

## Genetic Counseling in Developmental Disability

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**ABSTRACT** Genetic counseling (GC) is a communication process and has been described in the past 3 decades for its objectives, principles to be used, the process and the steps involved, various types of counselees encountered, the knowledge about the genetic condition, genetic evaluation using different diagnostic tests, occurrence or recurrence of the risk estimate, prevention modalities as well as for the psycho-emotional and ethical issues. The current research focuses on GC in the developmental disability (DD)/mental retardation (MR) which encompasses the global (mental and /or motor) developmental delay (GDD) emphasizing the role of the primary physicians in GC. The aetiology of DD/MR is varied and hence a genetic counselor needs to possess the knowledge about their causes, updates on diagnostic tests, mode of inheritance, therapy management and rehabilitation of the affected individual/family. The common genetic disorders associated with DD and their implication in the prevention of the recurrence risk which is one of the major goals of the GC is delineated in the Indian clinical set-up considering the parents/couples or the adult patients /family members who need to be counseled.

### INTRODUCTION

Genetic Counseling (GC) is a special health service that provides information and support to the people who have, or may be at the risk of genetic disorders. During a genetic counseling, the genetic professional, often referred as a genetic counselor, meets with an individual or the family to discuss the genetic risks or to diagnose, confirm, or rule to out a genetic condition (Fraser 1974). The American College of Medical Genetics (ACMG) defines genetic counseling as a communication process which deals with the human problems associated with the occurrence of or recurrence of a genetic disorder in a family (Curry et al. 1997; Harper 2010). The process involves an attempt by one or more appro-

priately trained persons to help the individual or the family to: 1) Comprehend the medical facts including the diagnosis, probable cause of the disorder and the available management; 2) Appreciate the way heredity contributes to the disorder and the risk of recurrence in the relatives; 3) Understand the options of dealing with the risk of recurrence and 4) choose the course of action which seems appropriate in view of their risk, their family goals, ethical and religious standards and act in accordance with that decision; 5) Make the best possible adjustment to the disorder in an affected family member and/ or to the risk of recurrence of that disorder.

The person who gives GC is called the 'Genetic Counselor' and person who seeks GC is called as a 'Counselee or Consultand'.

### OBSERVATION AND DISCUSSION

#### Types of Genetic Counseling

There are several different reasons why a person or couple may seek genetic counseling. On the basis of these reasons, genetic counseling is further categorized as Prenatal GC, General and Pediatric GC, Adult GC, Cancer GC and GC in Developmental Delay/Disability. In this research, the researcher has emphasized on the importance and the impact of genetic counseling in developmental disability and the principles and the goals to be observed during the GC process are given below:

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### **Principles of GC**

Genetic counseling is a process that overlaps with genetics testing and diagnosis. While doing GC in the case of DD which may be static or progressive, certain principles need to be followed such as : 1) It is very important to look for the accurate diagnosis of the previous or the deceased siblings as this makes it easier to arrive at the diagnosis of a possible familial genetic condition; 2) To follow a non-directive counseling- that means after giving the complete impartial information and options to the counselees, they should be left to make a decision and should never be given a personal opinion by the counselor (that is, directive counseling); 3) Timing of GC – When is the GC required? Is it during the pre-conceptional or prenatal period or after the birth of an abnormal newborn? This is important because the psycho-emotional factors such as fear, anxiety, denial, stigma and mental stress of the individuals seeking GC need to be considered; 4) To ensure that both the parents are present for GC because many a times the understanding and briefing by one partner to another may not represent the correct picture or information shared during the GC process; 5) It is a duty of the genetic counselor to disclose the accurate current and future information, whenever required by the re-contacting patients (Shevell et al. 2003; Harper 2010).

### **Goals of GC**

One of the primary goals of genetic counseling in DD is to prevent the birth defects and genetic disorders. However, the goal of an improved psychological well-being in client adaptation to a genetic condition has also been recently emphasized (Biesecker 2001). The communication process of GC thus ensures it by: i) providing concrete, accurate information about inherited disorder; ii) Reassuring people who are concerned that their child may inherit a particular disorder and that the disorder will not occur; iii) To allow people who are affected by the inherited disease to make an informed choice about future reproduction; iv) To educate people about inherited disorder and the process of inheritance; v) To offer support by skilled health care professionals to people who are disabled by the genetic disorders (Harper 2010).

At this juncture it is essential for a genetic counselor to have the updated knowledge about DD/MR, necessary genetic investigations and course of actions required in the different situations. With regards to the GC, the same information is depicted below in brief as the details are beyond the scope of this research and advised to refer to the literature.

### **Developmental Disability (DD)**

Developmental disabilities are a group of conditions which are due to impairment in the physical, learning, language, or behavior areas. These conditions begin during the developmental period, may impact day-to-day functioning, and usually last throughout a person's lifetime. Developmental disability (DD) can be categorized as a Global Developmental Delay (GDD) or the Pervasive Developmental Delay (PDD). Developmental disability that affects all areas of a child's development is generally referred to as GDD and evaluation of the child with GDD including parameters for clinical practice are available (Phadke 2004; Shevell et al. 2003). PDDs, refer to a group of conditions that involve delays in the development of many basic skills. Most notable among them are the ability to socialize with others, to communicate, and to use imagination. The term GDD is usually reserved for the younger children (that is, typically less than 5 years of age), whereas the term mental retardation is usually applied to the older children when the IQ testing is more valid and reliable (AAPC 2001). A child who has GDD clinically will not always be mentally retarded.

### **Intellectual Disability (ID)**

When a developmental disability is predominantly mental, it is referred to as mental retardation/ deficiency or subnormal intelligence or intellectual disability (ID) and can further be classified as mild, moderate and severe DD based on the neuropsychological assessment (Curry 1997).

Mental Retardation (MR) was coined by the American Psychiatric Association (APA) in 1961 and occurred in one to three percent of the population (Croen et al. 2001; De Vries et al. 2005). The overall prevalence of MR is still not known with certainty and in India too it is estimated to be 2-3 percent of the population (Kaur et al. 2003).

The term MR was later replaced by the term, 'Intellectual Disability' which is defined as the developmental disability that first appears during the developmental period (under the age of 18 years) and is defined as an intellectual functioning level (as measured by the standard tests for intelligence quotient) that is well below the average ( $IQ < 70$ ) and significant limitations in the daily living skills (adaptive functioning) (Luckasson et al. 1992). This particularly applies in school and similar settings if the behavior is impaired and clinically determined to be due to deficits in reasoning and judgment. Current valid instruments for assessing intelligence (such as the Stanford-Binet or Wechsler Preschool Primary Scale of Intelligence) are not generally applicable under the age of 3 years and the neurodevelopmental assessment (Bayley's Test for Infant Development) is used to judge the mental and the motor developmental milestones (AAMR 1992).

The DD/MR is a heterogeneous group of disorders and various genetic and acquired factors can be responsible, the earlier ones contributing to the hereditary or the familial nature of the disease requiring GC (Aggarwal et al. 2012). Once the acquired aetiology such as the infection, trauma, teratogens, radiation, toxicity, nutritional deficiency causing brain damage or mental and/or motor disability is excluded, the recurrence risk estimate is easy and genetic factors among others can be considered (Dave and Shetty 2010).

### **Causes of Developmental Disability**

Apart from the genetic factors, there are many social, environmental and physical causes for developmental disabilities which need to be first ruled out by a counselor (March of Dimes 2001), although for some a definitive cause may never be determined. Thus, non-Genetic /Environmental factors responsible for DD such as brain injury or infection before, during or after birth, growth or nutrition problems, babies born long before the expected birth date - also called extreme prematurity (Marlow et al. 2005), poor maternal and infant diet and health care, drug misuse during pregnancy, including excessive alcohol intake and smoking, child abuse and the socio-emotional deprivation need to be excluded. The causes and prevention of DD/MR/ID are well reviewed in the literature and will not be elaborated here (Loo and Martens 2007; Arc 2011).

### **Genetic Factors Causing Developmental Disability**

Most human genetic defects/disorders are caused by mutations, deletions, translocations (rearrangements of the arms of chromosomes) and other alterations in the genes or chromosomes.

Among the several indications of DD/MR, the common ones for genetic counseling are: Congenital malformations/Birth defects; Dysmorphism; Learning difficulties and slow learners; Autism / ASD/ PDD (Pervasive Developmental Disorder); Genetic Syndromes; Endocrinological problems; Neurological and Muscle disorders; Epilepsy/ familial seizures, Neuroregression; Known familial/inherited medical conditions (Buyse 1990; Moeschler et al. 2006). Those seeking GC may have an index case in the family or they may be parents of a child with a known or a suspected genetic / hereditary disease, or birth defects or DD and want to go for the next pregnancy. The GC offered at this stage is called "Prenatal GC" and is also offered in various other situations such as advanced maternal age, teratogen exposure, consanguinity and reproductive failures. The couples with a history of IUGR, stillbirth, neonatal and/ sib death and BOH (Bad Obstetric History), are also appropriately counseled for the future risk of DD. On few occasions, the post screening results as in the case of a Newborn Screening, the inherited metabolic genetic disease with DD is diagnosed which brings a couple to the prenatal genetic counseling (Dave and Das 2010).

After the genetic evaluation of the patient/family, the counselor based on his/her experience and medical genetic knowledge classifies the genetic disorder into 5 main categories: 1) Chromosomal Disorder, 2) Single Gene Disorder, 3) Polygenic Disorder, 4) Multifactorial Disorder, and 5) Mitochondrial Disorder. The latest 'Epigenetic Factors' can well be added to this list (Koolen et al. 2008).

**1) Chromosomal Disorders and Genetic Syndromes:** The most common chromosomal disorder causing DD is a neurodevelopmental aneuploidy called the Down syndrome with a trisomy of chromosome 21. In a retrospective study, various structural and numerical chromosomal disorders causing DD were reported in about thirty-three percent cases and non-chromosomal genetic syndromes in 9.5 percent and central nervous system structural defects in 7.4

percent cases (Aggarwal et al. 2012). The researcher's own experience at the tertiary genetic centre was when a special school for MR reported forty-five percent Down syndrome (250 of 555 MR cases), being the common chromosomal disorder with a mild to severe mental retardation with and without multiple congenital anomalies and dysmorphism (Dave and Shetty 2010). The chromosomal abnormalities were 31.5 percent with the males more than the females (2.1 : 1.0). When routine karyotyping, metabolic and Brain MRI tests were normal in a DD child, the genetic counselor recommended cytogenetic microarray analysis for submicroscopic chromosomal aberrations (De Vries et al. 2005; Koolen et al. 2008). The most well-known chromosomal micro-deletions and micro duplications syndromes are caused by a chromosomal deletion or the duplication of a smaller region less than 5 million base pairs (5 Mb) spanning several genes. Besides delineating a specific syndrome, the abnormality found in such DD using genomic microarray technique helped in the recurrence risk estimation and also served as a marker for the next pregnancy (Miller et al. 2010).

**2) Single Gene Disorders:** Any genetic disorder caused by a change affecting only one gene is called as a Single Gene Disorder. These usually follow simple Mendelian patterns of inheritance namely, autosomal dominant, autosomal recessive, or an X-linked. There are thousands of single-gene diseases including achondroplasia, cystic fibrosis, phenylketonuria, hemophilia, Huntington disease, muscular dystrophy, and sickle cell disease but all may not cause DD/MR. The majority of Inborn Errors of Metabolism (IEM) are single gene autosomal recessive disorders when parents are carriers of the defective gene and have twenty-five percent risk in every pregnancy of having a child with IEM. The accurate diagnosis using advanced metabolic, mass spectrometry and molecular tests becomes essential to arrive at the precise genetic diagnosis (Dave and Das 2010). Majority of neurodevelopment conditions do show IEM. The neurometabolic diseases are reported to be ten percent in the aetiologic spectrum of MR and developmental delay (Aggarwal et al. 2012).

The Fragile X syndrome, second most common chromosomal disorder with MR is a genetic disorder caused by a mutation in the Fragile X Mental Retardation 1 (FMR1) gene on the X chromosome by the mechanism of CGG repeat

expansion (Biancalana et al. 2015). Its incidence varies from five percent to nineteen percent (Chetan et al. 2002). In the institution, population can be diagnosed by characteristic facial dysmorphism, enlarged testes and the behavior pattern (Hagerman and Chronister 1996).

**3) Polygenic Disorders:** When more than one gene is responsible for a disease it is called a polygenic disorder and is often a challenge in DD. In William's-Beuren syndrome deletion of the chromosomal region 7q11.2 is present which harbors more than 20 genes and cytogenetic microarray technique are required to diagnose it. Most of the genetic syndromes fall into this category due to the multiple malformations of different organs/body systems. A number of rare genetic syndromes have been successfully reported with a copy number variation of pathologic significance using array Comparative Genomic Hybridization (aCGH) microarray technique (Koolen et al. 2008; Shetty and Dave 2016).

**4) Multifactorial Disorders:** Multifactorial disorders (complex disorders) are caused by the changes in multiple genes, often in a complex interaction with environmental, lifestyle factors such as diet or cigarette smoke and epigenetic factors. The neurodevelopmental disorder with a complex etiology like autism spectrum disorder (ASD) has been discussed for the contribution of the interaction of the genetic, environmental and epigenetic factors (Muhle et al. 2004; Loo and Martens 2007).

The Rett syndrome well recognized X-linked disorder is believed to be one of the leading causes of DD/MR in the females. The mild forms are reported in the males as well. It is caused by the mutations in the X-linked gene encoding methyl-CpG-binding protein 2 (MECP2) and eighty percent of the patients with Rett syndrome have MECP2 mutation (Shahbazian and Zoghbi 2001). Many ASDs are considered as multifactorial and polygenic disease, as more and more genomic tests are available.

**5) Mitochondrial Disorders:** Besides cytoplasmic DNA, small circular molecule of DNA (16,569 bases) resides in the mitochondria of the body cells. The mutation in this mitochondrial DNA (mtDNA) is characteristic of maternal inheritance and does not follow Mendelian inheritance. This is because the sperm hardly contains any cytoplasm, the mitochondria in a zygote derives from the ovum. Therefore the mutations in the mitochondrial DNA cause the de-

generative/ energy crisis diseases and clinical manifestation is the multi-organ involvement depending on which mitochondria of an organ are mutated. This heteroplasmy leads to various degree of mitochondrial dysfunction due to the disturbance in the respiratory chain function and deficiencies of enzymes for metabolic and mitochondrial membrane transport functions. Several diseases (example, MELAS, MERRF, LHON, Leigh Syndrome) are known (Fenichel 2001). The whole mtDNA genome analysis for the mutation testing is conducted to arrive at the precise diagnosis for GC as majority are progressive diseases.

**Genomic Imprinting**

Genomic imprinting is the epigenetic phenomenon by which certain genes are expressed in a parent-of-origin-specific manner (Desai et al. 2015). If the allele inherited from the father is imprinted, it is thereby silenced, and only the allele from the mother is expressed. Thus any change namely, duplication and deletion leads to the clinical manifestation of the disorder. Angelman and Prader-Willi Syndrome are the classical examples of a deletion of chromosome 15q11-13 of maternal and paternal inheritance respectively in this group (Shevell et al. 2003).

The grouping of genetic disorder as above helps the genetic counselor to explain various genetic investigations necessary to arrive at the appropriate and accurate diagnosis which is a prerequisite to genetic counseling. Despite the latest DNA diagnostic technology, about twen-

ty-five to thirty percent of cases with DD/MR remain undiagnosed.

**Steps in Genetic Counseling Process**

Genetic counseling is a multistep process and while dealing with DD/MR, it involves the following steps:

*1) Family History Taking and Pedigree Charting:* Often the index case or proband in case of DD is a child, who is to be interviewed with the parents and the relatives for the standard medical history and constructing the pedigree with the standard symbols. The affected individuals in a family tree can be looked upon at a glance and would indicate autosomal, sex-linked, dominant or recessive mode of inheritance (Fig. 1). Similarly, the pattern of inheritance can be described while GC with pictorial/ visual aids for a specific genetic disorder in question using Pedigree Charting (Harper 2010). The direct questions about the similarly affected person, early sibling death, miscarriages, consanguinity, congenital malformations need to be asked. The mode of inheritance, if any then becomes clearer.

*2) Clinical/Medical Examination:* A complete physical examination, anthropometric measurements, note and photographic evidence of dysmorphic /congenital features are essential. Examination of the parents may be relevant to verify the familial or the truly abnormal dysmorphic feature. Based on the physical features, anomaly noted and the degree of MR, the tar-

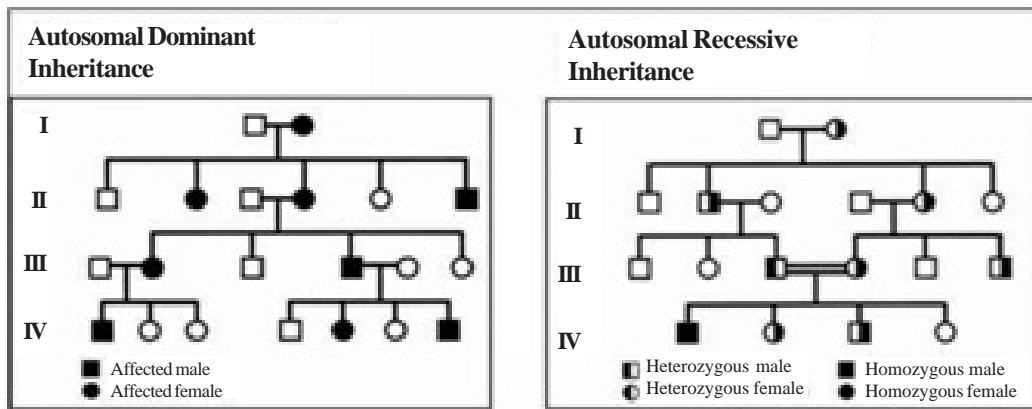


Fig. 1. The pedigree charting of four generations of families with dominant (Left) and recessive (Right) mode of inheritance

geted investigation approach becomes cost-effective giving a higher yield of the genetic diagnosis (Shevell et al. 2003; Aggarwal et al. 2012).

**3) Genetic Investigations and Diagnosis:** Based on the above information, a variety of genetic investigations may be required as discussed earlier to make the genetic diagnosis. The various biochemical, imaging and hematological investigations might give a sufficient clue of the genetic condition. But the majority, in the case of DD would require chromosomal, metabolic and / DNA testing. For example, for the chromosomal study in the Down syndrome the child is extremely important because the risk of recurrence may vary from one percent to hundred percent depending on the chromosomal abnormality. The diagnosis of genetic syndromes characterized by multiple congenital malformations/defects has become difficult with the ever increasing list of syndromes (Tabyi and Lachman 1996; Koolen et al. 2008). London Dysmorphology Database and Pictures of Standard Syndromes and Undiagnosed Malformations (POSSUM) are resourceful guides to a diagnostic approach (Aase 1990).

The targeted evaluation based on the clinical findings along with use of the latest genomic methods such as Multiple Ligation Probe Assay (MLPA) for the subtelomeric regions, microdeletion syndromes or X-linked MR loci increases the yield of genetic diagnosis. Currently, aCGH is taking over the conventional karyotyping for ascertaining chromosomal abnormalities (De Vries et al. 2005). Similarly, 'Clinical Exome Sequencing', 'Whole Exome Sequencing' or the 'Next Generation Sequencing (NGS)' are other, but costly approaches to arrive at the precise genetic diagnosis. Use of these genomic tests during GC could depend on the need, diagnostic satisfaction, psycho educational level and financial constraint of the counselee. No doubt at times, a rare genetic disorder can be diagnosed (Shetty and Dave 2014). The pre-test and the post-test counseling are important to explain all the aspects of the condition that allow informed decision-making, reduces the anguish, and helps in coping with the disorder.

**4) Recurrence Risk Estimation:** Patients or parents need to understand the inheritance pattern and a risk in recessive (25%) or dominant (50%) disorder. The meaning that this risk is for every, pregnancy should be clearly explained using pictorial aids. The parents or the family

members may also have to undergo investigations to precisely estimate the risk, especially in the case of the dominant disorders where variable clinical expression is manifested. For example, in Tuberous sclerosis (TSC), if one of the parents shows feature of TSC, then the recurrence risk is fifty percent while if both parents are normal, then the risk substantially reduces. The risk estimation in various single genes, polygenic and multi-factorial disorders are well depicted in the literature to help GC (Lubs 1977; Young 2006; Koolen et al. 2008). The precise mutational diagnosis is essential in autosomal recessive IEM disorder as it can help the parents in the future pregnancy and prenatal diagnosis when recurrence risk is twenty-five percent (Dave et al. 2016).

**5) Counseling and Follow-up:** Non-directive counseling is a guiding principle for GC that promotes autonomy or self-determination and personal control of the counselee (Biesscker 2001). Various studies and review literature in the past have indicated the significance, ways and means of GC as a communication process to achieve the best results (Fraser 1974; Hsia 1977; Kessler 1979; Shiloh et al. 1990; Young 2006; Harper 2010). The follow-up always completes the GC process besides giving the satisfaction to both, the counselee and the counselor, the latter becoming more confident to cite the example during next GC.

### Qualification and Qualities of a Genetic Counselor

Genetic counseling is done by a certified genetic counselor who has a good knowledge about the genetic disorders. Generally GC is done by the postgraduate health professionals with a graduate diploma or Master's in genetic counseling having experience in the areas of medical genetics and counseling. By combining the knowledge of basic science, medical genetics, epidemiological principles, counseling theory in genetic risk assessment and interpersonal communication skills, a genetic counselor provides services for a diverse set of genetic and genomic conditions causing DD or mental deficiency (NSGC Task Force 2006). A team of physician, nurse and a social worker who have undergone special training in genetic counseling also make eligible genetic counselors. Many engage themselves in research activities related to the field

of medical genetics and genetic counseling. Experience in the areas of medical genetics and counseling is a pre-requisite for genetic counseling.

Genetic counseling is both, an art and science involving not only the use of technical genetic knowledge and precise medical diagnosis, but also accurate dissemination of genetic information in a tactful, empathetic manner with the help of an accurate test. The care, sympathy, understanding and insight into emotional aspects of the clients are given the highest priority (Hsia 1977). The ability to judge whether they understand a scientific explanation and their reactions is a significant part of this communication. The counselor should also have the knowledge about the ancillary needs of the counselees such as he/she should be able to guide the parents of the MR children to an appropriate rehabilitation and a special educational centre or to a physiotherapist. The burden of the disease may vary from clinical \ social \ financial level to an emotional level and may differ from an individual to individual. Hence counseling is needed to promote informed choices and adaptation to cope with a genetic condition is a priority. For example, the prenatal diagnosis of a minor physical defect (cleft lip or palate) which can be post-birth corrected does not require termination of the fetus as compared to multiple congenital malformed fetus diagnosed on ultrasonography. Here, the explanation to the couple about the magnitude of risk is important. The baseline risk and the empirical risk based on the observed data in the population for Mendelian, Non-Mendelian, or chromosomal disorders is often used by the counselor to convince during GC. In the end, the counselor's role is to support, promote and help in taking decisions by keeping professional standards of respecting value, goals, beliefs and cultural integrity of the counselees.

### **Ethical Issues in GC**

The technological advances often pose some unique and significant ethical dilemmas. Some of the ethical issues like artificial insemination by the donor, genetic screening, in vitro fertilisation, surrogate motherhood, foetal tissue transplantation, and gene therapy have generated considerable concerns (Biesecker 2001). Other moral issues include veracity, the duty to disclose information or to be truthful, and respect for patient confidentiality. Individual's fam-

ily history, carrier status, a risk of genetic disease to self or offspring needs to be kept confidential. Non-directive counseling, a hallmark of this profession, is in accordance with the principle of individual autonomy. It also involves supportive counseling to enable patients to make decisions and to make the best possible adjustment to the presence or the risk of genetic disease. (Muthuswamy 2011). The GC process in the Indian scenario at times differs from the developed Western countries as other family members besides patients/couples have a predominant role in the decision making. The counselor should observe the ethical guidelines provided by the ICMR (2006).

At times some real dilemmas for the counselors occur when problems like previous abortions, abnormal births, and occasional false paternity are learned by a counselor. Studies suggest that the principal obstacles to the effective use of genetic counseling are emotional conflicts, and lack of knowledge of genetics and biology. Occasionally, disputes arise about the significance of laboratory findings especially about the possibility of contamination by maternal cells or genuine doubt of chromosomal abnormality present in the parents or revealing the findings and interpretations between professionals and the parents. All these need to be tackled by the counselor with the highest efficiency and confidence. The experienced and the mature genetic counselor tackles every issue with remarkable calmness and patience.

In conclusion, advancement in genomic technology in the recent years and the concomitant public awareness and interest in genetics has created an impact on genetic counseling. The new genetic technologies help in the selection of proper genetic test for diagnosis and further confirmation of a specific disorder. It then becomes practical to calculate the risk figures in DD/MR or regarding the unborn. The GC should finally ensure that parents must be thoroughly satisfied and must be able to take a decision instead of placing them in a state of dilemma.

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