Carrier Screening for Inherited Genetic Disorders

Inherited Genetic Disorders – Indian Scenario (1, 2, 3)

Almost all known reported genetic disorders are found in India. It is estimated that India probably has the largest number of infants affected by congenital and genetic disorders in the world.

Thalassaemias and sickle cell disease are the commonest monogenic disorders in India. There are an estimated 7500 - 12,000 babies with β-thalassaemia major born every year in the country. While the overall prevalence of carriers in different States varies from 1.5 to 4 per cent, communities like Sindhis, Punjabis, Lohanas, Kutchi Bhanushalis, Jains and Bohris have a higher prevalence (4-17%). Also, India probably has the largest number of carriers for haemoglobinopathies in the world. Haemoglobin S (HbS) is prevalent in central India and among the tribal belts in western, eastern and southern India, the carrier rates varying from 1-40 per cent. It has been estimated that over 5000 babies with sickle cell disease would be born each year. The prevalence of HbE varies among the different caste/ethnic groups in India and the carrier frequency may be as high as 30-40% in tribal communities. Both Hb E and Hb S when co-inherited with β-thalassaemia result in a disorder of variable clinical severity.

The pan-ethnic genetic conditions like Spinal Muscular Atrophy and Duchenne Muscular Dystrophy have prevalence and carrier rates similar to worldwide prevalence. Common genetic disorders like Hemophilia, Achondroplasia, Huntington disease, Lysosomal storage disorders, and many others have been reported in large numbers from all parts of the country. Also, all inborn errors of metabolism are seen in India.

Below an estimate of the birth prevalence of selected congenital and genetic disorders has been made for the GenTEE survey based upon hospital-based data.
Burden of congenital and genetic disorders, national estimate for the birth prevalence of selected disorders for India

Clustered distribution of single gene disorders in India

What is Carrier Screening (1, 4, 5)?
Carrier screening, according to the European Society of Human Genetics is defined as a type of medical investigation to detect whether or not carrier status for a recessive disorder is present in a couple or a person, who does not have an a priori increased risk of being a carrier based on their or their partners’ personal or family disease history. Carriers are usually not at risk of developing the disease, but have a risk of passing a pathogenic gene mutation to their offspring. Carrier screening accompanied by genetic counselling provides individuals with information about their reproductive risks by identifying gene mutations associated with autosomal recessive or X-linked disorders. Carrier screening can be considered at different life stages –
1. By individuals or couples before pregnancy (preconception carrier screening)
2. Before relationships commence (premarital, or pre-relationship carrier screening, for example, high-school screening)
3. By women during pregnancy and their partners (prenatal carrier screening)

Who Should Consider Carrier Screening?
1. Individuals may be considered for carrier screening based on a family history of a genetic condition:
   a. The individuals have a previously affected child with the genetic disease OR
   b. One or both individuals have a first- or second-degree relative who is affected OR
   c. One or both individuals have a first-degree relative with an affected offspring OR
   d. One individual is known to be a carrier OR
   e. One or both individuals are members of a population known to have a carrier rate that exceeds a threshold considered appropriate for testing for a particular condition
2. The genetic condition is associated with potentially severe disability or has a lethal natural history.

Significance of Carrier Screening
• Carrier screening helps identify individuals and/or couples at risk for having children with inherited genetic disorders.
• Knowledge of carrier status can aid in making reproductive decisions before and during pregnancy, thus increasing a couple’s reproductive autonomy and choice which can facilitate better perinatal diagnosis with early management of genetic disorders.
• Carrier screening may result in more couples deciding to –
  – have prenatal testing (amniocentesis or CVS) to determine whether or not the baby has inherited the two abnormal genes
  – accept this level of risk and have children without further testing
  – go through in vitro fertilization and test the embryos using preimplantation genetic screening (PGS)
  – adopt children; abstain from having children
  – use donor gametes
In some cultures, where the focus of screening is on spouse/partner selection or carrier matching, changing the choice of partner to prevent disease is an option.

- As a consequence, carrier screening may lead to reduction in number of children born with diseases that are screened for, further reducing birth prevalence of such genetic conditions.
- In addition to the impact for the individual or couple, identification of some sequence variants may have implications for the extended family members, leading to specific carrier testing and reproductive options.

**Interpretation**

A negative result significantly lowers, but does not completely eliminate, the risk of being a carrier. For autosomal recessive diseases, if the test determines that one is a carrier, the next step is for the partner to have carrier testing performed. Both parents must be carriers for the baby to be at risk for an autosomal recessive disease. X-linked diseases are inherited through the mother. If testing determines that a couple/mother is at high risk, prenatal testing (CVS or amniocentesis) during pregnancy can be done to see whether or not the baby has inherited the disease. A follow-up visit with a perinatologist and/or genetic counselor may be recommended.

**Expanded Scope of Diagnosis & Screening (5, 6, 7)**

For years, clinicians have offered gene-by-gene carrier screening to patients and couples considering future pregnancy or those with an ongoing pregnancy early in gestation for one or few relatively common recessive disorders associated with significant morbidity, reduced life-expectancy and often because of a considerable higher carrier frequency in a specific population for certain diseases.

Globally, however, around 7000+ rare disorders are reported so far and India is projected to have ~70 million individuals with or carrying these rare disorders. Approximately 80% of rare disorders (~5600) are genetic in origin many of them being monogenic (single gene disorders). Almost 50% of rare disorders onset at birth (neonatal) and the rest are late onset (adult). Diagnosis of these rare disorders is challenging and requires high index of suspicion. Genetic screening of mutations/variations associated with these disorders provides rapid means of confirmation in high index cases. For few of these disorders timely diagnosis leads to early treatment and may avoid acute and chronic complications, developmental compromise and even death.

With the introduction of new (faster and cheaper) genetic technologies, it is now possible to detect a much larger set of sequence variants, but also to simultaneously screen for many different diseases at a faster turnaround time without significantly increasing costs. **Next Generation Sequencing** enables high throughput screening of multiple genes thereby facilitating diagnosis of inherited disorders in one-step.

Moreover, while some current screening programmes are ancestry-based, “Expanded Carrier Screening” (sometimes referred to as ‘Panethnic’ or ‘Universal’) allows testing of all individuals regardless of ancestry, which in this respect increases equity and potentially reduces the risk of stigmatisation of ethnic groups.

SRL offers GDNExt panel which targets coding exons of 328 genes for almost 700 rare genetic disorders related to around 15 disease categories including the most common forms of inherited deafness, blindness, cardiomyopathies, Parkinson’s disease, immunodeficiency, and various ataxias, anemias, and treatable metabolic syndromes.

<table>
<thead>
<tr>
<th>Metabolic Disorders</th>
<th>Cardiomyopathies</th>
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<tbody>
<tr>
<td>Biotinidase Deficiency</td>
<td>Dilated Cardiomyopathy</td>
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<tr>
<td>Galactosemia</td>
<td>Familial Hypertrophic Cardiomyopathy</td>
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<tr>
<td>Phenylketonuria</td>
<td>Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy</td>
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<td>Maple Syrup Urine Disease</td>
<td>Long QT Syndrome</td>
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<td>Methylmalonic Acidemia</td>
<td>Brugada Syndrome</td>
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<tr>
<td>Argininosuccinate Lyase Deficiency</td>
<td>Atrial Septal Defect</td>
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<td>Congenital Disorder of Glososylation Type 1a</td>
<td>Short QT Syndrome</td>
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<tr>
<td>Beta-Hydroxyisobutyryl CoA Deacylase Deficiency</td>
<td>Cathexolaminergic Polymorphic Ventricular Tachycardia (CPVT)</td>
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<td>Ornithine Transcarbamylase Deficiency</td>
<td>Epidermolysis Bullosa Simplex</td>
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<td>Glycogen Storage Disease Type VI</td>
<td>Alpers Syndrome</td>
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<tr>
<td>Hydroxymethylbilane Synthase (HMBS) Deficiency</td>
<td>Limb-Girdle Muscular Dystrophy, Type 1B</td>
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**Significance of Inherited Genetic Disorders Testing**

The shift to pan-ethnic offering of any disorder screened can be summarized most simply as an equitable, effective model for an evolving population. Beyond reproductive decision-making, an expanded disease panel may also widen...
the scope of objectives that can be achieved through carrier screening. Prenatal awareness of substantial risk may confer even greater benefits, since certain diseases (e.g., medium chain acyl-CoA dehydrogenase deficiency) may cause long-term sequelae even before newborn screening results are available, or may be diagnosed at ages by which another affected pregnancy could have already occurred.

For some conditions carrier screening could also reveal increased risk of morbidity for potential carriers. For example, carriers of Ataxia Telangiectasia have an increased lifetime risk for breast cancer; and carriers of the Fragile X (FMR1) premutation have an increased risk of primary ovarian insufficiency and can develop a neurodegenerative disorder (Fragile X-associated Tremor/Ataxia Syndrome; FXTAS) in adulthood. In the future, more associations between carrier states and increased or decreased risks for diseases will likely be revealed.

It can be referred for –
- Carrier testing of individuals with relevant familial or clinical history
- Neonatal second tier diagnosis of suspected/index cases
- Presymptomatic testing for estimating the risk of developing adult-onset diseases
- Confirmation of diagnosis of a symptomatic individuals

**Conclusion**
The complex genetic architecture, the vast numbers, the high rates of consanguinity, all position India as a Pandora’s Box of inherited genetic disorders. Despite ongoing promising expansions in the field and availability of state of the art clinical and diagnostic facilities; a large volume of prospective subjects remain unaware of the significance and utility of carrier testing. The joint ACOG/ ACMGG/ NSGC/ SMFM/ PQF statement on expanded carrier screening is an important step toward recognition of carrier screening as a critical component of preconception and prenatal care (Nazareth SB 2015).

**References**
2. Genetic Testing in Emerging Economies (GenTEE) Summary Report 2013

**Tests Offered at SRL**

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<thead>
<tr>
<th>Test Name</th>
<th>Method</th>
<th>Test Code</th>
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<tbody>
<tr>
<td>GDNExT</td>
<td>Next Generation Sequencing</td>
<td>Will be available soon</td>
</tr>
<tr>
<td>CardioNexT</td>
<td>Next Generation Sequencing</td>
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