A new era for preventive genetic programs in the Arabian Peninsula

Ali N. Al-Odaib, PhD, Khaled K. Abu-Amero, PhD, Pinar T. Ozand, MD, PhD, Ali M. Al-Hellani, PhD.

ABSTRACT

In the Arabian Peninsula, high percentages of consanguineous marriages and the tribal nature of marriages have resulted in high incidence of genetically based disorders. The successful management of these disorders incurs a high financial cost, which is a great burden on the health care system. The practical solution to this problem is through prevention. Prevention of genetic disorders should be the utmost public health concern especially where these disorders are prevalent. Preventive genetics became possible with the advent of biochemical and molecular technologies. Biochemical neonatal screening based on tandem mass spectrometry technology and molecular technologies such as sequencing, DNA microarray and nucleic acid hybridization techniques are steadily being transferred to clinical practice. Preventive genetics could be best achieved through establishment of databases for common genetic disorders, premarital diagnosis, and pre-implantation genetic diagnosis and by genetic counseling. These preventive measures must take into account the social and cultural aspects.

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The social and economic conditions in the Arabian Peninsula have improved enormously in the last 3 decades. This led to the sharp decline in the incidence of infectious diseases and diseases related to malnutrition. Currently, genetically determined disorders account for an increasing proportion of death, morbidity, chronic handicap, and disability. A similar pattern has already been observed over the last 2 generations in industrialized countries.[1] During the period (1985-1989), 19% of pediatric inpatients in one Saudi hospital had congenital or genetically-determined disorders.[2] This high incidence resulted from the heavy consanguineous marriages practiced in this area and the tribal nature of the marriages, both of which led to the preservation of rare mutations kept in a genetically homogenous population. Several publications indicate that consanguineous marriages in the Kingdom of Saudi Arabia (KSA) are high (60%) and this has provided a background in which these genetic diseases abound.[3-4]

A genetic disease, even under the best management, burdens the family with the chronic care of an infant. In patients where the diagnosis is missed or when the disease is not manageable with a rewarding treatment, the family has to cope with a disabled child. This can stigmatize the family and most parents try to hide the disease from extended family members or friends with the fear of rejection from a contemplated marriage due to the question of inheritance. In these situations, the medical practice should contribute not only to the management of these genetic diseases but also to its prevention, which will lead to a healthy and a happy family environment. In the absence of prevention, successful management incurs a high financial cost, which in some instances is prohibitive. For example, enzyme replacement therapies in Gaucher's disease, Niemann-Pick's disease or Pompe's disease require medications that cost in the 5 or 6 figures per year, depending on age. Since in many diseases, treatment can be effective and the child may reach adolescence;

From the Department of Genetics (Al-Odaib, Abu-Amero, Ozand), Research Centre, and the Department of Pathology and Laboratory Medicine (Al-Hellani), In vitro Fertilization Laboratory, King Faisal Specialist Hospital and Research Centre, Riyadh, *Kingdom of Saudi Arabia*.

Address correspondence and reprint request to: Dr. Khaled K. Abu-Amero, Department of Genetics, King Faisal Specialist Hospital and Research Centre (MBC-03), PO Box 3354, Riyadh 11211, *Kingdom of Saudi Arabia*. Tel. +966 (1) 4647272 Ext. 32508. Fax. +966 (1) 4427858. E-mail: kamero@kfshrc.edu.sa

the medication cost, which happened to be reasonable in early infancy, becomes very expensive in adolescence (for example homocystinuria). This indicates that the prevention of genetic disorders in Middle Eastern countries should be the utmost public health concern. The prevention of genetic disorders has become possible with the elucidation of the primary structure of the human genome and with the outburst of new technologies burgeoning from this discovery that can be transferred to the field of clinical practice as soon as they are established in the laboratory. Thus, it is very important for countries of the region to take account and adopt such technologies. This review aims at discussing these new approaches and technologies and how adopting such technologies will help countries in this region in diagnosing and preventing genetic diseases.

There is evidence that prevention of genetic disorders leads to significant financial savings and social benefits. A neonatal screening service, involving organized examination of newborns in order to diagnose and treat specific disorders, is an important factor in preventing genetic disorders. There are clinical and biochemical aspects for neonatal screening and both are essential for a successful neonatal diagnosis. In the West, new paradigms for screening were developed with serious considerations for what should be screened and what should be developed aside from what was available. What was once a phenylketonuria (PKU) screening through a Guthrie card has exploded into screening for a vast number of diseases.[5-7] The initial effort of prevention by way of screening in this region was made through the development of a biochemical neonatal screening based on tandem mass spectrometry technology.[8-10] This approach is most successful in rapidly diagnosing and thus rapidly managing a large number of organic and amino acid disorders. An accumulated institutional experience indicates that at least half of the diseases diagnosed could be treated with rewarding results. As for the other half, the infant either died rapidly within 1-2 weeks despite aggressive intervention or the treatment, in some other instances, was not effective. In all instances, the management required intensive medical follow up, which posed a burden both to the health care system and to the families. Initiating a genetic anomalies registry is an important first step in obtaining the epidemiological data needed for service planning and ultimately the prevention of these congenital abnormalities. Such registries (databases) will be concerned with the data collection, storage and analysis.[11] Previously, databases were established for mutations[12] and for genes playing important roles in oncology.[13] Initially these efforts led to rapid screening for heterozygous carriers in the extended family or in the community where such a genetic disease prevails. These efforts were most fruitful in certain applications. In Cyprus where beta-thalassemia carrier screening has been adopted; only few new infants with this disease were delivered. In New York where couples to be wed are routinely screened for Tay-Sachs, Gaucher, Niemann Pick diseases, cystic fibrosis, along with others reduced the delivery of infants with such disorders to nearly nil. In Hong Kong and Montreal, beta-thalassemia screening prevented the birth of infants with this disease.[14] The first serious attempt to establish a database of genetic diseases among Arabs was established by Teebi et al[15] at the University of Toronto. The database (accessed at www.agddb.org) contains more than 1000 unique entries of disorders that occur in Arab populations.[15] Establishment of these databases have led to the emergence of new applications of genetic counseling where couples could be advised on the possibility of having a genetically defective offspring. Genetic counseling was acceptable by the health care systems since it prevented costly management and promoted good health. However, it was not widely accepted by families in societies where other social factors predominate marriages. An alternative approach was needed. This was the pre-implantation genetic diagnosis (PGD), which proposed the identification of an affected fetus from a single cell biopsied from an 8 cells embryo. It has been in practice in 40 centers worldwide and has almost universally assured the delivery of a healthy infant. With this historical background what should be the new technologies available at any tertiary care center for immediate application.

New technologies. 1. Biochemical screening. The most preferred method is tandem mass spectrometry.[8-10] The mass spectrometric technique is superior to neonatal screening based on molecular genetics. For example, the phenylalanine hydroxylase gene responsible for PKU is known to have more than 350 mutations. If one needs to screen PKU by means of molecular genetic approach involving all 350 mutations, it would become cumbersome. A variety of diseases may be rapidly detected by this method, and these diseases are listed in **Table 1**. The diseases being screened in KSA and the rest of the World emphasize differences in tested diseases among different cultures. For example, while organic and aminoacidemias are frequently encountered in KSA, which justifies their screening; only few are included in the neonatal screening programs in the West. On the other hand, newborns are routinely screened for HIV in most Western countries, while this is not the case in KSA. Neonatal screening can be used in several ways and these include: (i) Comprehensive neonatal screening of all the newborns in a country or a region; (ii) screening of newborns in certain high-risk families or tribes exclusively or (iii) screening of a variety of disorders in adults or adolescents.

Approximately 50% of the diseases identified by tandem mass spectrometry are manageable. However, for the rest of the diseases, either the referral is not

rapid enough, or the disease has a severe phenotype where in the crippling and morbidity outcomes cannot be prevented. In KSA, for example, this latter category includes a tribal variant of propionic acidemia and maple syrup urine disease (MSUD). The cost of health care varies among diseases. In some cases, the management is very rewarding and the child grows to be an adult. Lifelong treatment with drugs then becomes prohibitively expensive. A good example is tetrahydrobiopterin in the treatment of biopterin dependent PKU, whose cost is very high (exceeding $40,000 a year) in doses required for an adolescent. On the other hand, an adolescent found to have hyperhomocysteinemia due to methylene tetrahydrofolate reductase deficiency requires only a daily tablet of Folic acid (5 mg) to prevent strokes. The cost is negligible both to the patient and to the health care system. In addition to the tandem mass spectrometry, other biochemical screening approaches can also be applied on Guthrie cards (blood spots storage cards) to screen for hypothyroidism, biotinidase deficiency, congenital adrenal hyperplasia, and galactosemia using high throughput fluorometric assays.

In summary, a neonatal screening program with the use of tandem mass spectrometry is a good starting point in diagnosing and ultimately preventing genetic disorders. It should be available in most countries in the Middle East. Other programs of detecting carriers and pre-implantation genetic diagnoses should also be developed.

1. Molecular screening. a) Blood storage paper. A relatively new approach is to store biological samples, including blood on an absorbent cellulose-based paper that contains chemicals to protect DNA molecules from nuclease degradation and from bacterial growth. The blood spots on these papers could be stored for a long period of time. A recent example of such paper is the "IsoCode" paper (Schleicher & Schuell Inc., Keene NH, USA). These papers are very easy to use and the elution of amplifiable DNA from blood samples dried on these cards is accomplished in approximately 30 minutes. This makes the use of these cards easy and not labor-intensive. Furthermore, there is no need for the use of organic solvents for extracting DNA from the blood spots dried on these cards. The amount of extracted DNA will yield enough templates for as many as 20 amplifications. The extract can then be used directly for mutation analysis either through a sequencer or through the DNA microarray technology described in this review. These papers have small triangles at one end where the tip of the triangle can be placed into the blood, which will wick onto the IsoCode. The triangles when soaked with blood easily break into an Eppendorf tube by simply touching the side of it. We have used this method for heterozygote detection in 4 different diseases with known mutations without any difficulty. The "Schleicher and Schuell IsoCode" cards could also be used for storage of other complex biological samples such as saliva and other body fluids samples. Therefore, the availability of such a system for blood storage is essential for mass screening of heterozygotes in the extended family as well as throughout the population in order to establish the carriership and to estimate the gene frequencies of various inherited disorders in any given country.

b) Deoxyribonucleic acid microarray. It is widely believed that thousand of genes and their products (namely, ribonucleic acid [RNA] and proteins) in a given living organism function in a complicated and orchestrated way that creates the mystery of life. However, traditional methods in molecular biology generally work on a "one gene in one experiment" basis, which means that the throughput is very limited and the "whole picture" of gene function is hard to obtain. As a result, DNA microarray technology has attracted tremendous interests among biologists since it enables researchers to monitor the whole genome on a single chip. Deoxyribonucleic acid microarrays or DNA chips are fabricated by high-speed robotics, which imprint a piece of DNA, complete human genome or parts of chromosomes or a fragment of DNA with a mutation or polymorphism on a glass slide. Probes with known identity are used to determine complementary binding thus allowing massive screening for gene expression, detection of mutations and polymorphisms, chromosome aberrations and gene discovery.[16] Deoxyribonucleic acid microarray technology is currently being used in a wide range of applications, which include but not limited to gene discovery, disease diagnosis, mutation detection, gene expression experiments, pharmacogenetics and toxicogenomics. The possibility of mutation detection on a large scale using DNA microarray and the fact that the whole process could be completed within 24 hour period, make this technique especially attractive for mass screening of abnormalities in patients, feti, or carriers.

In summary, DNA microarrays should be developed as the main technology to detect mutations in possible heterozygotes due to its convenience, ability to screen for large number of mutations in one single slide and being reasonably fast compared to other techniques currently available for mutation detection.

c) Nucleic acid hybridization. Deoxyribonucleic acid could be denatured by heating and renatured by cooling. Single stranded nucleic acids with complementary sequences may undergo hybridization to form double stranded hybrids. The DNA/DNA, DNA/RNA and RNA/RNA hybrids are all possible. Hybridization is the basis of several analytical techniques used to detect specific nucleic acid sequences in complex mixtures. Most of the current hybridization techniques use probes to detect nucleic acid specific sequences. Cloned or polymerase chain reactions-amplified DNA, synthetic oligonucleotides and RNA obtained by in vitro transcription are all used

as probes. Probes used for techniques such as Southern, Northern and Western blotting used to be labeled with isotope such as ^{32}P, ^{35}S, ^{14}C or ^{3}H. However, due to the hazards associated with using isotopes labeled probes, the general trend now is to use probes labeled with fluorescein. The other common trend is to label the probe with steroid Digoxigenin (DIG), which can be detected by specific antibodies labeled with a dye or linked to an enzyme that catalyzes the formation of colored product.[17] In addition, the use of molecular beacons is gaining momentum. Molecular beacons are oligonucleotide probes that can report the presence of specific nucleic acids in homogeneous solutions. They are hairpin-shaped molecules with an internally quenched fluorophores whose fluorescence is restored when they bind to a target nucleic acid. Molecular beacons are useful in situations where it is either not possible or desirable to isolate the probe-target hybrids from an excess of the hybridization probes, such as in real-time monitoring of PCR in sealed tubes or for the detection of RNAs within living cells. Currently, there is a wide range of applications for molecular beacons, and those include early cancer detection.[18]

d) Other molecular technologies. Among the many molecular biology techniques, such as Heteroduplex analysis, Restriction Endonucleases, allele-specific Oligonucleotides, Single Strand Conformational Polymorphism, Denaturing Gradient Gel Electrophoresis, available for genetic testing, sequencing is still one of the most precise ways to characterize a segment of DNA and detect any abnormal variations. Once these variations are identified, it can be used to detect mutations in family members. Sequencing has come a long way since the Sanger and Maxam-Gilbert manual methods, which relied on the use of radioactive nucleotides. Nowadays, DNA sequencing analysis became fluorescein based and automated. Sequence automation has resulted in a very high throughput and a good example of this is the new MegaBACE 4000 from Amersham Biosciences. This machine is capable of processing 384 samples simultaneously and reading 2.5 million bases per day.

2. Databases. Databases for mutations are a valuable source of information for researchers. For any genetic program to succeed, it is essential to maintain a database for the mutations encountered in the community being investigated. An example of mutations so far found in major Saudi diseases is listed in **Table 2**. This table shows that among 7 diseases where the mutations were studied, 2 were mutations commonly detected in Middle Eastern countries. Of the remaining 21 mutations, 19 were from the Saudi population (90%). This suggests that every country, before venturing into a carrier-screening program, should first try to identify the specific mutations for their population as broadly as possible through conventional procedures. The vast majority of mutation databases list mutations common to Caucasians while one database lists mutations found in Arabs. The most common databases available on the World Wide Web are listed in **Table 3**. An example of recently established databases are the ones established by the National Institute of Health, United States of America for malignancies and the cancer genome anatomy projects. Such databases are very resourceful for researchers working in the field of genetics.

3. Preventive genetics. The importance of preventive measures, which could be taken to avoid the costly management of genetic diseases, were discussed earlier in the introduction. Preventive measures, which could be applied to the Arabian Peninsula include:

a) Genetic counseling. Genetic counseling is aiming to replace misunderstandings on the causes of genetic disease with correct information and to increase people's control of their own and their family's health by informing them of the resources available for diagnosis, treatment and prevention. Although counseling plays a role in many medical consultations, it is of particular importance in medical genetics due to the implications on family members in terms of difficult choices that have to be made and the important ethical problems involved. The responsibility involved in genetic counseling should not be underestimated. In the Arabian Peninsula, the physician usually handles most of the genetic counseling during routine clinical visits. The current medical teaching methods rarely prepare the physicians to discuss complex genetic issues with their patients in order to help the families in decision making, which have life long consequences. In view of the fact that trained genetic counselors is a rarity and that specialized training programs in genetic counseling are absent, there is an urgent need to have fully trained genetic counselors in this part of the world. This issue was recently highlighted when a survey among 500 parents, with children who have a metabolic disease, looked for their knowledge of genetic diseases indicated that the majorities were unaware of etiologies, symptoms, inheritance and therapies.[19] This was particularly true for parents with lower education. Until recently a genetic counselor only advised of possibilities of recurrence of such a disease in the immediate family. The new policy of genetic counseling is to help the family in making the correct decision for preventing the disease in the extended family and the prevention of a similar condition in future pregnancies. This can be carried out through advising families; a job best done by a genetic counselor.

b) Pre-implantation genetic diagnosis (PGD). Pre-implantation genetic diagnosis is usually performed by obtaining a single cell through a biopsy from embryos developing in vitro. This is carried out usually at the morning of the third day after the ova is fertilized.[20-21] At this stage of embryonic development, each cell is totipotent and even the removal of 30% of

them will not be harmful. Pre-implantation genetic diagnosis relies on the detection of mutations in each embryo and only those found to be free of mutations will be transferred into the uterus. Normal embryos that are not implanted can be kept in liquid nitrogen for future use. The pre-implantation diagnosis saves the mother from undergoing painful procedures for prenatal diagnosis as based on chorionic villus biopsy or amniocentesis; each of which carry the risk of a 1-2% loss of feti. Furthermore, in strictly religious cultures such as in the world of Islam, prenatal diagnosis for genetic disorders is usually banned by "Fatwa" and parents do not prefer it either. Nowadays, even in cultures where such prenatal interventions are not prohibited, the tendency to perform PGD is growing. Another advantage of PGD is that it can be offered to-be-wed couples who were tested and found to be carriers of a certain mutation. If they still decide to marry, PGD will offer them the chance of having a healthy baby. The risks of PGD could be related to the IVF procedure or the single cell diagnosis. A major limiting factor of PGD is the fact that only 40% of the transferred embryo could lead to a successful pregnancy. The other limiting factor is related to the accuracy of single cell diagnosis (<5%).

Who should be screened and who should be advised of pre-implantation genetic diagnosis? This depends upon the prevalence of diverse genetic disorders in any given community. In KSA, the distribution of major single gene diseases is shown in **Table 4**. This center has always closely collaborated with other health care centers in Kuwait, Bahrain, United Arab Emirates, Qatar and Oman for the diagnosis of genetic disorders. The distribution of these diseases in other parts of the Arabian Peninsula is almost similar to KSA. Therefore, this distribution dictates who should be screened for what and who should be advised of PGD. In order for a certain disease or a genetic disorder to be included for PGD the genetic disease must be (i) encountered frequently, (ii) be of known mutations, usually fatal or cause severe crippling and (iii) the disease management is costly or not feasible.

c) Premarital diagnosis. The advantage of premarital diagnosis is that affected births could be prevented if couples at risk were identified. This is

Table 1 - List of neonatal diseases screened in Saudi Arabia and Western countries.

List of neonatal diseases
In the Kingdom of Saudi Arabia
Maple syrup urine disease
Pyroglutamic aciduria
Hyperprolinemia
Homocystinuria
Congenital adrenal hyperplasia
Propionic acidemia
Methylmalonic acidemia
Isovaleric acidemia
Fatty acid oxidation disorders
Methylmalonic aciduria
Galactosemia
Urea cycle defects
Classical and variant Phenylketonuria
ß-ketothiolase deficiency
Tyrosinemia type I & II
B12 & folic acid metabolic defects
Hypothyroidism
3-hydroxy-3-methylglutaryl CoA lyase deficiency
Glutaric aciduria types I & II
In the West
Widely practiced for
Hypothyroidism
Congenital adrenal hyperplasia
Phenylketonuria
Hemoglobinopathies
G6P dehydrogenase deficiency
Usually tested for
Adenosine deaminase deficiency
Biotinidase deficiency
Fatty acid oxidation disorders
Maple syrup urine disease
Homocystinuria
Tyrosinemia
Neuroblastoma
Human immunodeficiency virus

Table 2 - Some of the mutations detected in the Saudi population.

Disease name	Mutation description
Niemann Pick disease type B	H421Y (Middle Eastern mutation) W533R* K576N*
Gaucher disease	Leucine 444 Proline (Norbottnian mutation common in the Middle East)
Glutaric Aciduria type 1	Histidine 403 Arginine* Glycine 390 Alanine* Alanine 382 Threonine* Glutamate 365 Lysine Glycine 354 Arginine* Arginine 313 Tryptophan* Phenylalanine 236 Leucine (Bahraini) Glycine 178 Arginine Leucine 179 Arginine* Serine 139 Leucine*
Biotinidase	Glutamine 466 termination* Frame shift and loss of bases 490-491* Two base deletion 544* Insertion or deletion G76:d7i3*
3-Hydroxy-3-Methyl Glutaryl CoA Lyase	Arginine 41 Glutamine* Frameshift Phenylalanine 305 (shift-2)*
GM 2 activator protein	Loss of lysine 88*
Galactosialidosis	Valine 132 Methionine* Lysine 453 Glutamate*

*Mutation unique to Kingdom of Saudi Arabia
GM2 - ganglioside M2 activator

Table 3 - List of some genetic resources on the Web.

Resources name	Website address
Genetic disease information	
MedWebPlus: Genetics	http://www.medwebplus.com/subject/Genetics.html
OMIM : Online Mendelian Inheritance in Man	http://www.ncbi.nlm.nih.gov/Omim/
Gene Clinics	http://www.geneclinics.org/
Online Directory of Genetic Resources	http://www.geneticalliance.org/diseaseinfo/search.html
Genatlas	http://www.citi2.fr/GENATLAS/welcome.html
Society for the Study of Inborn Errors of Metabolism (SSIEM)	http://www.ssiem.org.uk/
Alliance of Genetic Support Groups	http://medhelp-org/wwwlagsg.hgm
United Leukodystrophy Foundation	http://www.ulf.org
National Organization for Rare Disorders (NORD)	http://www.NORD_RDB.com/2orphan
Genetic testing	
Gene tests	http://www.genetests.org/
European directory of DNA laboratories	http://www.eddna1.com
Databases	
Phenylketonuria database	http://www.mcgill.calpahdbl
Human gene mutation database	http://www.uwcm.ac.uk/uwcm/mg/hgmd0.html
The genome database	http://www.gdb.org/
Cystic fibrosis mutation database	http://www.genet.sickkids.on.ca/cftrl
The polymorphism database	http://www.genome.wi.mit.edu/SNP/human
Mitochondrial mutation database	http://www.gen.emory.edu/mitomap.html
The tumor gene database	http://condor.bcm.tmc.edu/oncogene.html
The nucleic acid database	http://ndb-mirror-2.rutgers.edu/
Linkage database	http://www.genethon.fr
Genotype database	http://www.cephb.fr/cephdb/
Arab genetic disease database	http://www.agddb.org
Human dysmorphology database	http://www.hgmp.mrc.ac.uk/DHMHD/lddb.html
Educational resources	
National coalition for health professional education in genetics	http://www.nchpeg.org/
Glossary of genetic terms	http://www.nhgri.nih.gov/DIR/VIP/Glossary/
The human genome project information website	http://www.ornl.gov/hgmis/publicat/tko/index.html
Genetics Journals	http://healthweb.org/browse.cfm?categoryid=331
Genetics Education Center	http://www.kumc.edu/gec/
Genetics education materials	http://www.kumc.edu/gec/resource.html
Geenor books on genetics and genetic Engineering	http://www.geneticengineering.org/books/default.htm
Ethical resources	
Genetic Bioethics	http://www.med.upenn.edu/bioethic
National information resource on ethics and human genetics	http://bioethics.georgetown.edu/nirehg.htm

Table 4 - Diseases with higher priority for pre-implantation diagnosis, heterozygote and premarital screening in Saudi Arabia.

Disease category	Disease name
Organic acid disorders	Propionic acidemia, methylmalonic acidemia
Amino acid disorders	Maple syrup urine disease, phenylketonuria and Biopterin dependent phenylketonuria, homocystinuria
Storage diseases	Niemann-Pick disease type B, Gaucher disease Other lysosomal storage diseases according to their prevalence in the country,for example Sandhoff's disease and multiple sulfatase deficiency for Kingdom of Saudi Arabia
Neurodegenerative diseases	Duchenne muscular dystrophy, spinal muscular Atrophy, X-linked adrenoleukodystrophy
Hematologic disorders	Sickle cell anemia, thalassemia, hemophilia
Other disorders	Cystic fibrosis, familial mediterranean fever

Table 5 - Major Inborn Errors of Metabolism seen at the Pediatric clinic of King Faisal Specialist Hospital and Research Centre, Riyadh, Kingdom of Saudi Arabia (1998- 2002).

Disease category	Disease name
Organic acidemias (n= 294)	Methylmalonic acidemia (n=72) Propionic acidemia (n= 56) Glutaric aciduria type 1 (n= 29) 3-Hydroxy-3-Methyl Glutaryl CoA Lyase Deficiency (n=26)
Amino acid disorders (n= 223)	Other organic acidemias (n=111) Maple syrup urine disease (n=58) Classical phenylketonuria (n=33) Biopterin dependent phenylketonuria (n=29) Homocystinuria (n=33)
Lysosomal storage disease (n=172)	Other amino acid disorders (n=70) Niemann-Pick disease type B (n=36) Multiple sulfatase deficiency (n=30) Morquio's disease (n=25) Sandhoff's disease (n=19) Hurler-Scheie disease (n=18) Gaucher disease (norbottnian type) (n=8) Other lysosomal storage disease (n=36)

easier said than done in the Saudi society, where consanguineous marriages are high (60%). In the past, the tribal nature of marriages left very limited options for carrier couples. One of the options available to carrier couples was to marry, but not to have children. This option is also limited in family centered societies such as the one in the Arabian Peninsula. However, with the advent of PGD and fetal treatment, carrier couples have now more options. Recently, the Saudi government introduced a new legislation regarding premarital testing for 2 common genetic disorders; namely, sickle cell trait and thalassemia. The legislation might be extended to include other genetic disorders common to this region.

Discussion. In the past decade the field of genetics has achieved a quantum jump. So many new technologies became available that whatever is possible today could not even be imagined 10 years ago. Maybe the most important aspect of this explosion of knowledge is the immediate availability of whatever was developed in the laboratory to clinical practice. In its earlier years, genetics was considered to be a field of academic interest. When a mutation was found or when a new gene was hunted, its results remained in the archives of academy. Nowadays, the genetic discoveries are finding immediate and meaningful applications in clinical medicine.

Recently, new techniques involving the growth and differentiation of stem cells are creating many possibilities for clinical applications.[23] The same is also true of gene therapy.[24] Although this technique might still be years away from practical use, it certainly will join the field of expanding genetic applications. These technologies, stem cell technologies and previous technologies described in this review will have a great impact on carrier screening, which is an integral part of preventive genetics programs. However, before commencing such programs, diseases should be carefully selected. For example, **Table 5** lists various metabolic diseases encountered during our experience at King Faisal Specialist Hospital and Research Centre, Riyadh, KSA. This list does not include hemoglobin disorders since they are cared for by a different group of physicians in KSA. One of the most important group of disorders that should be subjected to carrier screening and PGD in the Arabian Gulf is the hemoglobinopathies; hence, the large number observed in various parts of the Peninsula.[25] Choice should be made according to the need of the country. For example, Familial Mediterranean Fever is a public health problem in Jordan, whereas homocystinuria and cystic fibrosis are major Qatari problems. Any single-gene disorder with an established mutation can be subjected to pre-implantation genetic diagnosis and heterozygote screening; the selection should therefore be based on the importance of the disease to the health care system of that country. At least initially, emphasis should not be placed on rare disorders. The same criteria should apply to carrier screening, which should be performed on members of the extended family. Another example of diseases that should be targeted for carrier screening programs are the ones with costly treatment. The medications required for the management of certain inborn errors of metabolism are so costly that few if any health care system can afford them. The available injectable enzymes for Gaucher and Niemann-Pick diseases cost approximately $30,000 per year for an infant. Since the dose is according to body weight, it increases proportionally with growth. The same is true for the tetrahydrobiopterin cost for biopterin dependent PKU and for the Betaine required for homocystinuria. In summary, the carrier screening and PGD for the aforementioned diseases should take precedence over others in the Arabian Peninsula.

The recent availability of DNA papers now enables the screening to be applied to the general population as well (refer to the section on DNA papers). Once the mutations of a disease are established it will be possible not only to test the carriers in the family but also to estimate the gene frequency in any given population. This Institute is in the process of establishing all the techniques and approaches aforementioned with the thought of helping other Institutions in the country as well as in the Peninsula. The consanguinity has created such a milieu that genetic diseases are certainly important, if not, the most important health problem in this part of the World. The most sensible way to combat this problem is prevention. Certainly, the techniques available permit such an effort to be applied on a mass scale.

What is needed is to ensure that the measures taken must take into account the social and cultural considerations. They also must obey the bio-ethical and religious principles as discussed recently by Alkuraya and Kilani.[25] A big effort must be spent to educate both the medical and general public with an open discussion of the available techniques, and their advantages and disadvantages.

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