

## **Genetic Diagnosis & Treatment-How far We are ?**

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### Introduction

Modern days treatment modalities include preventive, Curative (therapeutic & surgical), Palliative means, Radiation and chemotherapy, Laser treatment. Because of the research understanding study of disease, diagnosis and treatment modalities are now multifactorial and specific specially at molecular & genetic level. Genetic counseling & diagnosis has become a prominent feature in prevention and treatment of genetic disease which is a major cause of mortality & morbidity now a days. Efforts are on to start gene therapy and there are avenues where gene therapy can play an important role in treating disease.

### Global situation

Genetic disease is very common one in medical practice. It is estimated to be 670 per thousand in developed Countries. 50% of spontaneous abortions during early months of gestation are found to have a demonstrable chromosomal aberration. About 1% of all newborn infants possesses a gross chromosomal abnormality and about 5% of individuals under 25 years of each develop various disease with significant genetic component. Genetic discsea is one of the important cause of physical and mental retardation, various congenital anomalies, malformation and abnormalities in development of different organs and cause increase morbidity, mortality, social, familial and economic burden to the family, nation as a whole. It is desirable therefore to prevent this problem by early molecular diagnosis, genetic counseling and appropriate treatment.

### Indication for genetic disease testing

It is divided into prenatal, postnatal and acquired genetic abnormalities. Prenatal genetic analysis is indicated in patients who are at risk of having cytogenetically abnormal pregnancy, this include

- 1 A mother of advanced age (> 35 years) because of greater risk of trisomies
- 1 A parent who is a carrier of a balanced reciprocal translocation, Robertsonian translocation, or inversion (in these cases the gametes may be unbalanced, and hence the progeny would be at risk for chromosomal disorders)
- 1 A parent with a previous child with a chromosomal abnormality
- 1 A fetus with ultrasound-detected abnormalities
- 1 A parent who is a carrier of an X-linked genetic disorder (to determine fetal sex)
- 1 Abnormal levels of AFP, bHCG, and estriol performed as the triple test.

Postnatal genetic analysis is done on peripheral blood lymphocytes and indication include

- 1 Multiple congenital anomalies
- 1 Unexplained mental retardation and/or developmental delay
- 1 Suspected aneuploidy (e.g., features of Down syndrome)
- 1 Suspected unbalanced autosome (e.g., Prader-Willi syndrome)
- 1 Suspected sex chromosomal abnormality (e.g., Turner syndrome)
- 1 Suspected fragile-X syndrome
- 1 Infertility (to rule out sex chromosomal abnormality)

- 1 Multiple spontaneous abortions (to rule out the parents as carriers of balanced translocation; both partners should be evaluated)

**Indication of acquired genetic alteration include  
Diagnosis and management of cancer**

- 1 Detection of tumor-specific acquired mutations and cytogenetic alterations that are the hallmarks of specific tumors (e.g., BCR-ABL in chronic myeloid leukemia or CML)
- 1 Determination of clonality as an indicator of a neoplastic (i.e., nonreactive) condition
- 1 The identification of specific genetic alterations that can direct therapeutic choices (e.g., HER2/Neu [official name ERBB2] in breast cancer or EGFR mutations in lung cancer)
- 1 Determination of treatment efficacy (e.g., minimal residual disease detection of BCR-ABL1 by PCR in CML)
- 1 Detection of Gleevec-resistant forms of chronic myeloid leukemia and gastrointestinal stromal tumors

**Diagnostic modalities of genetic disease:  
These include  
PCR & DNA Sequence alteration**

Polymerase chain reaction or PCR is widely used as molecular biology technique in molecular diagnosis of human disease including genetic disease. PCR involves exponential amplification of DNA. By using appropriate DNA polymerase and thermal cycling the target DNA is greatly amplified, Producing millions of copies of DNA sequence between two primer sites, DNA can be sequenced to obtain a readout of the order of nucleotides and by comparison with a normal (wild type) sequence, mutations can be identified.

**Detection of DNA mutation by indirect methods**

- 1 One simple method is to digest DNA in the enzymes known as restriction enzymes that recognize and then cut DNA at specific sequences.
- 1 Another approach is identifying mutations at a specific nucleotide position. Example a

codon 12 mutation in KRAS oncogene that converts glycine (GAT) to aspartic acid (GAT). Here fluorescently labeled

Nucleotides C & T are added to PCR mixture. Since the two nucleotides are labeled with different fluorophores which detect presence or absence of mutations.

- 1 Mutations affecting the length of DNA is deletion or expansion can also be detected by PCR genetic Analysis.

**Molecular Diagnosis is done by**

- 1 Southern blotting - Specific loci can be detected by SB
- 1 Fluorescence in situ Hybridization - Recognise sequences specific to particular chromosomal regions.
- 1 Array based comparative Genetic Hybridisation (Array CGH) - DNA and a reference (Normal) labeled with two different fluorescent dyes Cy5 & Cy3 which stain red & green respectively.
- 1 RNA Analysis possible to use mRNA expression in disease in different genetic disease.
- 1 Epigenetic analysis- chemical modification of DNA in chromatin that does not alter the DNA sequence example methylation and acetylation of histones.

**Genetic testing in childhood-** this is important for proven treatments availability on appropriate screening like cystic fibrosis. Early therapy reduces disease progression or testing a child at risk of MEN2B when early thyroidectomy prevents medullary thyroid carcinoma.

**Genetic testing in Pregnancy-**

**Amniocentesis-**These include invasive tests like amniocentesis. This is done from 14 weeks onwards, have < 1% chance of miscarriage, Chromosomal, biochemical, NTD and alpha fetoprotein are some of the examples.

**Chorionic villi biopsy-**11 weeks onwards, 2% risk of miscarriage, chromosomal, DNA and biopsy can be done.

**Cordocentesis-** from 19 weeks onwards, 2-3% chance of miscarriage, a highly specialized test for chromosomal and DNA analysis.

**Genetic counseling** provides information about medical and family implications of a specific disease in a clear and nondirective manner. Clinical genetic service includes Medical geneticist who will diagnose and manage genetic disease, assess risk, manage screening programmes, genetic counselor assess genetic risk and provide genetic counselling, Modern DNA diagnostic laboratory, cytogenetic laboratory, Biochemical genetic Laboratory and New born screening laboratory. Some problems may be faced during genetic counseling which are accurate assessment of genetic risk, identification of children at risk of genetic diseases, increase in genetic risk associated with consanguinity, non paternity as an incidental finding in DNA diagnostic tests.

### **Gene Therapy**

Gene therapy mean insertion, attraction on removal of genes with an individual's cells and biological tissues. This technique is developed for corrections of defective genes that are responsible for disease development. Gene therapy involves insertion of functional gene into an unspecified generic location to replace a mutated, other forms involves directly correcting the mutated or modifying normal gene that enables viral infection. This technology is now in infancy but Limited use with screening has been reported.

### **Conclusions**

Although genetic disease is unwanted and bears a load to the family, nation as a whole however it can be prevented by early diagnosis, genetic counseling, therapeutic and surgical procedure. Recently gene Therapy has also been started in some develop countries. Much work have been done in the developed world in this regard but in Bangladesh we are lagging far behind these facilities. Limited diagnostic facilities like DNA testing, PCR, IHC are available in some selected centers in Bangladesh. The Government, members of Parliament, media people, intellectuals, doctors, think tank should raise their voice for implementation of these programmes. Government, Ministry of Health, Bank and other Financial Institutions should formulate Policy and sanction loan, import of

duty free essential to start genetic laboratory in private sector. As soon we do it will be better.

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