REVIEW ARTICLE

Genetic Race: Prevalence of Diseases and Guidelines for Prevention

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Abstract

Background: Endogamy in races and ethnic communities contribute to the prevalence of genetic diseases, especially recessive monogenic disorders. The demographic and epidemiological transition also increases the incidence of noncommunicable diseases in underdeveloped and developing countries, including India.

Observation: Among all, hemoglobinopathies, cystic fibrosis, Tay-Sachs disease (TSD), etc., prevail in populations of Jewish, Mediterranean, African, and Asian descends. The prevention of births with congenital anomalies of genetic etiology is possible through genetic counseling, carrier screening, and prenatal and/or preimplantation genetic diagnosis. Guidelines have been established by reputed organizations such as American College of Obstetrics and Gynecology (ACOG) and American College of Medical Genetics (ACMG) of different countries with a view to protect the genetic information and misuse of diagnostic samples, selection of the appropriate technologies, clinical application and interpretation of the test results, etc.

Conclusion: The integrated approach of community education and counseling in public health assessment can increase awareness about genetic disorders, and also establish an accurate estimate of its prevalence.

Keywords: Genetic counseling, Genetic disorders, Prenatal and preimplantation genetic screening, Prevention of genetic defects, Racial/ethnic origin.

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Introduction

Genetic race or ethnicity refers to different factors including ancestry, social identity, phenotype, genetic makeup, and living practices. Racial groups are susceptible to disease burden mainly due to social inequality and health disparities and, thus, intrinsically affected with high morbidity and mortality.[1,2] Ambiguous distinction between race and ethnicity could be resolved by the fact that the terms race, genetic population, ethnicity, ancestry, geographic population, etc. are their interchangeable use in a situation of application in different disciplines. Racial health disparities define population-specific differences in the prevalence of diseases, access to health care and outcomes, and life expectancy. Racial health inequity is mainly associated with socioeconomic status, education, gender, and access to medical care, diagnosis, and treatment.[3,4] The race of understanding the race has started with scientific basis of inheritance and technological challenges for investigation, which is concentrated on deciphering the genetic patterns in some races or ethnic groups. The modern-day admixture of racial groups is creating complexities in self-identification to one ancestry, biological research, and public health policies.[5] Biological ramifications and genetic intersection of race have established a database on the genetic predisposition of human diseases in different racial populations of different geographical provinces.[6]

Diseases of racial groups can perpetuate different biological effects that are not predetermined by biology such as lack of basic understanding of life and living, and, thus, adoption of preventive care. Sharing a genetic makeup among individuals from a common ancestry also result in share of certain propensity or resistance to specific diseases. In general, human individuals have 99.9% common genepool, and the difference of 0.1% causes a wide spectrum of variations in both the phenotype and the genotype.[7] In epidemiological risk-calculation of genetic disorders, the race is considered as an adjunct useful tool for the assessment of the variation in disease risks, which considers the genetic ancestry of a population such as Askenazi Jewish (AJ) population. Genetic information is largely determined by inheritance from parents in a 1:1 ratio, which is often confronted by imprinting and incomplete penetration, and thereby causing variation in health-risk. Genetic diseases can be ascribed to a single error in a single gene or more errors in multiple genes wherein environmental and epigenetic factors contribute to significant extents. Globally, over 10,000 human diseases (10/1,000 birth) are monogenic, which could be dominant, recessive, or X-linked (dominant/recessive) for inheritance. Some of the prevalent monogene disorders include thalassemia (most prevalent in populations having Mediterranean ancestry to the point that the disease's name is derived from Greek *thalasson*, "sea"), sickle cell anemia (most prevalent in populations with sub-Saharan African ancestry but also common among Latin-American, Middle Eastern populations as well as those people of South European regions such as Turkey, Greece, and Italy), hemophilia, cystic fibrosis (the most common life-limiting autosomal recessive disease among people of Northern European heritage), Tay-

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Sachs disease (TSD) (an autosomal recessive disorder more frequent among AJ than among other Jewish and non-Jewish populations), lactose intolerance (affects over lifetime as many as 25% of Europeans but up to 50–80% of Hispanics, along with AJ, but nearly 100% of Native Americans), fragile X syndrome, Huntington's disease, etc., of which thalassemia stands the most prevalent.[8] Multifactorial polygenic diseases differ in frequency between different populations and are highly complex due to the interaction of both genetic and environmental factors. Races are categorized as low or high risk for some polygene disorders depending on their exposure to certain risk factors. Beyond genetic factors, socioeconomic culture as well as the past and present environmental exposures influence a population's risk for specific diseases.

The present review article has a notion to understand the racial prevalence and the frequency of genetic disorders and their prevention. The genetic abnormalities cannot be treated as of now. Therefore, relying on the principle of "prevention is better than cure," recommended guidelines on prenatal (PND) and preimplantation (PGD) genetic diagnosis have been highlighted with a view to reducing the burden of genetic disorders, which further envisage the necessity of regulatory policies and ethical aspects for PND and PGD screening and diagnosis.

Prevalence of Genetic Disorders

Interethnic variation is known for a large number of common conditions, including migration, geographic variation, natural selective pressure, and other environmental variables. Information on the population-specific prevalence of genetic disorders is scanty in most of the developing countries including India. Despite multilingual and multicultural habits, Indian population constitute a distinct cluster having a low level of genetic heterogeneity.[9] A genome-wide search of South Asian populations has demonstrated that 81 different groups of people have descended from a single "founder event," which is more extreme than that of descendants of the AJ and the Finns.[10] Like other developing countries having demographic and epidemiological transitions, India is also experiencing an increase in obesity, diabetes, and heart disease due to the westernization of culture amidst poverty, predominantly in an urban setting. Also, the amalgamation of people from diverse cultural, social, religious, and tribal backgrounds is causing genetic diversity within racial groups.[11] Association of Indian immunological profile, particularly histocompatibility antigens (HLAs), varies significantly for a number of complex medical diseases and confers varying susceptibility to malaria, tuberculosis, HIV, leprosy, and other infectious diseases.[12,13] The incidence of heritable genetic disorders in the Indian subcontinents is largely unknown due to lack of defined and concerted estimation program established by the governmental agencies, and/or underestimated because many of the individuals/families remain undiagnosed and unreported. In India, there is no useful official resource to provide the collective national information on the prevalence and the frequency of genetic disorders for the benefit of medical care and/or offering preventive care of the inherited disorders. The reports available are largely from hospital-based small cohort studies and are insufficient to draw a true figure of the total burden of genetic disorders. Consanguineous and interstate (interreligious) marriages could further influence the incidence of genetic illness.[14]

Congenital anomalies are the leading cause of infant mortality (20%) across the globe.[15] Yearly, an incidence of 7.9 million birth defects is on the rise even in the post-genomic era. Of this, 3.2 million remain disabled for life. Apart from familial inheritance of single-gene and chromosomal disorders and the result of the multifactorial gene-environment interactions, approximately 50% of all anomalies remain undiagnosed.[16] Genetic etiology is characterized as chromosomal, monogenic, and complex polygenic wherein the genetic makeup is determined at conception following the nuclear event of fertilization, and the major developmental defects are manifested in the prenatal environment.

Chromosomal Disorders

Chromosome abnormalities in the form of aneuploidy and/or structural alterations in autosomes and sex chromosomes could be acquired *de novo* or inherited in the form of balanced or unbalanced rearrangements.[17–19] Of all, trisomy 21 is the most common one (1 in 700 births) causing the Down syndrome (DS) followed by trisomies 13 and 18 resulting in Patau and Edward syndromes, respectively (1 in 10,000 births each). Each one is having severe disabilities with specific characteristics and commonness of mental retardation and susceptibility to chronic illness.[20] DS patients can survive till 60 years, but other two die soon after the birth or at the neonatal age.[21,22] Sex chromosomal aneuploidy commonly includes monosomy X and XXY complements in Turner and Klinefelter syndromes, respectively.[17,23] Chromosomal aneuploidies occur due to meiotic nondisjunction during gametogenesis, and often influenced by the advanced maternal age. Unbalanced structural alterations could be clinically serious to fatal for a successful live-born delivery.[17] Moreover, ~95% of conceptuses with aneuploidy or structural alteration do not get embryonic development resulting in the first-trimester miscarriage.

Single-gene Disorders

Single-gene defects are inherited in a dominant or recessive manner from one or both parents. The central dogma of one-gene–one-enzyme hypothesis underlies the majority of single-gene defects such as *PAH* gene on chromosome 12, which encodes phenylalanine hydroxylase (PAH) enzyme and its malfunctioning causes phenylketonurea (PKU). There are many such metabolic disorders caused by single-gene defects, which are heritable and prevalent among ethnic groups such as sickle cell anemia reported prevalent among Africans, Indians, and Mediterranean descents (Table 1).

TSD and many other single-gene disorders are prevalent in AJ population, which are grouped as Jewish genetic diseases (JGD) (Table 2).[8] TSD is caused by an autosomal recessive mutation in the *HEXA* gene on chromosome 15 resulting in deficiency in hexosaminidase protein which affects the fatty buildup of the brain and eventually the nervous system. TSD mainly affects young children leading to progressive neural degeneration followed by death during the first few years of life.

Cystic fibrosis is another highly prominent single-gene defect in different racial groups with high frequency and detection rates (Table 3). The culture of endogamy and relatively low admixture increases the inheritance of heterogeneous recessive mutations. Around 1.5 billion population of South Asia has many small endogamous groups, which has presented 81 unique genetic groups with a higher incidence of recessive diseases.[10] The spectrum and the diversity of genetic diseases in this population may actually require a living lab.

Multifactorial Polygenic Disorders

Approximately, 50% of the birth defects remain undiagnosed and are characterized as multifactorial and polygenic. Polygenic defects

Table 1: Genetic disorders by ethnicity

Genetic diseases	*Ethnic population at highest risk*	*Assay system*
Sickle cell anemia	African, Southeast Asian, Mediterranean, Caribbean	Hb-electrophoresis
α-Thalassemia	African, Chinese, Filipino, Southeast Asian	CBC with indices
β-Thalassemia	African, Indian, Southeast and East Asian, Mediterranean	CBC with indices
TSD	Ashkenazi Jewish Eastern European, French Canadian, Cajun	Hexosaminidase A
Cystic fibrosis	Non-Hispanic Caucasian, Descendents of Ashkenazi Jewish communities (North America)	DNA mutation

Table 2: Carrier frequency of Jewish genetic disorders and detection rates

Disorders	*MIM #*	*Carrier frequency*	*Detection rates*	*Disease incidence*	*Residual risk*
Gaucher disease	230,800	1 in 15	0.95	1 in 900	1 in 281
Cystic fibrosis	219,700	1 in 23	0.94	1 in 2,500–3,000	1 in 368
Familial dysautonomia	223,900	1 in 31	>0.99	1 in 3,600	1 in 3,001
Canavan disease	271,900	1 in 55	>0.97	1 in 6,400	1 in 1,801
TSD	272,800	1 in 27	0.98	1 in 3,000	1 in 1,301
Fanconi anemia group C	227,645	1 in 100	0.99	1 in 32,000	1 in 9,901
Bloom syndrome	210,900	1 in 134	0.99	1 in 40,000	1 in 13,301
Mucolipidosis IV	252,650	1 in 89	0.95	1 in 62,500	1 in 1,761
Niemann-Pick disease A	257,200	1 in 115	0.97	1 in 32,000	1 in 3,801
Maple syrup urine disease	248,600	1 in 97	0.95	1 in 50,000	1 in 1,921
Glycogen storage disease Ia	232,200	1 in 64	0.95	1 in 20,000	1 in 1,261
Dihydrolipoamide dehydrogenase deficiency	248,600	1 in 107	>0.95		1 in 2,121
Familial hyperinsulinism	256,450	1 in 68	0.90	1 in 18,000	1 in 671
Nemaline myopathy	256,030	1 in 168	>0.95	1 in 47,000	1 in 3,341
Usher syndrome type IF	602,083	1 in 147	≥0.75	1 in 80,000	1 in 585
Usher syndrome type III	276,902	1 in 120	>0.95	1 in 45,000	1 in 2,381
Joubert syndrome	213,300	1 in 92	>0.95	1 in 34,000	1 in 2,200
Spinal muscular atrophy	253,300	1 in 40-60	~0.90	1 in 10,000	1 in 600
Walker-Warburg syndrome	236,670	1 in 149	>0.95	1 in 60,500	1 in 2,400

are mainly caused by gene-environment interactions, epigenetic factors, teratogens, use of anti-epileptic drugs, lifestyle, etc. The contribution of such multiple factors is known to cause abnormalities of the brain and spinal cord including anencephaly (lack most of the brain development), spina bifida (incomplete closure of the spinal cord), etc., which are collectively known as neural tube defects (NTDs). India has an estimate of over 30 million individuals with some kind of neurological disorders.[25] Centers for disease control and prevention (CDC) has presented the US National estimates for selected major birth defects (Table 4). NTDs are common with varying clinical significance and sometimes associated with trisomy 18. Micronutrient deficiencies such as folate and iodine have been attributed to various malformations including NTDs and mental retardation. Cleft lip and/or palate, autism-like behavioral disorders, etc., are not caused by a single gene but contributed by a set of genes and environmental factors.[26]

Table 3: Prevalence of cystic fibrosis in different ethnic groups[24]

Racial groups	*Detection rate (%)*	*Carrier risk before testing*	*Carrier risk after –ve test result*
Ashkenazi Jewish	94	1 in 24	1 in 380
Non-Hispanic White	88	1 in 25	1 in 200
Hispanic White	72	1 in 58	1 in 200
African American	64	1 in 61	1 in 170
Asian American	49	1 in 94	1 in 180

Table 4: CDC data on incidence of cephalic defects and syndromes (adjusted for maternal race/ethnicity)[27]

Birth defects	*Incidence per birth*	*Annual incidence*
Anencephaly	1 in 4,859	859
Spina bifida without anencephaly	1 in 2,858	1,460
Encephalocele	1 in 12,235	341
Omphalocele	1 in 5,386	775
Cleft palate	1 in 1,574	2,651
Cleft lip with/without cleft palate	1 in 940	4,437
Transposition of great arteries	1 in 3,333	1,252
Atrioventricular septal defect	1 in 2,122	1,966
Tetralogy of Fallot	1 in 2,518	1,657
Rectal and large intestinal atresia/stenosis	1 in 2,138	1,952
Gastroschisis	1 in 2,229	1,871
Diaphragmatic hernia	1 in 3,836	1,088
Down syndrome[a]	1 in 691	6,037
Patau syndrome[a]	1 in 7,906	528
Edward syndrome[a]	1 in 3,762	1,109

[a] Adjusted for maternal age

Prevention of Genetic Disorders

The catalog of the recessive mutations shall provide useful guidance on how to prevent or control the transmission of genetic disorders through generations. Such cataloging exercise of JGD has established the "Dor Yeshorim" program that follows premarital screening of AJ and Sephardi Jews with a view to preventing transmission of disease-causing mutations, and that has reduced TSD.[8] However, the burden of genetic diseases can be controlled through integrated approach including community education, population screening, genetic counseling and carrier screening, screening of the newborn, and PND and/or PGD. Carrier screening of hemoglobinopathies and glucose-6-phosphate dehydrogenase (G6PD) deficiency has lowered the incidences. However, the magnitude of the genetic disease and the feasibility of prevention program in a cost-effective manner stand important for controlling the alarming public health issue of birth defects. Nevertheless, awareness about the impact of parents' age, sequel of micronutrient deficiencies, vaccination for rubella and other infections, effects of smoking and alcohol intake, syphilis, other sexually transmitted diseases, etc., on the acquisition of new mutations would combat the development of complex polygenic disorders.

Antenatal screening techniques were described in the 19th century for the management of various genetic disorders and congenital malformations. Evidently, PND has become a norm with exponential evolution from biochemical triple screen to quadruple and then first-trimester double screening in the maternal blood along with ultrasound imaging (Tables 5 and 6).

Discovery of cell-free fetal DNA (cff-DNA) in the maternal blood-plasma in 1997 for the screening of trisomies (13, 18, and 21), which is similar to double screening but with a higher level of precision and sensitivity, has gained importance in prenatal management (Table 7). However, guidelines have been set for considering cff-DNA by ACOG and others (Table 8).[28,29] Altogether, reproductive screening relies on an acceptable test protocol, because the aim is not just early diagnosis for prevention and treatment but also to facilitate reproductive decision making.[28,29]

There is tremendous technological and knowledge-based advancement for screening genes and mutations associated with a growing number of diseases. Analytically, microarray-based comparative genomic hybridization (aCGH) and single-nucleotide polymorphism (SNP) array techniques have validated screening of several disease-causing genes. However, microarray techniques are not capable to detect balanced rearrangements. Sanger and next-generation sequencing (NGS) may generate extensive information on the genes and mutations with variants of unknown significance and potential incidental or unsolicited findings and, thus, the clinical use of NGS requires extensive validation. Nevertheless, time-consuming processing and analysis, and high cost debar its use in a clinical setting with the present status.[30,31]

Traditionally, biochemical assessment of hexosaminidase A in serum or leucocytes was followed for the screening of TSD. As the JGDs are caused by a small number of mutations, DNA-based carrier screening has been facilitated by the technological advancement with higher sensitivity and detection rates. Familial dysautonomia was characterized by two mutations in the *IKBKAP* gene with 99% exclusivity of type 1 mutation in Jewish descendents. Likewise, sequencing of the whole genome or exome may facilitate identification of more disease-causing mutations in the present era. Such development has improved the speed and sensitivity of detection rate at much lower cost.[32–34] Of 1,700 mutations identified in the *CFTR* gene, 23 mutations are recommended for carrier screening.[33] Complete analysis of the *CFTR* gene by DNA sequencing is not appropriate for clinical screening as it may yield unsolicited results that are difficult for interpretation. Therefore, ACMG has strictly recommended appropriate validation of the genetic techniques before their incorporation into routine clinical care for screening or testing. Sequencing of the entire *CFTR* gene would be meaningful for cases with a family history of the disorder, males with congenital absence of vas deferens (CAVD) or newborns with a positive screening, and when mutation testing with 23 mutation-panel results appears negative.[35]

Molecular screening of spinal muscular atrophy (SMA) carrier status involves mainly the deletion of exon 7 of the *SMN1* gene in 95% of cases; however, such diagnosis cannot detect heterozygous deletions. Gene dosage analysis has been found to be beneficial to many families with an affected offspring. Quantitative PCR assays have also been implemented for the detection of SMA carriers. Additionally, ~5% of the normal population is reported to carry three copies of *SMN1*, two copies in one chromosome and an *SMN1* deletion on the other resulting in balanced gene dosage. Therefore, the risk of false-negative condition and interpretations of SMA screen shall be managed by experienced genetic professionals and qualified laboratories having validated technologies.[36]

ACMG has established standards of care for preconception and prenatal screening of CF and SMA, and several other recessive conditions for reproductive decision-making for ethnic families.[34,35,37] Screening of an unprecedented quantity of disease-specific genetic variants is possible through preconception screening and also in a time-frame suited for PND.

Myths of PND and PGD

To know the genetic composition of an unborn child for a decision-making, it raises pertinent questions on the benefits and harms of the PND and/or PGD (Table 8). The religious and racial culture might have myths to pose an additional restriction on the approach. The first anxiety of the risk of a miscarriage of invasive sampling (CVS: 1–2% and amniocentesis: 0.5%) is an additional concern of the expecting parents.

To alleviate the fear of inaccuracy of the diagnosis, and selection of the appropriate diagnostic samples and techniques, standard guidelines have been set by the authorized organizations (Table 9).

Conclusion

The prevalence of diseases has a significant link to diet, environmental, and cultural habits. India having one-sixth of the world population, several thousands of endogamous groups indicate a strong potential for recessive diseases and birth defects. Miscarriages with genetic and congenital anomalies contribute to a considerable amount of perinatal and neonatal mortality, on the one hand, and blood-loss and anemia of the mother, on the other hand. Community genetics services for extending counseling, carrier screening and antenatal and PND/PGD could reduce the prevalence of genetic diseases. Clinical diversities of recessive and dominant mutations in the vast human population pose an urge to changing the system of genetic research. Genetic investigation of natural genetic information in human shall replace the manipulation of knock-out genes in experimental primates. Information on the disease prevalence and frequencies in racial and ethnic cultures has governed major attractions in the postgenomic research. Congenital malformations

Table 5: Prenatal screening techniques

Name of the test	*Sample*	*Technique*	*Time of screening*	*Detection*	*Likelihood of diseases*	*Non-/invasive*	*Risk: false +ve/–ve*	*Recommendation*	*Insurance coverage*
NIPT	Cell free fetal DNA (cff-DNA) in maternal plasma	Molecular techniques (a-CGH/ SNP-array/ sequencing)	Any time after 8 weeks	Validated for trisomy 13/18/21 (detection of gene mutations possible)	Down/Patau/Edward syndromes (does not detect NTD)	Noninvasive	Low 99% accurate for Down syndrome	• Integration with first trimester NT screen, and CVS/amniocentesis for confirmation • Recommended only for ≥35 years women and/or having h/o high risk, and not for low-risk women (ACOG 2015)	Most likely not covered by insurance companies. In absence of national coverage determination, varies on gestational age/ resource/countries
Double screen	Maternal blood serum	Biochemical screening	10–13 weeks	hCG, PAPP-A	Down/Edward syndrome, cardiac defects	Noninvasive	High	Integration with first trimester NT screen	May be covered as a part of routine prenatal care
Nuchal translucency (NT) screening	Expecting mother's womb	Ultrasound imaging	10–13 weeks	Collection of fluid beneath the fetal skin in the region of the fetal neck	Trisomy 21/other chromosomal anomalies	Noninvasive	High	Integration with first trimester double screening	Covered as a part of routine prenatal care
Triple screen: normally considered for ≥35 years women or other history and indicative NT/double screen	Maternal blood serum	Biochemical screening	16–18 weeks	AFP, hCG, EU	↑AFP: spina bifida or anencephaly; ↓AFP and abnormal hCG/ EU: Down/Edward syndrome, other chromosomal aberrations	Noninvasive	High	CVS/amniocentesis for confirmation; ultrasound imaging	Most likely covered by insurance companies
Quad screen	Maternal blood serum	Biochemical screening	14–20 weeks	AFP, hCG, EU, inhibin A	Chromosomal aberrations and NTD	Noninvasive	High	CVS/amniocentesis (less accurate than integrated screen for which time has gone)	Most likely covered by insurance companies
Diagnostic testing: in cases with indicative NT/NIPT/double screen, and women of ≥35 years age	CVS	Genetic (tissue culture)	11–13 weeks	Chromosomal aberrations and gene mutations (does not detect NTD and anatomical defects)	Numerical/structural aberrations, and recessive/dominant disorders	Invasive (transvaginal or transabdominal); carries risk of miscarriage	Nil (~99–100% accurate)	NT screen for NTD, genetic counseling for whether it's right for the parents and/or the best next steps if the results are positive	Generally covers CVS but it may not if women is below 35, "low-risk" for certain problems, and/or normal results from first trimester screens
Diagnostic testing: in cases with indicative NT/NIPT/ double/triple/quad screen, and women of ≥35 years age	Amniotic fluid	Genetic (tissue culture)	16–20 weeks	Chromosomal aberrations, gene mutations, and NTD (does not detect anatomical defects)	Numerical/structural aberrations, and recessive/dominant disorders; NTD	Invasive (transabdominal); carries less risk of miscarriage	Nil (~99–100% accurate)	NT screen for NTD genetic counseling for whether it's right for the parents and/or the best next steps if the results are positive	Generally covers CVS but it may not if women is below 35, "low-risk" for certain problems, and/or normal results from first or second trimester screens

AFP, α-fetoprotein; CVS, chorionic villus sampling; EU, unconjugated estriol; hCG, human chorionic gonadotropin; NIPT, noninvasive prenatal testing; NT, nuchal translucency; NTD, neural tube defects (spina bifida)

Table 6: Prenatal genetic testing

Sample	*Tests*	*Detection system*	*Target detection*	*Sensitivity*	*Genome coverage*
CVS/amniotic fluid	Diagnostic: chromosome analysis	Microscopic and imaging of chromosomes	Aneuploidy, structural aberrations	CVS: ~99% Amniotic fluid: >99%	Screens all chromosomes structurally and numerically
CVS/amniotic fluid	Screening: aneuploidies by FISH	Microscopic and imaging of interphase nuclei	Aneuploidy (13/18/21)[a]	~99%	Screens numerical changes of selected chromosomes
CVS/amniotic fluid	Diagnostic in cases with known hereditary history	PCR/chromosome microarray/sequencing	Single gene disorders (recessive/dominant mutations), e.g., thalassemia, Huntington disease	~99%	Targeted genes/copy number variations (CNVs)/uniparental disomy (UPD)
Cff-DNA	NIPT (molecular)	Digital PCR/massively parallel sequencing (MPS)/targeted sequencing/shotgun sequencing	Fetal chromosome dosage/ Single gene disorders	~96–99%	Targeted genes/allelic ratios

[a] Prenatal test of sex chromosomes is restricted in India; Cff-DNA, cell-free fetal DNA; NIPT, noninvasive prenatal testing

Table 7: Cell-free fetal DNA (cff-DNA)-based noninvasive prenatal screening

Features	*Strength*	*Weakness*	*CLIA-approved NIPT tests*
Fetal cell trafficking in pregnancy: 1/10,000 maternal cells; equivalent to 20 cells in 20 mL maternal blood (1 µg DNA in 20 mL blood)	It relies on noninvasive prenatal sampling and does not contact the growing fetus directly	Isolation and characterization of less-frequent fetal cells in maternal blood is beyond the practice in different geographical regions due to lack of resources	Sequenom MaterniT21™ Plus: trisomy 13/16/18/21/22, del (1p/4p/5p/8q/11q/15q/22q/) for microdeletion-syndromes: MPS reports as positive or negative
~6–10% of cff-DNA of total cff-DNA in maternal plasma	It is possible as early as 8–10 weeks	Tests are unable to perform in cases with ≤4% DNA	Ariosa (acquired by Roche in 2015) Diagnostics Harmony™ test: direct DNA analysis for +13/18/21 as risk-score
It is a screening test and should not be considered as diagnostic test, and should not be considered in isolation from other clinical findings	Detects chromosomal aneuploidies with 98–99% sensitivity in high-risk pregnancies (1:200)	Unable to detect all-chromosomal alterations at genomic level	Natera Panorama™ prenatal tests risk-score for trisomies and microdeletions on SNP-technology
This critical distinction shall be explained to every patient carefully. NIPT for +21 is not recommended for low-risk pregnancies	Detects microdeletions/CNVs/ uniparental disomies	Prenatal detention of microdeletion-syndromes are not recommended for NIPT in many countries, and not validated clinically	Illumina (formerly Verinata Health) verify® reports not detected/ detected/suspected +13/18/21 based on MPS
Confirmation by invasive karyotyping is mandated by ACOG and other regulators (false positives occur because of DNA sequenced can represent both maternal and fetal origin, and the fetal fractions derives from placenta as well as the developing fetus)	Detects recessive and dominant mutations with reliable detection limit	The techniques are not yet validated for calling disease-specific mutations and interpreting unwanted mutations	Integrated genetics (LabCorp Specialty Testing Group) InformaSeqSM prenatal test uses illumina platform following similar reporting
Analytic validity, clinical validity and clinical utility shall be established for cff-DNA prenatal test	High sensitivity and specificity of +21 in high-risk singleton pregnancies	Sequencing-based detection of +13/18 and sex chromosomes requires validation on large data	Quest Diagnostics QNatal™ tests aneuploidies
Possible confounders: early gestational age, maternal obesity, multiple pregnancies, placental mosaicism, maternal chromosomal aberration	May require fewer cases of invasive diagnosis and sampling-related miscarriage	Limited data is available on +21 in twin, discordant and multiple pregnancies	Quality control and analytic performance metrics of clinical sequencing is not standardized/regulated by US-FDA
NIPT clinical trials: PreNATUS using SNPs (NCT01545674); NCT01597063 on low-risk women; PEGASUS (NCT01925742)	ACOG (2012) recommended for +21 screening for high-risk singleton pregnancies	May miss Down syndrome and other aneuploidies, though less, due to risk of false negatives of NIPT	In-house laboratory-developed marketable NIPT tests shall meet the general regulatory standards of Clinical Laboratory Improvement Act (CLIA) and approved by CLIA

Cff-DNA, cell-free fetal DNA; NIPT, noninvasive prenatal testing

Table 8: Benefits and harms of prenatal genetic screening and testing

Screening/testing	*Purpose*	*Benefits*	*Harms*
Screening: collects indication of genetic abnormality, but does not confirm its presence	Maternal blood sample is screened to know whether there are chances of developing genetic disorders, like Down syndrome, NTD, and trisomy 18	Noninvasive sample collection does not increase any risk of fetal demise	The results can only indicate whether the baby is at a high/low risk of developing one of these diseases. In other words, the test cannot show accurately whether the baby will definitely acquire this disease or not
	For an indicative screening result, testing shall be recommended for confirmation of the presence of the genetic impairment in the fetus	Likelihood of having a child with chromosomal disorders (Down/Patau/Edwards/Turner/Klinefelter syndrome), thalassemia and cystic fibrosis are detected. Two carrier parents must test the fetus for the expected genetic condition	If the screen only detects indicative genetic markers, this can create a difficult situation to make a decision of approach towards management
			A false-positive screening and/or straightforward approach towards invasive sampling for a diagnosis might affect the normal fetuses negatively
Testing: confirms the presence or absence of a genetic condition with known clinical significance	Couples who have a family history of a genetic disease; have child with genetic defects; have gone through more than one miscarriage in the past or woman is >35 years old shall consider genetic testing	*In utero* rectification of problems based on prior knowledge If this is not possible, the doctors/parents can prepare themselves to manage the condition as soon as the baby is born or for a special delivery	Tests are very expensive and not all insurance companies cover the expenses of prenatal/preimplantations tests
	Women above the age of 35 are recommended for prenatal test because such women are at a high risk of developing genetic disorders in the child	Parents have a choice to terminate the pregnancy if they are not ready to take the responsibility of a child who has genetic abnormalities	Terminating a pregnancy just because there is risk of developing a clinical complication is not acceptable by many. Religious sects believe that only God has the right to take the life of a person (child)
	Testing is accompanied with counseling sessions that help the parents to deal with the situation and to take the final decision	Many parents do not want their baby to suffer from genetic defects and die from extreme sufferings (e.g., TSD). Hence, these parents opt to abort their pregnancy	A positive screen/test result and associated anxiety are the biggest disadvantages
	Using tests to prepare for	Sometimes, screen/test is meant for preparing themselves mentally to take care of the child if he/she is born with abnormalities, but not to abort. Predelivery preparation of medical management for pregnancies with known genetic aberrations can save time and money	A mutation of unknown clinical significance, if detected in an unborn baby, does not surely correlate with disease-development
		This may include: special needs for a delivery or nursing an infant; immediate medical insurance facility; taking out life insurance policies on their child; having a donation fund set up well in advance	Accuracy of the test always raises a question before terminating a life. Also it depends on information about the abnormality is presented to the parents and interpretation of the screening/testing result
		Prenatal diagnosis is helping to-be-parents to abort a child based on any indication of a birth defect, no matter what the severity is	Tailoring of tests can lead to controversy, particularly on gene-markers that indicate the tendency for homosexuality, autism, and violence. This has led to a public outcry to stop the screening and/or research
Direct-to-consumer (DTC) test	Many people who opt for this test even when their doctors do not recommend it. This type of testing is called DTC, i.e., direct-to-consumer genetic testing	People have a direct access to genetic testing along with the privacy of the results	People may misinterpret the results that causes a lot of anxiety which may also lead to improper decisions

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Screening/testing	*Purpose*	*Benefits*	*Harms*
		Better to get these tests done only under the supervision of a health practitioner	The present-day practice of selection of genetically normal/affected embryos for delivery/termination is diminishing the research for a cure of a genetic illness in the scientific communities or funding agencies Social acceptability of abortion, pressure from health insurance companies, medical professionals and government agencies are all possible negative consequences of PND Psychological costs, including anxiety, loss of confidence about the pregnancy, negative attitude towards the baby may be detrimental People may increasingly become intolerant and hostile towards disabled child and their parents

Table 9: Practice guidelines and position statements on cff-DNA-NIPT screening

ACOG and SMFM (2015)	*ASHG/ESHG (2015)*	*NSGC (2013)*	*ACMG (2013)*	*ISPD (2015)*
Risks/benefits/alternatives of various prenatal screening and diagnostic testing methods, including the option of no testing, should be explained to all women	NIPT yield higher sensitivity and specificity for common aneuploidies compared to integrated 1st trimester screening	NSGC supports cff-DNA-screening for woman who wants aneuploidy screening	cff-DNA is a prenatal screening and does not confirm diagnosis	cff-DNA-NIPT leads to high sensitivities and specificities for fetal aneuploidy screening
Conventional screening methods remain the most appropriate choice for first-line screening for most women in the general obstetric population due to limitations of cell-free DNA screening performance, and the limited data on cost-effectiveness in the low-risk obstetric population	A positive NIPT result does not guarantee genetic defects in fetus	The screening shall be considered for high-risk pregnancies	Limitations of cff-DNA-screening for unbalanced chromosomal rearrangements, deletions, duplications exist	Definitive diagnosis of +21 and other aberra shall be achieved through karyotyping in CVS/amniotic fluid
Although any patient may choose cell-free DNA analysis as a screening strategy for common aneuploidies regardless of her risk status, the patient choosing this testing should understand the limitations and benefits of this screening paradigm in the context of alternative screening and diagnostic options	Positive NIPT results shall be confirmed through diagnostic testing before terminating a pregnancy	Cff-DNA-screen shall not be considered as routine first-tier screen for low-risk population	Cff-DNA cannot detect NTD	Maternal age alone is not recommended to assess fetal +21
The cell-free DNA test will screen for only the common trisomies and, if requested, sex chromosome composition	Better NIPT-performance shall be corroborated with better standard of pre- and post-test information and counseling, especially with meaningful options of reproductive choice	The screening shall not be considered as diagnostic	Cff-DNA-NIPT takes longer time than biochemical screening of maternal serum analytes	Integrated NT and serum screening shall be available for considering cff-DNA screening
Given the potential for inaccurate results and to understand the type of trisomy for recurrence-risk counseling, a diagnostic test should be recommended for a patient who has a positive cell-free DNA test result	Information and counseling shall be provided in other linguistics for people with less literate (health) backgrounds	Abnormal screen-results shall be confirmed through conventional diagnostic procedures	Pretest and posttest counseling shall be performed by trained professionals	Quad screen shall be available to women completed 13 weeks 6 days and when cff-DNA-screening can be provided
Parallel or simultaneous testing with multiple screening methodologies for aneuploidy is not cost-effective and should not be performed	Additional information on structural rearrangements (translocations/insertions/deletions) collected during aneuploidy screening shall be made available as a part of information			Markers of 1st and 2nd trimester conventional screening are valid

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ACOG and SMFM (2015)	*ASHG/ESHG (2015)*	*NSGC (2013)*	*ACMG (2013)*	*ISPD (2015)*
Management decisions, including termination of the pregnancy, should not be based on the results of the cell-free DNA screening alone	Clinical relevance and implications of additional findings shall be explained with sufficient details			2nd trimester ultrasound imaging can be a useful adjunct of prenatal screening
Women whose results are not reported, indeterminate, or uninterpretable (a "no call" test result) from cell-free DNA screening should receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy	Pregnant women's interest on receiving or not receiving specific information on additional findings shall be recorded and act accordingly			Detection of microdeletions and microduplications shall be relevant clinically
Routine cff-DNA screening for microdeletion syndromes should not be performed	Expanded NIPT-based screening and reporting on sex chromosomal anomalies and microdeletions is currently not recommended based on the issues of ethical concerns and counseling-challenges			Rates of false-positive, detection limit, and interpretation of clinical significance of a positive test shall be available
Cff-DNA screening is not recommended for women with multiple gestations				
If a fetal structural anomaly is identified on ultrasound examination, diagnostic testing should be offered rather than cell-free DNA screening				
Patients should be counseled that a negative cell-free DNA test result does not ensure an unaffected pregnancy				
Cell-free DNA screening does not assess risk of fetal anomalies such as NTDs or ventral wall defects; patients who are undergoing cell-free DNA screening should be offered maternal serum alpha-fetoprotein screening or ultrasound evaluation for risk assessment				
Patients may decline all screening or diagnostic testing for aneuploidy				

SMFM, Society for Maternal–Fetal Medicine; ESHG, European Society of Human Genetics; ASHG, American Society of Human Genetics; NSGC, National Society of Genetic Counselors; ISPD, International Society for Prenatal Diagnosis

of genetic and nongenetic etiology can be controlled by the public health and governmental agencies. PND and/or PGD shall be recommended as a routine practice with a view to lower the incidence of heritable genetic disorders. Regulations and policies shall be framed to ensure the judicial utilization of technological advances such as embryonic gene editing by CRISPR/Cas9[38] and to follow the concept of personalized medicine and nutrition.[39]

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