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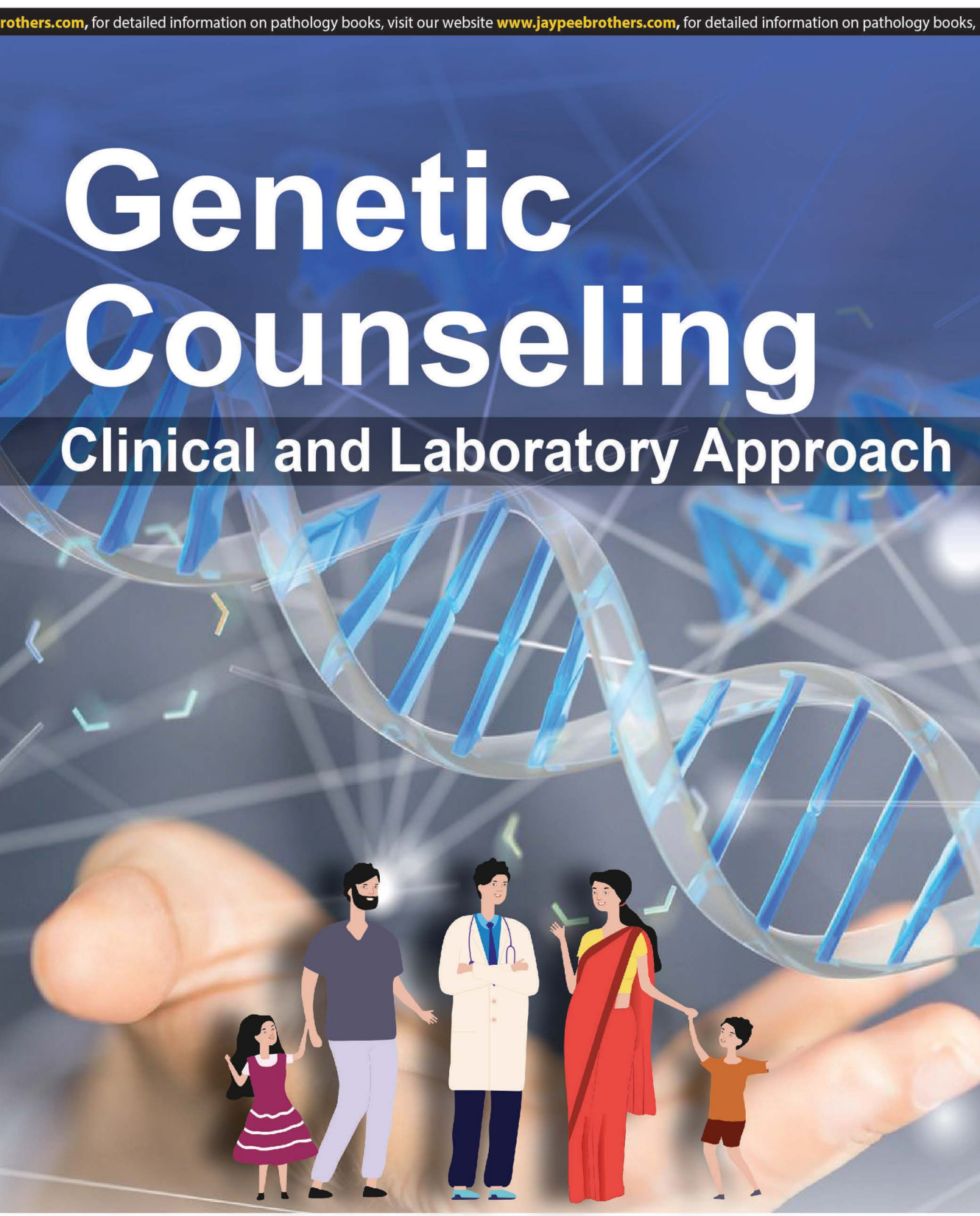
Genetic Counseling

Clinical and Laboratory Approach



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2 Carrier Screening and Genetic Risk Prediction

Sunita Bijarnia-Mahay, Kanika Singh

INTRODUCTION

Genetic carrier screening is rapidly becoming part of clinical practice in prenatal and preconceptional reproductive medicine. Carrier screening typically alludes to detection of carrier status of autosomal or X-linked recessive disorders in couples, for which there may be risk of disease in their offspring(s).

The new millennium ushered in a brand-new phase of human life, in terms of health and opportunities. Not only did we gain control over infectious diseases, and improved the quality of life, but got enormous benefits from the advancing technologies. The culmination of the human genome project in 2003 was the ultimate boon for clinical genetics, as it opened the doors for the then "unthinkable" exome and genome sequencing. The genome is the complete set of DNA that each individual carries in our cells. The exome is 1–2% of genome and is the collection or set of all the coding regions of the genes in our cells. Using these technologies, it is possible to study every gene in our body known till date.

Application of the genomic technology was initiated in the "diseased" population for diagnosis of genetic disorders. Once this was established in the second decade of this century, the focus gradually shifted to "carrier" or "at risk" population, with aim of preventing the occurrence of at least the profound and severe "untreatable" genetic disorders. This is applicable to all the autosomal recessive and X-linked recessively inherited disorders and is rapidly gaining momentum as the awareness increases among the young adult population, creating the need for the test. The inheritance of autosomal and X-linked disorders is explained in **Figure 1A**. This chapter focuses on the "carrier screening" for these genetically inheritable disorders. Screening for chromosomal disorders such as Down syndrome is out of scope for this chapter.

HISTORICAL AND CULTURAL PERSPECTIVE

Since the target population for genetic carrier screening are couples who are planning pregnancy, the carrier screening draws many analogies to the traditional Indian method of pairing two adults by "*Kundli matching*" for marriage. *Janam Kundli* (called birth chart in English) is an integral part of Indian culture. It is a map of the sky *(stars)* as seen at the time of birth. It is the basis of predicting future in astrology. *Kundli milan* or Horoscope matching refers to the compatibility analysis between couples as per Vedic Astrology. Accurate *Kundali* match making or *Gun Milan* is critical for a happy, long-term, and successful married life and thus considered extremely important as per the Indian tradition before finalizing the marriage. The "*Gun Milan*" can be compared to the modern day "carrier screening", in some ways. Almost every human being is a

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carrier of at least 1 or 2 faulty genes among the 20,000+ genes in our body. In case of autosomal recessive genes, a heterozygote state is a carrier state, which if passed on from both husband and wife, to offspring can translate into disease, in homozygous state **(Fig. 1B)**. This is preventable by screening for such carrier status in a given couple, which forms the gist of this chapter.

The history of strategies to prevent disorders from occurring dates back to 1960s when beta-thalassemia was recognized as a genetic disorder that could be prevented by carrier screening of couples or prospective couples in Cyprus. The awareness of genetic disorders in Ashkenazi Jews of Tay-Sachs and Gaucher disease was later translated into successful carrier screening for these disorders in the 1970s. The later decades saw a progressive rise in number of disorders screened. The American College of Medical Genetics and Genomics (ACMG) as well as of Obstetrics and Gynecology (ACOG) chose cystic fibrosis (CF) as a screenable condition because of its wide prevalence in Caucasian population and the significant morbidity associated with the condition.

With the advent of Next Generation Sequencing (NGS) in the second decade of the century, many private laboratories started to offer carrier screening as panels—with a defined number of genes and particular mutations. This has now given way to the NGS based sequencing of full genes instead of known mutations to upgrade and increase the yield of detection.

WHAT IS RISK PREDICTION?

The genetic disorders are inherited in various ways leading to different risks for different disorder. The autosomal disorders can be either recessive or dominantly inherited. The autosomal recessive (AR) disorders are inherited from two carrier partners and thus there is a 25% prediction for both the abnormal alleles reaching the offspring and giving rise to disease. The autosomal dominant (AD) disorders have a 50% risk of transmission to the next generation—but the prediction of the disorder in a person's life time depends on the penetrance of the gene. For example, some genes have nearly 100% penetrance such as neurofibromatosis type 1 (NF1), and others have low penetrance. The cancer susceptibility genes are another category which are inherited dominantly but do not necessarily lead to cancer. Then we have the X-linked disorders which are typically inherited in recessive manner, but many of them may show symptoms even in the heterozygous female carriers. Thus, the prediction of either 25% overall, or up to 50% depends upon the gene and is not very accurate.

The mitochondrial DNA (mtDNA) is inherited maternally via the egg, and thus all offsprings would receive the mtDNA, but manifestation of a mitochondrial disease depends upon the relative heteroplasmy in the individual and the organ systems involved. Thus, it is impossible to predict the risk of developing a mitochondrial disorder in offsprings, which also creates challenges and difficulties in prenatal diagnosis for the same.

CARRIER SCREENING, RISK PREDICTION: WHEN, WHY AND WHAT TO SCREEN?

Carrier screening can be done on any individual (adult) or couple who may be planning or are in early stages of pregnancy. The screening process involves pretest and post-counseling which will be explained in detail later. An informed consent is an essential part of the screening that

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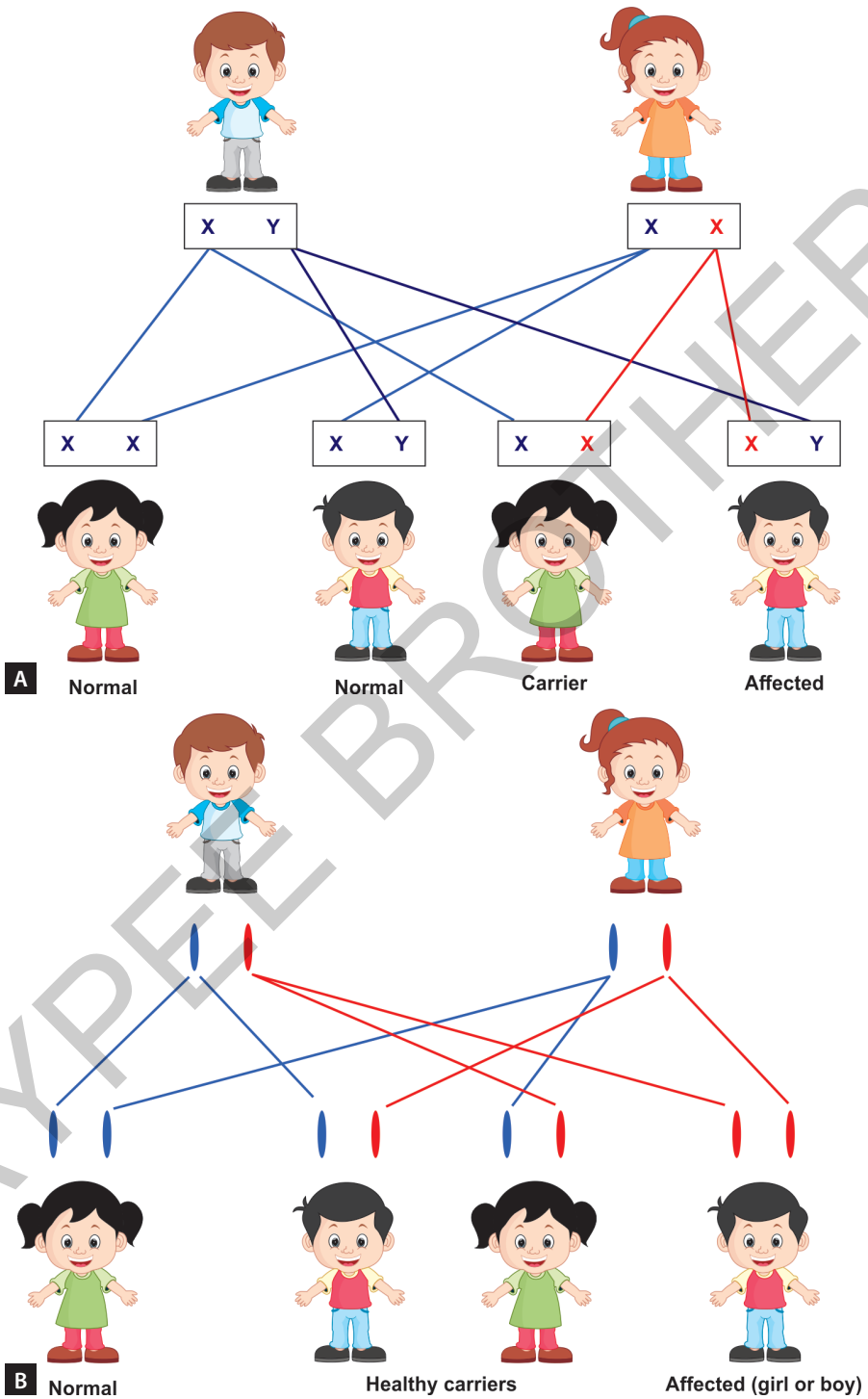

Figs. 1A and B: (A) X-linked pattern of inheritance; (B) Diagrammatic representation of autosomal recessive inheritance.

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is why it is performed on adults. The test can be performed together in a couple or sequentially, one partner after the other, in case of couples.

The screening helps an individual or a couple to learn about any potential risks to their offspring of an untreatable or severe life-threatening or life limiting genetic disorder. This usually refers to those with no family history or known risk of a disease. The screening, if positive, allows couples the opportunity to consider the most appropriate reproductive option as a preventative measure. The test may be either during pregnancy [prenatal diagnosis (PND)] or prior to pregnancy [in vitro fertilization with preimplantation genetic diagnosis (IVF-PGD)]. Although performed on asymptomatic individuals, the screening tests may also include some presymptomatic carriers such as Fragile X syndrome (FXS) and other semi-dominant conditions for which genetic counseling are recommended.

The screening is ideally performed for preventable disorders. These disorders should be severe enough to cause significant morbidity and mortality.

DISORDERS FOR CARRIER SCREENING

Screening for Blood Disorders: Thalassemia and Sickle Cell Disease

Beta-thalassemia is the most common autosomal recessive disorder and the predominant type of hereditary anemia in the Indian subcontinent and Mediterranean region. Carrier frequency of β-thalassemia is shown to be 3–4% on an average in India, being higher in certain communities such as Punjabis, Sindhis, Gujaratis, etc. It is now well-recognized that it must be offered in the preconception and early pregnancy stage to all couples irrespective of state and caste.

Screening for beta-thalassemia carrier or trait is primarily being offered on hematological tests like complete blood count with indices which shows a microcytic hypochromic anemia in carriers and hemoglobin electrophoresis or HPLC which displays HbA_2 greater than 3.5%. However, there are certain pitfalls to detecting carriers by this method. Coinheritance of α or δ thalassemia can obscure the indices or HbA_2 values. Rarely some individuals may be silent carriers, that is, carrying very mild pathogenic variants with normal blood indices and normal or borderline HbA_2 values. Hence, expanded carrier screening is emerging as good diagnostic tool to pick up all types of carriers. However, multiplex ligation dependent probe amplification (MLPA) or polymerase chain reaction (PCR)-based methods are required to pick up deletions like that seen in δβ thalassemia or α thalassemia.

Sickle cell disease occurs due to a single known mutation (p.Glu6Val) in the HbS alleles of an individual. It can also cause disease with HbC and β thalassemia mutations (including D Punjab, a common benign variant in North India and HbE variant, a common benign variant in North East India). Its carrier frequency is high in African Blacks and certain states and tribal communities of India (Bihar, Madhya Pradesh, and Maharashtra). It can easily be detected by Hb electrophoresis and confirmed by genetic testing in carrier individuals.

Screening for Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a degenerative disease of the neurons and can present with muscle weakness at any age from infancy to adulthood. It occurs due to absence of both copies of *SMN1* gene. It causes early mortality if it presents early and

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considerable morbidity in later presenting cases. Its carrier frequency has been reported to be one in 45 in White Caucasians and one in 71 in Asian Indians in one study. Another more recent study from north India reported carrier frequency of one in 44. Hence, SMA is common in all populations and carrier screening is now recommended to be offered to all irrespective of ethnicity. Carrier status is detected using MLPA technique and cannot be picked up by NGS which has weak sensitivity for identifying larger deletions. Special mention, for a small number of individuals (2% of population) who have two copies of *SMN1* gene on one chromosome and none on the other and show normal carrier screening results. This is an important point in counseling individuals with normal carrier screening results as it reduces their risk of having an affected child considerably but does not make it zero, incase their partner is also a carrier.

Screening for Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is the most common X-linked recessive neuromuscular disorder in boys with a universal prevalence of 1 in 3,500. Despite the X-linked inheritance 30% cases are new mutations and the mother is not a carrier. Majority of the cases are caused by deletions (65%) or duplications (5–8%) of single or multiple exons in the *dystrophin* gene. About 25–30% cases are attributable to point mutations and small insertion/deletions. A combination of MLPA and NGS is required to detect female carriers for DMD with no prior family history.

Screening for Fragile X Syndrome

Fragile X syndrome is the most common inherited cause of intellectual disability and inherited in an X-linked manner. Females may be affected with a lesser frequency. It also accounts for roughly 2% of the cases of autism spectrum disorder. It occurs due to expanded CGG repeats (>200) in the *FMR1* gene promoter region. The mother of an affected child is almost always a carrier of repeats in premutation range (55–200) or full mutation. There is variability in the prevalence of FXS reported in studies although almost all studies report a high prevalence. A meta-analysis revealed the premutation frequency to be 1:291 in women and 1:855 in men. A methylation based test MLPA is essential for the accurate diagnosis of carrier women.

Screening for Cystic Fibrosis

Cystic fibrosis is characterized by chronic lung disease with or without gastrointestinal problems and is life limiting. Screening for CF, a highly frequent genetic disease in the Caucasian population, with a carrier frequency of 1/25 individuals, is another milestone in the history of carrier screening. It has evolved from being restricted to the p.Phe508del (deltaF508) mutation to detection of 100 or more mutations and *CFTR* sequencing. The p.Phe508del mutation accounts for 70% of CF mutations in the white population, whereas p.Trp1282Ter (W1282X) is the most common mutation in the Ashkenazi Jews.

Studies for carrier frequency of CF in India are limited. The frequency of p.Phe508del was reported to be one in 238 in one study. A recent NGS based expanded carrier screening reported a much higher carrier frequency of one in 22. Growing literature from India suggests that this disorder is much more common than previously thought and many cases are being missed in view of the different phenotypes, variable clinical severity, and lack of availability of sweat testing, and absence of new born screening. There is lack of founder or common mutations

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in *CFTR* gene and this emphasizes the need for sequencing of all coding regions of the *CFTR* gene in suspected cases in the Indian population.

Screening for Tay-Sachs Disease

Tay-Sachs disease was the second disorder to be screened in 1970s among the Ashkenazi Jewish population owing to its high incidence in this population. Tay-Sachs has a carrier frequency of 1 in 25 to 2 in 30 in this population. This disorder occurs due to the deficiency of the enzyme β-hexosaminidase and accumulation of GM2 gangliosides in the lysosomes throughout the body, particularly the central nervous system. Affected patients present most frequently in infancy with developmental delay, seizures, increased startle response to sound and cherry-red spot in the fundus of the eye. Carriers are detected with low enzyme levels in the blood but it was the systematic screening using targeted gene study that resulted in 90% reduction in its incidence in the Jewish population.

Carrier Screening Inborn Errors of Metabolism

The prevalence of amino acid disorders in India is reported to be 1:3,600 collectively, that for phenylketonuria (PKU) is 1:18,300. The actual prevalence may be higher due to the unavailability of free newborn screening and missed diagnosis resulting in early neonatal death. Most inborn errors of metabolism (IEM) are autosomal recessive (AR) and occur due to point mutations in single genes making it easy to detect carriers on NGS based carrier screening panels. The index case in the family is generally first diagnosed and parents are then screened for the carriers for the specific mutation which also helps in future pregnancy to prevent the recurrence risk in that family.

Historically, PKU was the first disorder to be screened in 1963 in newborns using Guthrie filter paper cards. This screening was however for babies who were "affected" with PKU.

While these disorders were earlier considered incurable, early diagnosis and treatment and dietary modifications can improve quality of life and longevity in these patients. Thus, genetic counseling for carrier couples will have to be tailored according to the disorder identified, for example, biotinidase deficiency can easily treated with oral biotin supplements (easily and cheaply available in India) from birth in infants.

Screening for Congenital Hearing Loss

Hearing loss is the second most common form of disability reported by the WHO. The disabled persons survey carried out in 2003 in India, revealed that about 7% individuals suffer from congenital hearing loss. The knowledge and attitude toward congenital hearing loss in a resource poor country like India differ considerably from the West due to lack of adequate government and social support and rehabilitation. Recently carrier studies in India as well have reported the carrier frequency for genetic deafness to be high (1 in 17). Congenital deafness can occur due to mutations in one or more of several genes and it shows all patterns of inheritance—autosomal dominant, autosomal recessive, X-linked, digenic and mitochondrial depending on the gene. These factors make NGS the ideal testing modality for carrier screening for genes related to congenital deafness in young couples. A careful pretest counseling for such disorders is essential as there is availability of treatment and there may be less uptake for such disorders.

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Screening for Congenital Adrenal Hyperplasia

The prevalence of congenital adrenal hyperplasia (CAH) in India is reported to be around 1:5,762, although regional differences may occur. There are several types of which 21α-hydroxylase deficiency is the most common and can present with salt wasting, dehydration, shock, and early death in newborn males and disorder of sexual differentiation or virilizing features in girls. Although, it is a treatable disorder, treatment must begin in utero in female fetuses and soon after birth in males and is lifelong. An almost equal proportion of cases occur due to deletion/duplications (identified by MLPA) and point mutations (identified by sequencing) in the *CYP21A2* gene and combination carrier screening is ideal for detecting majority of carriers.

FOUNDER MUTATIONS IN INDIA

Owing to the prevalence of endogamy and consanguinity in India, many founder mutations have been reported in India. A founder mutation is a genetic alteration observed with high frequency in a group that is or was geographically or culturally isolated, in which one or more of the ancestors was a carrier of the altered gene. These must be carefully looked at during the analysis of reporting of carrier screening by NGS. Several founder mutations are reported in India and **Table 1** summarizes some of the common genes are their reported pathogenic variants. The complete list is very long and beyond the scope of this chapter. The utility of founder mutations is that it allows cascade testing of several family members using targeted mutation testing which is cheaper and genetic counseling during premarital or

TABLE 1: Some of the common genes and their founder mutations reported from India.

S. No.	*Disorder*	*Gene*	*Pathogenic variant*	*Region*
1.	AR limb girdle muscular dystrophy type 2A	*CAPN3*	p.Asp780His, c.2099-1G>T	Agarwal community
2.	Hereditary fructose intolerance	*ALDOB*	c.324+1G>A	Agarwal
3.	Pantothenate kinase-associated neurodegeneration (PKAN)	*PANK2*	c.216dupA	Agarwal
4.	Heme-oxygenase 1 deficiency	*HMOX1*	p.Arg44Ter	Agarwal
5.	Megalencephalic leukodystrophy with subcortical cysts (MLC)	*MLC1*	c.135dupC	Agarwal
6.	β-thalassemia	*HBB*	• c.92+5G>C • 619-bp deletion c.92+1G>T • c.124_127delTCTT c.27dupG	North India
7.	Gaucher disease	*GBA*	p.Leu483Pro	All parts of India
8.	Tay-Sachs disease	*HEXA*	p.Glu462Val	Gujarati
9.	Primary hyperoxaluria type I	*AGXT*	p.Leu101Pro	North India
10.	Nonsyndromic hearing loss	*GJB2*	p.Trp24Ter	Not known
11.	Oculocutaneous albinism	*OCA1*	p.Arg278Ter	Asian
12.	Progressive pseudorheumatoid dysplasia	*WISP3*	p.Cys337Tyr	South India

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preconceptional stage to prevent the birth of an affected child.

Methodology

Since 2009, with rapid advancement in technology and availability of NGS, carrier screening transformed from a single test based on ethnicity to simultaneous screening for approximately 100 disorders, regardless of ethnicity, via various commercial laboratories. This panel-based screening for multiple disorders is referred to as expanded carrier screening (ECS).

While NGS can identify point mutations and small insertion/deletions reliably it cannot identify larger deletions such as those seen in SMA, DMD and CAH or methylation disorders such as FXS, all of which have a high carrier frequency. Hence, any carrier screening panel should test these disorders separately using appropriate methods. In addition, studies have now shown that approximately 5% of individuals are carriers of significant copy number variations (CNVs) which can cause disease with a point mutation on the other allele. Standard NGS techniques fail to identify such CNVs which are typically identified by microarray or especially developed PCRs. Genome sequencing has emerged as the single answer to identify both point mutation and CNVs. However, cost till date remains high and availability is still limited. In such a scenario, it is imperative to add a disclaimer to ECS reports regarding the sensitivity of NGS. Individuals should be counseled that there is considerably reduced risk of genetic disease in offspring but not zero.

GENETIC COUNSELING AND THE ROLE OF GENETIC COUNSELOR

Genetic counseling is essential both before (pretest) and after (post-test) the carrier screening. This is to provide the individuals or couples a reasonable understanding of the disorders, the severity and the variability of each disorder, the feasibility of testing (number of disorders to be tested, cost involved, time taken) and also some uncertainties involved (lack of precise predictability for certain disorders and genetic variants). This is essentially to help the couples to be able to take crucial reproductive decisions either at prepregnancy stage or prenatal stage. Understanding severity, consequences, graveness of carrier screening testing and communication of the same is the primary role of a genetic counselor.

Salient points of counseling from recommendations published in 2015 are discussed here.

Pretest Counseling

- Discuss and broadly describe the diseases being screened and that some conditions may have less severity or less well-defined phenotypes.
- Testing is voluntary for the individual.
- Screen negative results reduce the likelihood of carrier state for conditions screened, but the residual risk of being a carrier always remains.
- Most conditions on ECS panels are autosomal recessive or X-linked, but some may be autosomal dominant which may have implications for the health of those screened and separate consent should be obtained for it.
- If each partner is found to be a carrier for a different autosomal recessive condition, offspring are not likely to be affected. Only if both partners are carriers of pathogenic variants for the same disorder the offspring is likely to be affected. Being a carrier has no clinical consequences for the individual carrier.

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- In some cases individual might learn they have an autosomal recessive, dominant or X-linked condition themselves which might affect their health.

Post-test Counseling

- There is a risk of 25% for the fetus to be affected if both partners are carriers and up to 50% risk if an X-linked condition is identified. The condition and its inheritance should be discussed in detail.
- Prenatal testing should be discussed in an ongoing pregnancy in the above scenario. Preimplantation genetic diagnosis is now available in the country at many centers and avoids the need for prenatal testing although cost is high.
- If both partners are not carriers for the same disease risk is considerably reduced and prenatal testing is not indicated. However residual risk remains there.
- The significance of the carrier status for other family members should be discussed and written information to be shared should be offered.

CHALLENGES IN COUNSELING IN CARRIER SCREENING

- Novel or variants of uncertain significance may be identified. Currently, it is not recommended to report these. Prenatal diagnosis should not be performed on these without clear evidence of pathogenicity.
- Some individuals may experience stigmatization or anxiety on being identified as a carrier, particularly women who are carriers of X-linked disorders. Such situations need to be handled with sensitivity and discreetness. Information may be limited to the couple and any other family member who are directly at risk. The individual should be provided adequate psychosocial support and information about the severity of the disorder and morbidity and mortality associated with it, as well as available treatment and support.
- Information should be discussed and shared in a language and format (diagrams) best understood by the individuals especially belonging to semiurban and rural areas.
- There may be initial denial by the individuals or their families and they may need some time to accept the situation.
- The legal limit for a termination of pregnancy in India is 20 weeks (recently increased to 22 weeks). Thus, time required to complete any prenatal testing, if desired and the gestation of pregnancy should be kept in mind.

GUIDELINES ON CARRIER SCREENING

The 2013 ACMG statement on prenatal/preconceptional expanded carrier screening suggested that certain criteria should be met when a disorder is introduced into a carrier screening panel for population based screening. The disorders should be such that couples desire prenatal diagnosis for it. Disorders with variable expressivity or incomplete penetrance should be made optional. Adult-onset disorders can have implications for the individuals own health and the individual's consent should be obtained for testing for it. Patients should be informed about residual risk and undergo a post-test counseling. The laboratories need to maintain adequate quality control.

The 2015 joint statement of ACMG, ACOG, National Society of Genetic counselors, Perinatal Quality Foundation and Society of Maternal and Fetal Medicine (SMFM) clearly defines the components of

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TABLE 2: Current recommendations for carrier screening in the West.

Racial/Ethnic category	*ACOG recommendations*		*ACMG recommendations*	
	Disease name	*Gene name*	*Disease name*	*Gene name*
To all patients	Cystic fibrosis	*CFTR*	Cystic fibrosis	*CFTR*
	Spinal muscular atrophy	*SMN1*	Spinal muscular atrophy	*SMN1*
	Hemoglobinopathies	CBC for all and electrophoresis based on CBC and ethnicity	Not mentioned	
Family history of ID/ovarian insufficiency	Fragile X	*FMR1*	Fragile X	*FMR1*
Ashkenazi Jews	Canavan disease	*ASPA*	Canavan disease	*ASPA*
	Familial dysautonomia	*IKBKAP*	Familial dysautonomia	*IKBKAP*
	Tay-Sachs disease	*HEXA*	Tay-Sachs disease	*HEXA*
			Fanconi anemia type C	*FANCC*
			Gaucher disease	*GBA*
			Mucolipidosis type IV	*MCOLN1*
			Niemann Pick disease type A	*SMPD1*
			Bloom syndrome	*BLM*

(CBC: complete blood count; ID: intellectual disability)

consent for expanded carrier screening, the points of pretest and post-test counseling, the conditions which should be included on ECS panels and interpretation of molecular findings. They suggested the development of a curated Data Repository of Variants and associated phenotypes as ECS is implemented on more and previously untested ethnic and racial groups.

An ACOG committee opinion was published in 2017. They stated that ethnic-specific, pan-ethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening and each obstetrician-gynecologist should establish a standard approach for this. Screening for CF and SMA and blood investigations for hemoglobinopathies should be offered to all women pregnant or planning a pregnancy. Fragile X screening maybe offered to those with a suggestive family history. Additional screening maybe offered in case of specific ethnicity or family history. Couple with consanguinity should be offered genetic counseling for the risks. Further reproductive options should be discussed based on the reports. Carrier screening panels should include disorders with a carrier frequency of greater than 1 in 100 and have an early onset in life with a detrimental effect on quality of life **(Table 2)**.

CARRIER SCREENING IN SPECIFIC SCENARIOS

Apart from the general carrier screening which has been described earlier whether targeted or extended, there are certain specific situations where such testing is fruitful. These are situations where couples give a history of a previous death in the family (child or sibling) with a genetic disorder, but no specific testing had been performed to confirm the diagnosis.

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This is a common scenario in genetic clinics, at least in India. In such situations, attempt is made to first narrow down the diagnosis by detailed history, noting relevant points, studying the available medical records and investigations of the affected person, and drawing a pedigree chart to determine the risk to the couple of such disease in their offspring. In majority of autosomal recessive or X-linked disorders, where some clinical diagnosis has been made, testing can be offered. Testing can be performed via NGS or targeted testing as the case may be. It is usually performed both on husband and wife, except where there is consanguinity, and if the history is suggestive of an X-linked disorder in which case the woman is tested. There is utility as well as futility in such cases. Two cases are described—two unrelated couples presented for preconceptional counseling, with a history of neonatal death each. Both the neonates had died of metabolic acidosis, and the tandem mass spectrometry (TMS) on their dried blood spots had shown elevated propionyl carnitine. While the elevated C3 was quite suggestive of an inherited organic acidemia [methylmalonic or propionic acidemia (MMA/PA)], however there were several other nongenetic differentials for the elevation. Taking a clue from this report, both the couples were offered clinical exome sequencing (CES), starting with women. While couple 1 was successfully identified to be carriers of pathogenic variant in *MMAA* gene, leading to a successful prenatal diagnosis, the second couple could not be confirmed with the same as the CES was negative. They also planned a pregnancy and delivered a baby boy who was tested using TMS and ultimately diagnosed with MMA. This baby was then identified to have a homozygous deletion of a single exon in MMAA, which was not picked up in the CES of both husband and wife in heterozygous states. Thus, NGS also may have fallacies which need to be identified and addressed.

CONCLUSION

Expanded carrier screening via NGS marks a new era of preventive genetics. It empowers the couples to make informed reproductive choices. The tests are increasingly becoming available, and are also affordable.

The role of a genetic counselor or geneticist is very crucial, as the information passed on to the couples should not only be accurate but also relevant and helpful. The disorders to be screened should be carefully chosen, tailored toward couples' requirements. The prenatal or preimplantation genetic diagnosis should be performed according to the available guidelines and legislations. The best time for a couple to undergo expanded carrier screening is prepregnancy.

Lastly, it is important to remember that with all the methodologies available, some disorders or genetic variants could still remain undetected, thus not eliminating the chances of a genetic disorder completely in the offspring.

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Usha Dave PhD DHA started her postdoctoral career by establishing the Centre for Research in Mental Retardation (CREMERE) in 1985 to offer clinical and laboratory diagnostic services in the area of genetic and associated neurological disorders. She started first gas chromatography/mass spectrometry (GC/MS) metabolic diagnostic service in 1998 in India. Being a postgraduate (PG) Research Guide of Mumbai University and National Professor at Haffkine Institute, Mumbai, she guided several MSc and PhD students successfully.

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