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Genetic Counselling: the biomedical bridge between molecular diagnosis and precision treatment

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Abstract

Background: Since the development of genomics, we are able to understand backgrounds of differential pathogenicity of metabolic disorders. Molecular diagnosis has become inevitable for metabolic, neuro-psychiatric and genetic disorders due to highly overlapping pathophysiological symptoms. The present lacuna between clinical prescription and molecular diagnosis is very prominent and can only be filled up through experts who can function as the bridge in between.

Main body: In this present review, the authors tried to focus on the role of genetic counselors in disease diagnosis as well as scopes of disease biology in utilizing the expertise of genetic professional for precision treatments of patients. We summarized four major disease areas, Cancer management, Obstetrics and Gynecology, Newborn Screening and Rare Genetic Disorders, where molecular diagnosis and genetic counseling can highly support the clinicians in precision treatment of the patients. Idiopathic reproductive failures, clinically overlapping neuro-psychiatric disorders, chromosomal aberrations in progressing tumors, rare genetic disorders all the disease areas can find out fruitful intervention when enlightened with molecular diagnosis and genetic counseling. Though, genetic counseling is commonly practiced in intervening reproductive problems, newborn screening and cancer, still the scope of genetic counselor in successfully intervening multiple rare genetic diseases as well as common hereditary life style disorders, remain extremely high.

Conclusion: The liaison between clinicians and geneticists, specifically clinical prescription and genetic diagnosis is one of the key demands of present age, which can be successfully fulfilled by the genetic counselors. For these reasons, genetic counseling is predicted as the biomedical career of future due to being in the vital position for successful implementation of precision medicine.

Keywords: Genetic counselling, Precision treatment, Molecular diagnosis, Newborn screening, Recurrent pregnancy loss, Infertility, Cancer genetics

Background

Demanding or assuring specific familial traits for the children from would be mothers are being practiced by the human civilization since eternity. At ancient times, even without knowledge of modern-day genetics, people used to predict the probable characters of the newborns. Those were probably the oldest versions of genetic counseling (GC) in the history of human civilization. Genetic diseases can occur due to structural or numerical anomalies of chromosomes, insertion/deletion (in/del) mutations and single nucleotide polymorphisms (SNP). Though karyotyping is being used to detect chromosomal anomalies for decades, detection of in/del and SNP were impenetrable until development of sophisticated genetic

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tools. With the advent of modern cutting-edge technologies for healthcare and diagnostics, it has become much easier to identify exact cause(s) behind any genetic disease. A competent geneticist, can predict the probable genetic problem, suggest specific molecular diagnosis, and interpreting the results can report details of the genetic disease to the clinician, so that precision treatment/advice can be offered to the patient or consultee. But since, practicing clinicians are rarely geneticists and vise versa, therefore a collaborative effort of geneticist and clinician is very much essential for successful patient care. Not only that, the personal interaction with patient/consultee should always be empathetic as well as non-directive. The consult and requires specific training to do such empathetic interaction, which introduces the scope of a genetic counselor, who is simultaneously a genetic expert and a counselor. The requirements, importance and the biomedical roles of genetic counselors in UK has been reviewed very well by Patch and Middleton, 2018 [1].

What is genetic counseling

Though the subject started earlier in late sixties or early seventies of the past century, a proper definition was seriously lacking for years. There were a few descriptions but all were somehow incomplete. In 2003, National Society of Genetic Counselors (NSGC), Chicago, USA, appointed a task force to find out a proper definition of genetic counseling. The task force submitted a definition and the Board of Directors of NSGC adopted it in 2005 [2]. The NSGC definition of genetic counseling is as follows –

"Genetic counseling is the process of helping people understand and adapt to the medical, psychological, and familial implications of the genetic contributions to disease. This process integrates:

- *Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.*
- *Education about inheritance, testing, management, prevention, resources and research.*
- *Counseling to promote informed choices and adaptation to the risk or condition."*

A proband with a family history of any disorder among more than one family members, needs to evaluate the genetic component, hereditary pattern and mode of transmission of the disorder. To serve the entire purpose one genetic counselor will be the perfect person.

The role of a genetic counselor is typically comprehensive, he/she is designated to identify the disease trait transmission pattern in the family using family history; estimate the probability of the proband and his / her next generation getting the trait; suggest specific molecular diagnostic tests for confirmation or even identification of any novel genetic disorder; and analyze and interpret the results of tests and comment on the best specific options for the proband. In this context, it also needed to be mentioned that, families with hereditary cancers or recurrent pregnancy loss, require compassionate psychological support even during the counselling session by a genetic counsellor. A comparison of the pathological diagnosis with molecular diagnosis is given in Fig. 1. Molecular Diagnosis for genetic diseases has remained the basic procedure to make precision treatment.

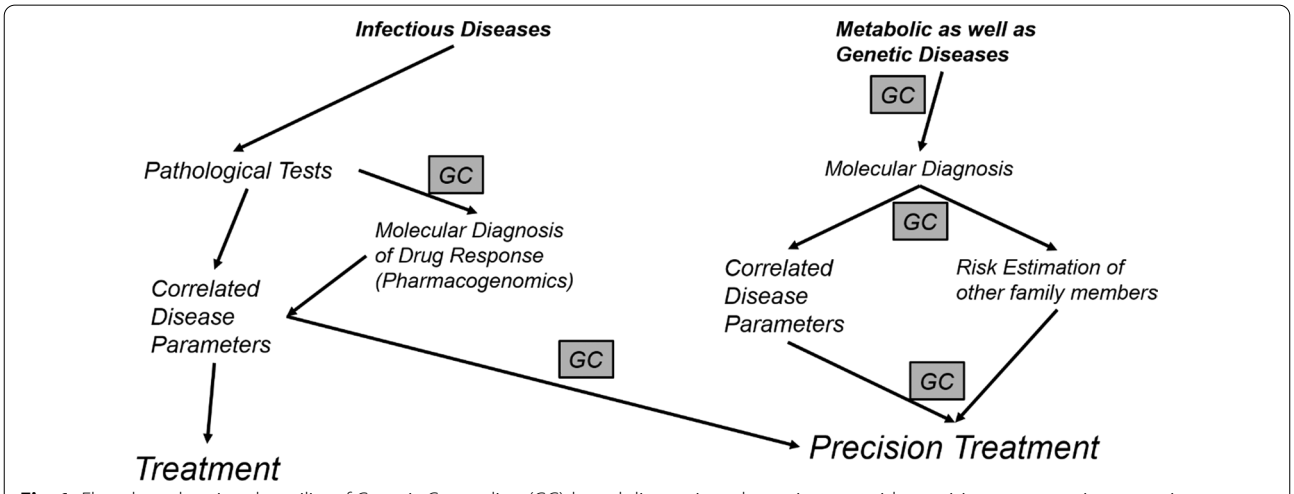

Fig. 1 Flowchart showing the utility of Genetic Counseling (GC)-based diagnosis to the patients provide precision treatment in comparison to commonly practiced procedures

Scopes of genetic counseling

From identification of disease to psychological support, a genetic counselor is required for every purpose as an empathic fellow passenger in this journey of overcoming the disease. However, if specifically stated, there are major areas of biomedical diagnostics where role of a genetic counselor is inevitable, like diseases or disorders caused due to chromosomal aberrations or point mutations. Broadly, major interventional areas could be cancer management, reproductive biology, newborn screening and rare genetic disorders.

Applications in cancer management

Not all cancer types are sporadic in nature, some major types are also familial with hereditary components reflecting autosomal dominant as well as autosomal recessive inheritance patterns. Table 1 includes hereditary nonpolyposis colorectal cancer (HNPCC), familial breast and ovarian cancer, neurofibromatosis type 1, familial retinoblastoma and many more [3].

All the tests mentioned in Table 1 are specific genetic tests which not only can identify the specific damage type but also can help in progressive evaluation of chromosomal aberrations in cancer patients. Such accurate diagnosis is extremely important for decisive precision treatment. Emergence of next generation sequencing (NGS) of liquid biopsy samples has escalated the scope of non-invasive molecular diagnosis. Not only accurate identification of chromosomal aberration patterns but also, in case of familial types of cancers, risks of other family members to develop that specific type of cancer, could be estimated. A very recent study based on GLOBOCAN 2020 data has shown that incidence of global cancer in 2020 is at around 19,292,789 [4], out of which more than 40% are genetic and thus the number of at-risk persons is increasing enormously. These at-risk persons should enroll in GC supported specific molecular screening programs as early as possible to avoid major pathological damages in patients [3]. Such enrollments can only be possible with more and more awareness programmes targeting common people as well as clinicians.

Table 1 Hereditary cancer types and corresponding Genetic tests for their diagnosis

Sl No	Type of cancer	Mode of inheritance	Genetic test for risk detection
1	Hereditary Non Polyposis Colorectal Cancer (HNPCC)	Autosomal Dominant	MSH2, MSH6, MLH1, PMS2 gene specific sequencing/ Clinical exome/Microsatellite Instability (MSI) test
2	Familial Breast & Ovarian Cancer	Autosomal Dominant	BRCA1, BRCA2, ATM, TP53, CHEK2, PTEN, CDH1, STK11, PALB2 panel screening by NGS
3	Neurofibromatosis type 1	Autosomal Dominant	Confirmatory Diagnostic NF1 Gene Sequencing, Prenatal and Preimplantation Testing is also available to determine risk
4	Familial retinoblastoma	Autosomal Dominant	Diagnostic and risk assessing RB1gene mutation scanning, can be done at prenatal level
5	Multiple endocrine neoplasia type 1 (MEN1)	Autosomal Dominant	Confirmatory Diagnosis and risk analysis by MEN1 gene Sequencing
	Multiple endocrine neoplasia type 2a (MEN2a)	Autosomal Dominant	Confirmatory Diagnosis and risk analysis by RET gene Sequencing
	Multiple endocrine neoplasia type 2b (MEN2b)	Autosomal Dominant	Confirmatory Diagnosis and risk analysis by RET gene Sequencing
6	Familial adenomatous polyposis (FAP)	Autosomal Dominant	Diagnostic and risk assessing APC gene variation scan
7	Von Hippel-Lindau disease	Autosomal Dominant	Can only be diagnosed with variation and deletion detection in VHL gene
8	Li-Fraumeni syndrome	Autosomal Dominant	With positive family history can only be diagnosed by TP53 gene testing
9	Cowden Syndrome	Autosomal Dominant	Confirmatory Diagnosis by PTEN gene scan
10	Basal Cell Nervous Syndrome (BCNS) Gorlin Syndrome	Autosomal Dominant	Confirmatory Diagnosis by PTCH gene mutation scan and or microarray/MLPA for 9q22.3 microdeletion
11	Peutz-Jeghers Syndrome	Autosomal Dominant	Confirmatory diagnosis by STK11 gene scan. Risk analysis, prenatal and preimplantation testing
12	Wilm's Tumor	Autosomal Dominant	Risk Analysis by Whole Exome Sequencing using CNV pipeline
13	MUTYH-associated polyposis (MAP)	Autosomal Recessive	Diagnosis and risk analysis can be done by MUTYH gene testing
14	Ataxia teleangiectatisia	Autosomal Recessive	Diagnosis and risk assessment by ATM gene mutation scanning
15	Fanconi anemia	Autosomal Recessive	Diagnosis by chromosomal breakage test, identifying the defecting gene by clinical exome panel

Application in reproductive biology

GC plays very crucial role in Gynecology. The process of becoming parents of a genetic disease-free child requires extensive screening in different phases. Pre-conception screening of willing to be parents, pre-natal screening in case of all pregnancies and pre-implantation screening exclusively for Assisted Reproductive Technology supported pregnancies.

Preconception screening is very much essential for Autosomal Recessive (AR) and X-linked Recessive (XR) disease carrier identification. When followed up for 25 years from birth, the global incidence rate of congenital genetic disorders among newborns were found to be 5.32% [5], which is fairly high in number. Since premarital genetic counseling or screening could be judgmental it is better to opt for pre-conceptional screening and counselling to identify specific disease traits among the would-be parents. Apart from the common causes of infertility and recurrent pregnancy loss (RPL) summarized in Table 2, there are several other genetic causes which can lead to so-called idiopathic infertility as well as RPL.

Among these, balanced translocation, where a person can live a normal life but can never transmit a normal gamete for its next generation; presence of extra satellite regions (termed as ps+) in acrocentric chromosomes or extra heterochromatin regions (termed as h+) of some chromosomes are found to associated with RPL [6–9]. These so-called idiopathic problems can be solved to a major extent through GC-based genetic diagnosis. Apart from these idiopathic problems there are some known genetic diseases that can cause infertility as well as RPL and are summarized in Table 3.

Fetal screening is very important to find out any chromosomal aneuploidies or to identify the chromosomal integrity status of the foetus. Maternal chronological age has been correlated to be associated with increased risk of chromosomal non-disjunction during oogenesis or embryo development [10, 11]. Gestational age specific genetic/biochemical/structural markers are in practice for specific identification of genetic aneuploidies. Non-invasive prenatal testing (NIPT) has significantly reduced the risk of fetal damage that was previously there when assessments were done through amniocentesis. Amniocentesis and chorionic villus sampling (CVS)/cordocentesis were not only painful for the mother but also had the risk of fetal damage. Couples with history of RPL/

Table 2 The general causes of recurrent pregnancy loss and common remedial measures

	Reasons	Diagnostic measures	Possible solutions
Recurrent Pregnancy Loss (RPL)–2 or more spontaneous abortions	Uterine Structural Abnormalities	HSG, 2D & 3D Ultrasound, saline infusion	Evidence-based Surgery
	Anti-Phospholipid Syndrome	Blood test of mother for aPL if found positive then test for LA, aCL and b2GP1	Low dose Aspirin, prophylactic dose of heparin
	Inherited Thrombophilia	Mutations in Prothrombin, Factor V Leiden, MTHFR gene and Protein C, Protein S deficiency	Treatment with blood thinners
	Problems with Immune System	Blood test of mother for HLAG, IL15 (in luteal phase),	No specific treatment available
	Problems with Endocrine System	Blood test of mother for Thyroid hormones, Progesterone, Prolactin, Insulin, AMH, Vit D	Hormone supplementation by drugs
	Environmental and Lifestyle Problem	TORCH infection panel, chlamydia, mycoplasma, ureaplasma, listeria infection in mother. Smoking, excessive alcohol, caffeine intake, obesity	Vaccine for Rubella, medicines and healthy lifestyle
	Male Factors	DNA fragmentation test in semen ejaculate	Dietary and life style change along with antioxidant medication

Table 3 Common Genetic Problems that can cause infertility and RPL

Infertility	Recurrent pregnancy loss
Structural and numerical chromosomal abnormalities in male and female; Y chromosome microdeletion; Cystic fibrosis; Fragile X; Premature Ovarian Insufficiency; Kallman Syndrome	Structural and numerical chromosomal abnormalities; Variation in genes implicated in embryo development; Deletion or duplication in gene Thrombophilia

infertility may opt for in vitro fertilization (IVF) where pre-implantation genetic testing (PGT) can identify normal embryo before implantation in the mother's womb. Such precision treatment through molecular diagnosis can be a medical boon when Clinicians and Genetic Counselors work hand-in-hand.

Applications in new born screening (NBS)

New borns with metabolic, hormonal and genetic disorders which can be prevented if diagnosed early and taken care off for the rest of their life, can be identified through New Born Screening (NBS). In NBS only two drops of blood are taken from the baby through heel pricking for identification of any genetic disorders among the new born. It has been observed that a lot of genetic disorders affecting nervous system can share overlapping symptoms and thus could be very confusing for symptom-based diagnosis. The Genetic diagnosis always helps in proper identification of the disease. However, number of diseases covered under NBS varies in different countries. Phenylketoneuria (PKU), congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), glucose 6-phosphate dehydrogenase deficiency, cystic fibrosis and galactosemia, lysosomal storage disorders (LSDs), amino acid disorders (AADs), fatty acid disorders (FADs) and organic acid disorders (OADs) are the common panel covered by most of the countries. Details of region or country specific NBS coverage panels are summarized in Table 4.

Though all the provinces/countries of these regions do not screen for all the diseases. There is a need of NBS guideline to be country and region specific depending on the prevalence of different genetic disorders.

Applications in identification of rare genetic disorders

Rare and very rare genetic disorders with prevalence rate of ≤ 0.0005 (like POMC deficiency, thanatophoric displasia, KID Syndrome etc.) as per genetic and rare disease information center (GARD) [15] can only be identified and diagnosed through genetic testing. Any delay in reaching developmental milestones by the newborn could be associated with a genetic disorder. In all such cases, proper genetic testing supported with GC can identify the proper disorder. Early detection is very much essential to reduce the extent of pathological damage and initiation of proper testing.

Future prospects of genetic counseling

GC is being termed as one of the most promising biomedical careers in coming years. The complete decoding of Human Genome has led to understand that genes and their variations play a major role in our body's response to the external world.

Pharmacogenomics is the branch of study to know how a human body can respond to a particular

Table 4 Main diseases being covered by New Born Screening (NBS) programs in different regions of world. Following the Wilson-Jungner criteria CH, PKU, Galactosemia, amino acid disorders, Fatty acid oxidation disorders and organic acid disorders are almost being screened worldwide

Disease	USA	CANADA	Middle East & North Africa	Asia	Latin America	EUROPE	Specific Country, if Any
PKU	√	√	√	√	√	√	
CH	√	√	√	√	√	√	
CAH	√	√		√	√	√	
G6PD Deficiency	√	√	√	√	√	√	
Cystic Fibrosis	√	√		√	√	√	
Galactosemia	√	√	√	√	√	√	
Hemoglobinopathies		√		√		√	
Biotinidase Deficiency		√			√	√	
Guanidinoacetate Methyltransferase Deficiency							Qatar
Primary Immuno Deficiency Disease	√					√	Lebanon
Lysosomal Storage Disorder (LSD)	√		√	√	√	√	
Amino Acid Disorder	√	√	√	√	√	√	
Fatty Acid Oxidation Disorder	√	√	√	√	√	√	
Organic Acid Disorder	√	√	√	√	√	√	
Toxoplasmosis	√						

Primary Immunodeficiency diseases like SCID are being screened using Quantitative PCR, from 2018 onwards this is being included in the NBS panel Germany, Qatar and few more countries. PKU Phenylketonuria, CH Congenital Hypothyroidism, CAH Congenital Adrenal Hyperplasia [12–14]

pharmacological agent. Pythagoras (around 510 BC) recognized that some individuals are affected with haemolytic anaemia after consumption of fava bean while others do not complain about any complications [16]. This was probably the first correlative documentation for pharmacogenomics which was later discovered as caused due to G6PD deficiency [17, 18]. Isoniazid, the anti-tubercular drug, has very high hepatotoxic effects [19]. *N*-Acetyl Transferase 2 (NAT2) has three polymorphic variants that can acetylate Isoniazid either rapidly or moderately or slowly [20]. Persons with rapid acetylating enzymes can metabolically clear isoniazid more rapidly resulting less toxicity, whereas, the slow acetylators are affected with highest level of hepatotoxicity [20, 21]. There are several other examples also that describe the relation of genetic variations with pathophysiology. Pharmacogenomics is emerging rapidly for the last three decades to identify someone's genetic capability of drug metabolism and tolerance to systemic intoxication. Biomedical advances to assess drug specific genotypes and/or genotype specific drugs will definitely open a new age of clinical treatment as well as health supplementation related industries where patients and professionals can be successfully guided by GC.

Conclusion

Genetic Counseling as a profession is becoming very popular through the last two decades. Though it emerged only around 50 years ago but its importance in connecting genetics to clinicians have made it inevitable as a medium for better understanding of diseases/disorders from both clinicians as well as patient's points of view. Since, successful development of molecular and genetic diagnosis has been established and there still remains a lacuna of knowledge of genetics among the medical practitioners. A prudent liaison between the clinicians and the diagnosis service was the demand of the time, which can be fulfilled successfully by a genetic counselor. As a career of future GC requires more well-trained professionals to perform counseling. Therefore, not only professional training courses, but inclusion of this branch as higher academic degree under universities will definitely promote GC to be a perfect translational science.

However, on a precautionary concluding note it must be stated that an international as well national legal regulatory framework is definitely required throughout the globe to check any misuse of gene checking.

Abbreviations

AAD: Amino acid disorders; aCL: Anti cardiolipin; AMH: Anti mullerian hormone; APC: Activated protein C; aPL: Anti phospholipid; ATM: Ataxia telangiectasia mutated; b2GP1: Beta 2 glycoprotein 1; BCNS: Basal cell nervous syndrome; BRCA1: Breast cancer type 1; BRCA2: Breast cancer type 2; CAH: Congenital adrenal hyperplasia; CDH1: Cadherin 1; CH: Congenital hypothyroidism; CHEK2: Checkpoint kinase 2; CNV: Copy number variation; CVS: Chorionic villus sampling; DNA: De-oxyribo nucleic acid; FAD: Fatty acid disorders; FAP: Familial adenomatous polyposis; GARD: Genetic And Rare Disease Information Center; G6PD: Glucose 6-phosphate dehydrogenase; GC: Genetic counselling; HLAG: Human leukocyte antigen G; HNPCC: Hereditary nonpolyposis colorectal cancer; HSG: Hysterosalpingography; IL15: Interleukin 15; IVF: In vitro fertilization; LA: Lupus anticoagulant; LSD: Lysosomal storage disorders; MEN2a: Multiple endocrine neoplasia type 2; MLH1: MutL protein homolog 1; MLPA: Multiplex ligation-dependent probe amplification; MSH2: MutS homolog 2; MSH6: MutS homolog 2; MSI: Microsatellite instability; MTHFR: MethyleneTetrahydroFolate Reductase; MUTYH: MutY DNA glycosylase; NBS: New Born Screening; NF1: Neurofibromatosis; NGS: Next generation sequencing; NIPT: Non-invasive prenatal testing; NSGC: National Society of Genetic Counselors; OAD: Organic acid disorders; PALB2: Partner and localizer of BRCA2; PGT: Pre-implantation genetic testing; PKU: Phenylketoneuria; PMS2: PMS1 homolog 2; PTCH: Patched gene; PTEN: Phosphatase and tensin homolog; RB1: RetinoBlastoma; RET: Ret proto-oncogene; RPL: Recurrent pregnancy loss; STK11: Serine/threonine kinase 11; TORCH: Toxoplasmosis, rubella cytomegalovirus, herpes simplex, and HIV; TP53: Tumor protein 53; VHL: Von Hippel-Lindau disease.

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