Marriage between related individuals is an ancient practice that has taken various forms ranging from what is now considered unlawful incest to one in which a couple does not readily recognize a common ancestor other than the perceived shared tribal origin. Consanguinity refers to the union between related individuals with an identifiable common ancestor, and in the strict sense of limiting the coefficient of relationship to that of second cousins about one tenth of the world’s children are born to consanguineous parents (1, 2). Aside from early humans where consanguinity was not so much an option as it was the reflection of a very limited reproductive pool, consanguinity continues to persist in a world that topped 7 billion in its population size. Several factors are believed to encourage consanguinity, including preserving wealth within families, maintaining a privileged social class (commonly seen in ruling families of different cultures), easy identification of potential mates (common in conservative societies with arranged marriages) and simply the continuation of a tradition that became deeply rooted in culture (3–5). The latter should be borne in mind when today’s consanguinity map is examined as the apparent overlap between the predominance of the Islamic faith and consanguinity in Middle East can be misinterpreted as a causal association. Indeed, the practice of consanguinity in Middle East is ancient and predates the advent of Islam, and many members of Christian and Jewish communities in Middle East also practice consanguinity (6).
Consanguinity renders autozygous (homozygous or identical by descent) a portion of the offspring’s genome (referred to as the autozygome) proportionate to the degree of relatedness between the parents (7). Because autozygosity unMASKs the recessiveness of pathogenic alleles that are present on the shared ancestral haplotype, consanguinity is known to predispose to autosomal recessive disorders (1). Detailed discussion about the proposed effect of consanguinity on fertility as a compensatory mechanism, the ‘purge’ effect of protracted population history of consanguinity on pathogenic alleles or the effect of consanguinity on common disease burden can be found elsewhere (8, 9). Instead, this review discusses the impact of new genomic tools on the practice of clinical genetics in consanguineous populations (Fig. 1).

Because the global distribution of consanguinity largely overlaps with that of low and middle income countries, the dissection of the consanguinity-related autosomal recessive disease burden from the overall disease burden is not straightforward (1). These countries typically have poor infrastructure for epidemiological assessment of disease burden and tend to have a high rate of communicable diseases that tends to eclipse that of genetic diseases. Because most autosomal recessive diseases are individually rare, they rarely feature prominently in healthcare policies even though their collective burden can be substantial by any measure. In addition, the perceived lack of cost-effectiveness of primary prevention (e.g. carrier screening, premarital and preconception testing) and secondary prevention (e.g. neonatal screening) is often cited as an obstacle even though the cost of diagnosing and managing these conditions is rarely included in the cost-effective analysis (10). In fact, the level of available evidence is strongly in support of the implementation of preventive strategies for genetic diseases as the overwhelming majority of them are untreatable, costly in their management and highly debilitating (11). This is part of the reason for the recent recommendation by WHO that low and middle income countries should adopt new genomic tools for the prevention of genetic diseases despite the recognized limited resources (12). Several projects have been underway in countries with high level of consanguinity to curb the alarming level of genetic disorders and these have been the focus of previously published work (13). Similarly, a perspective on the use of new genomic tools in low and middle income countries has recently been published (10). However, little is known about how the utilization of these new tools has actually impacted consanguineous communities. This author has been utilizing the latest genomic tools in one of the world’s most highly consanguineous countries, and communicated mutation information to and counseled hundreds of consanguineous families. The aim of this review is to draw lessons from this experience that can be applicable to other similarly consanguineous populations and to inform future healthcare policies that should take into account the changing landscape of community genetics brought about by the advent of the new era of genomics.

**Saudi Arabia: consanguinity not the only variable**

The Kingdom of Saudi Arabia (KSA) is the world’s 12th largest country by land area (occupying most of historical Arabia), and although it is relatively sparsely populated with a population size of 28.3 million, it has a high fertility rate of 2.8 and high birth rate of 19.19 birth/1000 population, which translates to 569,000 births per year (14). Average consanguinity rate is 56% although this can be higher than 80% in certain regions (15, 16). The tradition of consanguinity is ancient and has persisted after the advent of Islam in Arabia >1400 years ago. Tribal structure is also an ancient feature of the societies that inhabited Arabia, and although Islam played a significant role in suppressing tribal pride in its early days, loyalty to the tribe regained its strength following the collapse of central government in later stages when most of Arabia essentially was outside the rule of any form of central government until the foundation of the modern KSA in 1937 (17). Tribe-restricted marriages are still common but there is a growing trend of openness toward more mixed marriages. Literacy level approaches 90% and is rising. The healthcare system in KSA is a hybrid between the socialized medicine structure of Canada and the insurance-based private medicine structure of the United States (18). All Saudi citizens are eligible for free healthcare in state-run medical facilities that range from primary care centers distributed throughout villages, towns and cities to advanced tertiary care facilities that are restricted in their geographical locations to major metropolitan centers although new plans are underway to increase their distribution to all provinces. Those citizens who work in the private sector are eligible for healthcare coverage by their employer, which enables them to receive healthcare in private medical facilities. The government spending on healthcare infrastructure has greatly reduced infant mortality rate and mortality from...
New genomic tools on the practice of clinical genetics in consanguineous populations

Communicable diseases in general, a factor that may have contributed to the increased visibility of the burden of autosomal recessive diseases (19). Availability of genetic services is largely restricted to state-run facilities mostly because of perceived lack of demand and cost-effectiveness by the private sector. This strains the limited pool of qualified geneticists whose wait time is typically measured in months. Termination of pregnancy is generally illegal but exceptions can be made when a committee of physicians agrees that the fetus has a severe and untreatable disorder as long as the procedure is performed before 120 days from the time of fertilization (around 19 weeks of gestation), the time at which a fetus is believed to have acquired full human status in Islam (20). This brief profile of Saudi Arabia is shared to a significant extent by many other Middle-Eastern countries in which consanguinity is common; therefore, the impact new genomic tools have had in Saudi Arabia is potentially comparable to these other countries as well (6).

Homozygosity mapping
Identifying causal autosomal recessive mutations in patients born to consanguineous parents by tracking patterns of homozygosity that result from the biparental inheritance of a shared ancestral haplotype that harbors the mutation is known as homozygosity mapping and is extensively reviewed elsewhere (7). Despite the appealing nature of this approach, it has only recently been incorporated into clinical practice (this author was among the first to advocate its use as a diagnostic tool) (21). This is partly because homozygosity mapping used to be a complicated procedure limited to a few research laboratories before SNP chips became widely available. In addition, the expertise in homozygosity mapping was mostly restricted to research laboratories that had little incentive to investigate the clinical utility of this approach as they are usually located in countries where consanguinity is generally uncommon. Shortlisting candidate genes for sequencing and revisiting the clinical diagnosis are among the many advantages of homozygosity mapping (21, 22). This approach is now made simpler with the availability of online tools that automatically interrogate regions of homozygosity (ROH) for clinically relevant candidate genes (22). We routinely run a homozygosity scan on our patients with suspected autosomal recessive diseases unless the diagnosis is confirmed clinically and is known to be genetically homogeneous (23). Despite the significance of lineage to Arabs, emphasis is usually placed on the patrilineal lineage only, hence matrilineal shared ancestors are often unrecognized. Therefore, homozygosity scan is indicated even in the apparent absence of identifiable consanguinity. It can be argued that homozygosity scan is one of the most cost-effective clinical genetics tests in a highly consanguineous population and has quickly and efficiently aided in the diagnosis of the majority of our patients. Homozygosity mapping has its own set of limitations. The ROH where the mutation resides may evade detection, the disease presentation may be atypical such that one may fail to recognize it among the list of diseases whose genes reside within the ROH, and the disease may be so genetically heterogeneous that sequencing of the shortlisted candidate genes still poses a significant challenge (23). Most challenging, however, is when the disease gene is novel, in which case this becomes a research project but one whose results are immediately translational as we will discuss below.

Next generation sequencing
Correlating sequence variants to disease state is an important step toward the realization of genomic medicine but is limited by several factors including our incomplete understanding of the link between the gene in which these variants reside and the disease in question. Obviously, Mendelian diseases are the best candidates in realizing the potential of whole-genome sequencing (WGS) as these diseases are usually caused by single mutations (24–28). Virtually, all the above-mentioned limitations of homozygosity mapping can be overcome with WGS. However, the cost of WGS is still prohibitive to their routine clinical use although this is changing very rapidly. Furthermore, our limited capacity to interpret the massive amount of genetic variation revealed by WGS poses a formidable challenge. These two reasons make whole-exome sequencing (WES) an attractive alternative. Fortunately, the causal mutations in autosomal recessive diseases in consanguineous populations are usually homozygous, and these are usually easier to call by next-generation sequencing and when the homozygosity scan filter is applied, the search for the causal variant is made even easier (23, 29). In the presence of a family history consistent with autosomal recessive inheritance, WES can reveal the underlying causal variant in virtually all cases where the disease gene is known and at least 70% where it is novel (unpublished data). This advantage has been put to use in more than 300 of WES tests on our patients and numerous mutations have been identified, some of which could not be identified by homozygosity mapping alone even when they involve known disease genes (23, 30).

Molecular karyotyping
Autosomal recessive diseases do indeed account for a large portion of Mendelian diseases in consanguineous populations. However, it is important to bear in mind that the frequency of de novo genomic disorders is not expected to be significantly different from outbred populations but rather their relative contribution to disease burden. Therefore, clinical genetics evaluation of patients in consanguineous communities should always consider that possibility particularly in the absence of family history. As in outbred populations, the use of high-resolution molecular karyotyping is the method of choice for the detection of genomic disorders (31–33). Indeed, preliminary analysis of an ongoing study in which molecular karyotyping on
patients with developmental disorders whose parents are consanguineous but lack positive family history suggests that the yield is comparable with that observed in outbred populations (unpublished data). Identifying such de novo mutations often elicits a great sense of relief to the parents who are usually told without evidence that their child’s illness is likely related to their consanguinity.

**Incorporation of mutation discovery into medical care**

Inadequate genetic literacy among healthcare professionals is not unique to KSA or other countries where consanguinity is common; however, the resulting losses are disproportionately more profound (34). For example, failure to refer a patient with multiple congenital anomalies for proper clinical genetics evaluation is more likely to represent a lost opportunity to identify a genetic cause compared with a similar scenario in an outbred population (35, 36). The ramification of this lost opportunity extends well beyond the patient and his/her parents because the relatives on either side of the pedigree are likely to marry from each other, which represents an ideal window of opportunity in which cascade carrier testing can aid in the primary prevention of the disorder (5, 37). Contrast this scenario with an outbred population in which carrier relatives identified by cascade carrier testing are only as likely to have carrier partners as the population carrier frequency of the mutation dictates, which tends to be extremely low. In our experience, failure of healthcare professionals especially pediatricians and OB/GYN specialists to recognize the fact that a given birth defect in a child born to consanguineous parents is more likely to represent an autosomal recessive entity that is amenable to prevention when the proper diagnosis is made contributes to the high recurrence even in families that are highly receptive to genetic counseling. Additionally, there are erroneous pre-conceived notions about the hopelessness of a genetic diagnosis even in terms of prevention because of perceived religious and cultural barriers (38).

We study strongly advocate the dismissal of such pre-conceived notions and the delivery of unbiased but culturally sensitive genetic counseling that clearly lays out the various reproductive options that are available to parents whose child’s (children’s) autosomal recessive disease is molecularly diagnosed. Preliminary analysis of an ongoing survey involving our patients suggests that less than 10% of families remain undecided after they have been counseled about their child’s mutation. Another 10% opt to have no more children while the overwhelming majority (80%) pursues more active preventive strategies, specifically preimplantation genetic diagnosis (PGD) or early prenatal diagnosis (unpublished). Contrary to what many believe, early prenatal diagnosis with the option of terminating an affected pregnancy is favored upon PGD (45 vs 35%). Almost all attend the counseling session with the pre-conceived notion that therapeutic termination is banned by religion and by law but experience a significant change in attitude after they are presented with the official Fatwa about the 120-day post-fertilization cutoff and are told of the current regulation of termination of pregnancy in the country. This is highly consistent with what has been shown more than 10 years back in terms of the importance of cultural sensitivity in conducting genetic counseling in these communities (39). It appears unlikely that the limited availability of PGD to the city of Riyadh is the reason behind the preference of early prenatal diagnosis because those residing in Riyadh are not more likely to consider this option compared with those residing elsewhere. Importantly, the consideration of prenatal diagnosis and terminating an affected pregnancy are not merely hypothetical as more than 150 CVS/amniocentesis procedures have been performed just in 2012 for single gene mutations in our institution alone and several therapeutic abortions have been carried out after achieving the required approval.

Cascade carrier testing is another important area that is particularly suited to highly consanguineous populations but one that deserves special consideration (40). In our experience, identifying a familial mutation tends to be highly traumatic and stigmatizing to the parents especially when positive family history is lacking. In addition, fear of spreading the stigma to the entire family is a common obstacle toward effective implementation of cascade carrier testing. Specifically, there is typically a concern that if the word spreads that a family carries a particular mutation, its members will be deemed unfit for marriage in the future, a phenomenon that has been documented in other communities as well (41). It usually takes a lot of explaining, often over several sessions, to encourage parents to disclose to relatives that they are at risk of being carriers of a particular mutation. We typically just require the parents to deliver that information and to request permission from at risk relatives to be contacted by us to counsel them about their risk and the benefit of determining their carrier status. In our community, this approach is much more effective than a passive approach in which relatives are expected to contact us because they often fail to realize the value of determining their carrier status and we have found standardized letters conveying this message as used elsewhere to be socially less acceptable. We have found that properly informed individuals are capable of acting responsibly on their carrier status by encouraging future mates to be tested by our lab. Although the funds to conduct cascade carrier testing currently come through a research protocol (The Carrier Phenome Project), this effort has to be expanded as part of a national strategy to maximize its potential. In the absence of an unbiased comprehensive test for carrier screening such as whole-exome or targeted exome sequencing (see below), cascade carrier testing is the only available practical solution (38). Indeed, most of these debilitating autosomal recessive disorders are rare enough individually to warrant population carrier screening. Furthermore, we have shown in many publications in the past the remarkable degree of allelic heterogeneity in our population, even for very rare
disorders and within the same tribe, which we believe to be the direct effect of consanguinity (42). Owing to the lack of founder mutations for many disorders, effective population screening for any of these disorders will require sequencing-based protocols to capture all likely pathogenic alleles.

**Future opportunities**

Next-generation-based carrier screening

Although family-oriented cascade carrier testing can be cost-effective, it has the obvious significant limitation of being applicable only after the identification of an affected index within a family. A truly primary preventive intervention should commence before the disease occurs. The recent availability of next-generation sequencing provides an unprecedented opportunity to realize the dream of medical geneticists of offering comprehensive preconceptional carrier testing instead of the currently available ethnic-specific and targeted carrier testing whose significant limitations are well recognized. One remarkable proof-of-concept study has shown the clinical and analytic validity of the targeted exome sequencing of a pre-selected group of genes that are known to be associated with severe pediatric onset autosomal recessive diseases (43). Although test packages that offer an extensive list of mutations in many genes are now clinically available, the above-mentioned observations about allelic heterogeneity in consanguineous populations greatly limit their utility and call for sequencing-based approaches instead. Cost is currently an issue but the breathtaking decrease in the cost of sequencing should make this a serious consideration for implementation at a population level within the very near future. We believe that a country with such a high rate of consanguinity and a government capable of such a generous spending as KSA is ideally positioned to be among the first to reap the benefits of sequencing-based population carrier screening. Obviously, an undertaking of this magnitude faces formidable challenges that need to be addressed, but it is worth the effort as the alternative of simple opposition to consanguinity is unlikely to be effective (38). The nearly decade-long implementation of the mandatory pre-marital carrier testing for sickle cell disease and thalassemia in KSA should be a starting point at much has been learned from that experience. For instance, much of the failure to prevent ‘incompatible’ couples from proceeding with marriage stems from poor pre- and post-test counseling and recent data suggest a remarkable decrease in the marriage of incompatible couples when this gap was addressed (Al Sulaiman, unpublished data). The inevitable identification of variants of unknown significance even when a list of known disease genes is pre-selected should not be a reason for abandoning this strategy as the benefits are expected to outweigh the risks. A project that pilots the use of targeted exome sequencing for carrier screening preconceptionally is in the planning phase, and although it does not necessarily recapitulate the premarital setting, important lessons about cost-effectiveness can still be learned. In addition, one can envision a two-tier system in which all couples are offered the mandatory routine limited pre-marital test but are offered an optional extended carrier test even after marriage. The list of genes covered by the latter test should be constantly updated as more novel autosomal recessive genes are identified. The expansion of the gene list can take the form of relaxing the bioinformatic field of view to include more genes in the analysis when WES is used or through the actual inclusion of these new genes in a capture assay. The above-mentioned pilot project will also aim at comparing the two approaches.

**Conclusion**

Consanguineous populations have greatly contributed to our understanding of the human genome as it relates to health and disease, but have received disproportionately little attention in terms of community genetics approaches that address health issues that are unique to them. There is a multitude of factors that contribute to this gap mostly related to the fact that the utilization of consanguineous populations for genetic research has largely been carried out by investigators from other parts of the world where consanguinity is not a public health issue. This review hopefully shows the great potential new genomic tools have to reshape healthcare delivery to these communities and suggests ways to maximize this potential for future public health opportunities. Clearly, a coordinated effort is needed to realize this potential and it is hoped that this review will encourage further debate and the exchange of ideas from countries with comparable demographics to improve the delivery and execution of policies that are tailored to serve the unique needs of consanguineous populations.

**References**