been reported in many cases of absence of said history [10], This can be due to the formation de novo variants, parental germ line mosaicism [15], increasing incidence of smaller nuclear families, low penetrance and recessive inheritance masking an inherited syndrome. Hence, a combination of the aforementioned factors should be taken into account when making a genetics' referral. Moreover, the future holds the possibility population based genetic testing for cancer predisposition syndromes.

Oncologists are confronted with the possibilities of identifying whether reported variants are indicative of somatic changes or inherent germ line susceptibility [16] and thus subsequent referral to a genetics' clinic for their particular expertise becomes necessary.

Timing of Genetic Counselling Initiation

The optimal timing of the first genetic counselling session is at the time of tumor diagnosis or after the initiation of treatment in cases of poor prognosis, to ensure that the possibility of prophylactic surgery is considered. The genetic counsellor is qualified to advise the patient on many issues associated with the patient prognosis, associated treatment plans and psychological developments [17,18]. In the case of poor prognosis, DNA banking should be administered, and genetic testing organized in a timely manner in order to assess and counsel their relatives to minimize the economic and psychological burden of post-mortem testing.

Pre-Test Genetic Counselling

Informed consent should be obtained from the patient before they undergo any genetic testing procedure. This involves complete discussion of all aspects related to the test and consequent implications, including information regarding tests most suitable to the patient (based on the various factors that have prompted the referral), the surveillance protocol that may follow (especially in cases of transition from childhood to adulthood), psychosocial [11], ethical and privacy concerns, which all vary in accordance with the laws of different countries, and plans for disclosing results to at-risk relatives [6,19]. Adults are required to provide verbal and written assent towards the procedure; minors should be guided through these discussions in an age-appropriate manner and adolescents should provide verbal and written consent in conjunction with their parents or primary guardians [9]. This allows older children to become involved with and more accustomed to their unique situation and have any fears or misconceptions addressed. The basic tenet of genetic counselling is to give patients the tools required for them to make informed autonomous decisions [20] regarding the testing and management options available to them based on factual (stratified) risk information [21-25]. Despite concerns of exacerbating patients' anxiety, genetic testing in the absence of prior genetic counselling is linked with negative outcomes including the violation of ethical standards, ordering of unnecessary, perhaps costly, genetic tests, misinterpretation of these results and adverse effects on the patients' psyche.

Genetic Testing

The invention of Next Generation Sequencing (NGS) technology is the biggest advancement in genetic testing seen in recent years wherein analysis is performed at a multiple gene level, or even whole transcriptomic, genomic and exomic levels, at a relatively lower cost, especially when the increased sensitivity and efficiency of obtaining results are taken into account [16]. A test should be ordered after consultation with a genetic counsellor and the choice of laboratory should be based on the type of test, its level of analysis, methodology and their variant interpretation techniques, expenses involved, time factors and their policies on privacy and ethics. The variants are reported in accordance with the five-tier classification proposed by The American College of Medical Genetics and

Genomics (ACMG), namely, pathogenic, likely pathogenic, variant of uncertain significance, likely benign and benign [9,26]. Despite the succinctness of this model, further interpretation by an expert is important especially when deciding the significance/ level of pathogenicity of variants (Table 1).

Table 1: Genetic tests for cancer gene mutation.

Type of test	Details
Single gene test	• Single known familial variant analysis
WES/WGS	• Exons, intron/exon borders or entire genome analysis
	• Ambiguous cancer phenotypes or multisystem phenotypes
	• NGS technology
Single gene	• Intron/exon borders of the selected gene
	• Phenotypes attributed to a known syndrome
	• Sanger sequencing/ NGS technology
Multi gene panel	• Exons, intron/exon borders of the particular genes
	• Ambiguous phenotypes; increased chances of finding causative variant.
	• NGS technology
SNP microarray	• Analysis of large chromosomal aberrations (genome level) that may not be detected by WES/WGS, single/ multiple gene tests
	• Test recommended when patient displays phenotypes (developmental/ intellectual/ congenital disabilities) characteristic

Note: {WES – Whole Exome Sequencing; WGS – Whole Genome Sequencing, NGS – Next Generation Sequencing, SNP – Single Nucleotide Polymorphism}

The sensitivity of these tests for identification of pathogenicity varies from greater than 95% to less than 50% and thus, a genetic counsellor must provide counsel on risk perception and management options based on empirical data and in conjunction with the oncologist. Identification of variants without certain significance tailors the advised management options to include surveillance protocols and the possibility of family variant tracking. Relatives can be tested for these only when consent is provided by the patient [6]. The inheritance patterns associated with the identified pathogenic variant determine the relatives who are at-risk. For example, if a syndrome follows an autosomal dominant pattern of inheritance, there is a 50% risk of inheriting a pathogenic variant, and its associated risks, to first-degree relatives of the proband [16,27].

Post- Test Genetic Counselling

For those individuals with a positive diagnosis, post-test counselling involves specific treatment/ management options and the necessity of periodic evaluation. In cases of childhood diagnosis of a hereditary cancer syndrome, reproductive and psychological implications especially, change over increasing age. Hence, lifelong risk management, and understanding of the options for reproductive (post- and pre-natal) counselling [28], testing post-birth, adoption, and/or utilizing donors is disseminated with increasing age of the patient in an appropriate manner suited to the child's developmental stage8,9. Surveillance options [29] and information regarding the advent of new testing options can only be provided for at-risk individuals/ families if periodic follow-up with the genetic counsellor is maintained.

Psychological and Sociological Implications

Negative effects on the psyche of a patient with a positive diagnosis are primarily concerned with surveillance protocols and the reality of a life-long economic burden8. Invasive medical procedures [30], procedures requiring sedation or general anesthesia, false positive results, incidental findings are implicated by various studies in causing psychological distress to the patient and their families. There arises a general frustration with lack of positive results when it comes to therapies advised, inconclusive outcomes of tests and the delivery of false-positive results (increased in whole-body MRIs) [31], impaired quality of life, reduced satisfaction with care, and worse overall survival. Patients undergoing surveillance may experience anxiety with regards to scanning, referred to as "scanxiety", and children especially may feel adversely towards repeated blood draws and the claustrophobic confinement experienced during MRI scans [9]. Young adults face an ever-increasing economic burden as they are as of yet not financially secure enough, and may not even possess insurance cover [20], to support life- long management programs.

On the contrary, proactive surveillance and psychological support, from say, cancer survivor groups, may empower the patient and are viable avenues to lead a more well-adjusted life. The patient relies on the care team in such scenarios due to generation of trust and confidence in their counsel [32,33]. Cancer genetic counselling in India. In India, there are about a million cases of cancer diagnosed yearly. When the population of the subcontinent is taken into account, these rates of incidence and mortality, match those seen in high-income countries [34]. These elucidate the lack of early-detection strategies and positive results of treatments within the medical landscape of the country [35].

Studies show that breast, lung, oral, cervical, gastric and colorectal cancers [36] have the highest incidence rates in India. It is evident that most causative agents implicated in cancer in the Indian population are avoidable (tobacco and alcohol consumption, lack of education with respect to female hygiene) [34,37]. There is a general lack of education and support for the low-income, socially underprivileged families owing to the fallacies of an increasingly capitalist state of government [38-40]. Even governmental policies regarding general health are found to be inadequate in the face of

growing mortality due to cancer. It is the second-leading cause of death amongst the Indian population.

A patriarchal society has also generated the spread of female reproductive cancers as the importance of feminine hygiene is not acknowledged by many; additionally, a greater economic burden to finance health care is placed on women [41]. In conjunction with the lack of resources and such a mind-set, most evidently seen in under-privileged communities, the incidence of cervical cancers has witnessed an increase over the past 5-10 years. In India, the age of onset of the female reproductive cancers is around a decade earlier than that of developed nations (45-50 years in the former, compared to >60 years of the latter) [42]. Moreover, oncofertility can be improved by developing management, treatment strategies that comprise of professionals from multiple specialties, say a counselling team that includes a reproductive endocrinologist [43] apart from an oncologist, psychologist and the geneticist. Hence, advancement of cancer-associated clinical programs with respect to diagnosis, screening, management/ treatment particular to the Indian race [44] are a necessity in the mission to better the state of women's health in India [42,45].

Conclusion

Cancer testing and management is an ever-growing field primarily due to our increasing understanding of unknown syndromes and their underlying genetics, and the expansion of available information of known cancer syndromes. In accordance with these basic developments, there should be a correlating evolution in the various genetic testing and counselling practices available for the same. These take the form of improved access to aforementioned resources and formulations of government policies that tackle health care from this perspective [45]. One such advancement can be the necessitation of population-based genetic screening [46,47] and testing for common pathogenic variants of the most abundantly found cancer syndromes, e.g. BRCA 1 and 2 testing for breast cancer [4,42,48]. This type of policy can hold many implications in reducing the burden of cancer in many developing economies, like India. In the same vein, there have been discussions on the use of e-health interventions [49] like psycho-educational interventions delivered via web-based environments with auxiliary methods of communication, which includes support with professionals and peers, offer improved awareness and access to the required support for informed, autonomous decision-making. Personalized medicine is an avenue of modern medicine gaining quick popularity as it is tailored to an individual and their needs. Corroborating advancements in cancer genetic testing and counselling to personalized care will initiate the incidence of more positive outcomes as it pertains to lifelong care and management practices [5,11,18,50,51].

Declarations

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Consent for Publication

Not Applicable.

Availability of Data and Materials

Not Applicable.

Competing Interests

None.

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Author's Contributions

Gatika Agrawal(GA) and Venkatachalam Deepa Parvathi(VDP) have contributed equally to the conception, drafting, revising it critically and intellectual content. Arunasalam Dharmarajan (AD) contributed to reviewing the manuscript.

Conflict of Interest Statement

Authors, Gatika Agrawal, Venkatachalam Deepa Parvathi and Arunasalam Dharmarajan declare that they have no conflict of interest.

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