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REVIEW ARTICLE

Implementation of public health genomics in Pakistan

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Abstract

There has been considerable recent progress in the implementation of public health genomics policy throughout the developed world. However, in the developing world, genetic services still remain limited, or unavailable to most. Here, we discuss challenges and opportunities related to the implementation of public health genomics in developing countries. We focus on Pakistan, a country with one of the world's highest rates of inter-family marriages and prevalence of inherited genetic conditions. Pakistan still lacks a national newborn screening programme, clinical genetic testing services, or public health genomics framework. The medical infrastructure in Pakistan, characterized by limited publicly-funded health services and a significant burden of infectious disease, may contribute to de-prioritization of genetic health services. In addition, there are a number of societal, cultural and religious factors to consider. Recently a number of large research studies have been conducted in populations of Pakistani descent, mostly in collaboration with major US, UK and European institutions. Some of these have yielded high-impact scientific findings, but have yet to translate into public health outcomes in Pakistan. Before the benefits of genomics can be realized in developing countries, the first initial steps towards strategic prioritization, resourcing, and long-term goal setting are required. We propose some practical recommendations and possible first steps forward.

Introduction

Genomics has the considerable potential to improve public health outcomes, including prevention and treatment of human diseases, at the population level. The goal of public health genomics (PHG) is to provide effective and responsible translation of genomics research into population health [1]. In the developed world, genomics is already delivering considerable health benefits across a range of clinical settings, and is moving rapidly towards delivering benefits at the population level. However, because most progress in public health genomics, to date, has been conducted in the developed world, there is a 'genomic divide' emerging between developed and developing countries [2].

In 2002, the World Health Organization (WHO) released a report on genomics and world health [3]. This report assessed the current and future status of international genomic research, including issues related to the integration of genomics into healthcare, ethical issues and the equitable sharing of benefits between developed and developing countries. In 2018, many of the challenges identified by the WHO report still remain, as the gap between developed and developing appears to be widening.

In the literature, there are numerous accounts describing the inherent challenges and barriers to the implementation of medical genetic services in developing countries, compared with the developed world [2, 4, 5]. However, few of these have addressed challenges in the specific context of an individual national healthcare system. In this article, we discuss the challenges and barriers to the implementation of public health genomics in Pakistan (as a model for other developing countries), and consider possible short and medium-term steps which might be taken towards progress in this area. We also acknowledge and discuss the many potential opportunities and benefits that genomics could offer Pakistan specifically, if genomic health policy implementation can be achieved.

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Public health genomics in developed versus developing countries

In developed countries, such as the USA, UK and Australia, genomics is already delivering tangible public health benefits. The USA, for example, has been incorporating genomics into public health policy for over 20 years [6]. In the UK, the National Health System (NHS) has made considerable recent progress towards the mainstreaming of genomic medicine [7]. In Australia, the Australian Health Ministers Advisory Council recently endorsed the National Health Genomics Policy Framework, which aims to integrate genomic knowledge and technology into the healthcare system, to maximize public health benefits [8].

In Australia, clinical genetic screening and testing services are routinely funded by State health systems. These include pre-natal screening for chromosomal abnormalities and fully funded testing for individuals with a high risk of hereditary cancer [9, 10]. Further, Australia has had a newborn screening (NBS) programme since the 1960s. In 2018, the Australian Government endorsed an updated Newborn Bloodspot Screening National Policy Framework, including provision for structured decision-making for the inclusion of new diseases [11].

In most developing countries, clinical genetic services were established at the end of the twentieth century [4]. However, developing countries, such as Pakistan, face numerous public health challenges, particularly related to the burden of infectious diseases, malnutrition, limited resources for health education, lack of regulation of medical genetics services, limited resources for developing clinical genomics expertise, and the fragility of health systems [5]. In addition, population growth and the prevalence of non-communicable diseases (NCDs) are increasing in many developing countries, creating challenges for the allocation of resources and prioritization of genetic health services [2, 4]. These challenges will likely continue to overshadow the implementation of genomic policies unless intentional, strategic steps are taken to counter these issues.

In 2011, the WHO launched the Grand Challenges in Genomics for Public Health in Developing Countries programme [12]. This formulated the top ten priorities for the effective development and application of genomics-based public health interventions in developing countries [12]. In 2014, the programme's Executive Committee published five main challenges that developing countries could address in implementing public health genomics initiatives (Table 1) [5].

The highlighted challenges are generally applicable to all developing countries, but each developing country requires its own national agenda, policy framework and implementation plan for addressing these challenges and integrating genomics into the healthcare system.

Table 1 World Health Organization: Five grand challenges faced by developing countries in implementing public health genomics initiatives

	Grand challenges
1	Mainstreaming genomics into the national development agenda
2	Building and strengthening infrastructure and capacity in research & healthcare
3	Integrating research & healthcare
4	Engaging the public with genomics to ensure public support & 'responsible' translation
5	Enhancing & strengthening international cooperation

Challenges for Pakistan

Pakistan is a developing country with an estimated population of over 200 million, with an increasing burden of non-communicable diseases [13–15]. In 2010, the WHO published a report describing collaborative centres related to public health genomics globally [16]. Of the 48 collaborative centres in 22 countries, 36% were located in (or focussed on) developing countries. Notably, however, none of these centres were in Pakistan, or working on genomic issues directly related to Pakistan.

There are many current issues in Pakistan that act as barriers to the implementation of public health genomics. These include both health-system and cultural issues (Table 2).

Here we focus on two imminently addressable issues: (1) the lack of clinical genetic services to prevent and provide care for children with birth defects, and (2) the failure to translate research findings from foreign-based studies of Pakistani research participants back to the local health system.

A major burden on the public health system in Pakistan is infectious diseases [17]. In addition, non-communicable diseases such as diabetes, obesity and cardiovascular conditions are on the rise [13–15]. With regard to genetic conditions, consanguineous marriage rates in Pakistan are estimated to be 46–62%, where autozygosity leads to high rates of severe inherited genetic conditions and infant mortality [18, 19].

According to the WHO, 70% of birth defects globally could potentially be prevented or treated if clinical genetic services in developing countries were strengthened adequately [20]. Genetic testing services, such as pre-natal or newborn screening, provide an opportunity to improve clinical care and prevention of genetic conditions at the community level. Although a limited number of non-government organizations (NGOs) have recently started internationally collaborative NBS programmes, there is no national public NBS programme in Pakistan. NBS generally involves taking blood from the heel of a newborn, using

Table 2 Barriers to the implementation of public health genomics in Pakistan

1.	No established public health system or network of health services [23]
2.	80% home birth rate [17]
3.	Shortage of professionally-trained genomics workforce [31]
4.	Limited genomic literacy in both the general population and health care professionals [31]
5.	Limited or no public funding for genetic health services [30, 69]
6.	High rate of inter-family (consanguineous) marriages, estimated at 46–62% [18, 19]
7.	Urban and rural class system divide in health facilities [34]
8.	Prioritization of other public health concerns, such as high rates of infectious disease and hospital emergency services [34]
9.	An increasing population with limited public health budget [70]
10.	Cultural and religious factors [4, 27]
11.	Low literacy level in women (especially amongst rural populations—estimated at 26.6% [34]

tandem mass spectrometry and genomic sequencing technology (if required) to test for up to 54 known genetic conditions which are treatable in early childhood [21].

In 2013, private/welfare trust funding facilitated a pilot programme of free NBS in 20 Government hospitals in Pakistan [22]. Through this programme, samples are tested for congenital hypothyroidism in a local laboratory. High risk samples (identified through positive family history of disease) are also sent to Jordan for more comprehensive testing [22]. To date, more than 6000 samples have been tested through this programme. While this is commendable, there are over 4 million births in Pakistan annually, meaning that without a national NBS programme, most births still receive no testing. No information is publicly available regarding the reach of the pilot programme, but the authors understand from personal communications that it has been unsuccessful in its bid to secure government funding.

In the private sector, the Aga Khan University Hospital is the only organization operating a screening programme - the Congenital Hypothyroidism Screening Programme [17]. Implementation of a national NBS programme faces numerous challenges, including the high home birth rate of over 80% [23], a lack of diagnostic facilities, absence of national disease registries, and unknown prevalence of many inherited diseases.

Other reproductive genetic health services in Pakistan, such as preconception carrier screening or pre-natal screening for chromosomal abnormalities, are rare and not offered in routine clinical practice. Pakistan has a high rate of hemoglobinopathies, including β-thalassemia. However, no national registry is available, despite an estimated 5000–9000 children born with β-thalassemia in Pakistan every year, and an estimated 11–15% carrier frequency in the population [24]. Treatment for β-thalassemia involves lifelong monthly blood transfusions and an iron chelating agent. Bone marrow transplantation is a permanent treatment, but donors are limited, with only four public hospitals in Pakistan providing transplantation services for β-thalassemia [25].

In 2012, the government of Punjab (the largest province of Pakistan) launched the Punjab Thalassemia Prevention Programme [26]. This provides pre-natal genetic testing for couples with a child affected by β-thalassemia, and carrier screening for family members of at risk-couples, as well as some volunteer individuals who wanted to know their carrier status. In addition, genetic counselling is provided by an internationally-qualified geneticist to inform at-risk couples about pre-natal screening and reproductive options [26].

Termination of pregnancies affected by genetic anomalies in Pakistan, including β-thalassemia during the first trimester, is generally accepted as permissible in the Pakistani religious community [27]. However, pre-natal testing and carrier screening for β-thalassemia are not available in most government hospitals in Pakistan. There is currently only a limited number of diagnostic laboratories operating, and a general lack of public awareness, which limit access to screening [28]. Further, there is no publicly-funded screening or pre-natal testing available for other genetic conditions, such as Down syndrome and sex chromosome aneuploidies [29].

A shortage of medical genetics specialists in Pakistan further compromises the provision of genetic health services in Pakistan. The College of Physicians and Surgeons (FCPS) of Pakistan does not offer a clinical genetics speciality [30], and genetic counselling is not offered as a study programme by any institute in Pakistan. No government hospitals in Pakistan currently offer genetic counselling (GC) services, which is attributed to the lack of genetic screening programmes, despite unanimous support by medical doctors in 2013 for the provision of genetic services by GCs in the healthcare system [31]. Furthermore, Pakistan has limited rehabilitation and education services for children with disabilities due to genetic conditions.

In the future, Pakistan could consider offering access to emerging reproductive technologies in public hospitals to address the burden of genetic conditions. In-vitro fertilization (IVF), pre-implantation genetic diagnosis (PGD), preconception carrier screening (PCS) and non-invasive pre-natal screening (NIPT) are already being implemented in developing countries for this purpose [4]. In Pakistan, NIPT is offered in some private hospitals, but not in the public sector. A recent study conducted on the attitudes of obstetricians towards NIPT in Pakistan showed that 97% of obstetricians considered that pre-natal genetic screening should be made available in the public hospital setting. However, they also showed concern that increasing the availability of NIPT will

increase the social burden on women for pre-natal testing and termination of pregnancy [32].

Implementation of these technologies and related PHG policies in the Pakistani healthcare system will require addressing a range of ethical, cultural and religious issues. Ethical considerations include ensuring informed consent, data privacy and sharing, the return of genetic risk results to research participants and their families (and follow-up genetic counselling), government regulation of genomic research, and community engagement [33]. Cultural issues include limited literacy of Pakistani women, (especially in rural areas—estimated at 26.6% [34]), resulting in a gender gap in education; lack of genomic literacy in the general public; low rates of pre-natal or carrier testing; a divide between rural and urban standards of living; and differing attitudes towards abortion and reproductive choices.

Further, doctors and other healthcare providers face challenges in discussing inter-family marriage (consanguinity), which is a sensitive topic for Pakistani families, who still value marriage within close family or clan. Consanguinity is still commonly practiced, which at least in part, may be due to limited understanding in the community of the increased risk of inherited genetic conditions [35]. Greater education and support for doctors and healthcare providers regarding these risks, and ways of discussing these sensitively with the community, is required. Further, support for researchers to disseminate information about the application of medical genomics research through social and print media would be beneficial.

Finally, there are significant religious factors to consider in Pakistan, in order to engage with the wider community on the issue of genetics and healthcare. Globally in the Muslim world, disease prevention and research through genetic-based clinical care is widely permissible on religious grounds, based on rulings by respected religious scholars [4, 36–39]. The International Islamic Fiqh Council (IIFC) is an Islamic institution affiliated with the Muslim World League in Saudi Arabia. The members of IIFC represent various Muslim countries, including Pakistan, and are selected by their respective governments as their countries' senior Islamic scholars. IIFC discusses and gives authoritative Islamic rulings regarding contentious issues affecting Muslims around the globe. For example, some time ago the IIFC issued a ruling allowing for termination of pregnancy up to 120 days, at the discretion of both parents, if a foetus is found to have serious anomalies [4]. This finding must be based on an examination using appropriate laboratory equipment, and approved by a committee of two competent and trustworthy doctors.

Despite this ruling, there are disparities among some Islamic scholars regarding the permissibility of abortion, and until what gestation, even for medical reasons. Although the majority agree that termination of pregnancy for foetal anomalies up to 120 days of pregnancy (generally accepted as the time of ensoulment) is permissible [37, 40, 41], there is variation in religious views across many Muslim countries. However, scholars agree that it is impermissible to terminate a pregnancy after 120 days, even if foetal anomalies are present [36, 41]. Differences in personal beliefs, attitudes and preferences, in addition to the variation in religious interpretation, mean that discussions around abortion must be handled sensitively.

Islamic religious scholars from Muslim countries including Saudi Arabia also agree that the use of PGS or PGD to prevent the birth of children with genetic conditions is acceptable, but their use for sex selection or other non-medical purposes is unacceptable [4, 36–39]. However, the general Pakistani public, especially those living in rural areas, are often not aware of these Islamic rulings, which may prevent uptake of genetic testing, even where it is available. The Pakistani Government faces not only the challenges of developing and implementing PHG policy and medical infrastructure, but also the challenge of providing public education about the religious, cultural and ethical aspects of medical genomics.

To overcome the above-mentioned challenges, Pakistan could consider approaches used in comparable countries with similar religious and cultural backgrounds, such as Qatar, UAE and Saudi Arabia [42, 43]. For instance, UAE has implemented routine pre-marital screening for couples before marriage, to check for genetic defects of blood disorders such as Beta-thalassemia [43]. Further, Saudi Arabia implemented a NBS programme in 2005, screening 775,000 newborns from 2005–2012, reporting 743 cases with newborn defects as a result of the program [44].

In 2013, both Qatar and Saudi Arabia launched national genomics projects for the prevention, diagnosis and treatment of genetic diseases [36]. More than 11,000 individuals have now been sequenced as part of the Qatar genome project. Religious issues have been addressed under an Islamic ruling (Fatwa) that it is permissible to provide biospecimens for genetic research [45]. These Middle Eastern countries have two main advantages compared with Pakistan; (1) relatively smaller population sizes, and (2) more readily accessible funding available to perform genomic research at a national scale. Yet given the similarities in religious and cultural backgrounds between these countries, the experiences of Saudi Arabia, Qatar and UAE provide an important framework to inform future progress in Pakistan.

Genomic research in populations of Pakistani descent

Pakistani universities offer science degrees such as biotechnology and molecular genetics, at the undergraduate

and postgraduate level. Researchers in Pakistan have been able to conduct high-quality genetic research, despite limited research funding and medical infrastructure. This has been achieved largely through international collaborative relationships. For instance, whole exome sequencing of 10,000 individuals of Pakistani descent recently led to identification of the world's first reported human homozygous knockout for the *Apolipoprotein C-III* (*APOC3*) gene [46]. This followed several previous studies reporting that heterozygosity for *APOC3* loss-of-function mutations results in lower plasma triglyceride levels, and subsequently reduces the risk for coronary heart disease [47–49]. The recent study, conducted on a Pakistani population, showed that a homozygous mutation in the *APOC3* gene, previously thought to be harmful for human health, actually lowers plasma triglycerides, increases high-density lipoprotein levels, and provides significant protection against heart disease [46].

Several research groups from different institutions in Pakistan have also reported novel genes and genetic risk factors associated with genetic conditions and multifactorial NCD diseases, including inherited retinal diseases, familial hypercholesterolemia, cancer, intellectual disability and glaucoma, from Pakistani populations [50–56]. These studies demonstrate how the Pakistani population, with its unique genetic characteristics, has contributed to vital research findings. The significant potential for using Pakistani cohorts for discovery of loss-of-function genetic variation to inform novel drug targets has been specifically highlighted in recent analyses [57]. However, despite the progress to date, these findings have not yet been translated into improved health outcomes for the Pakistani population.

The East London Genes & Health (ELGH) study investigates the health of British-Bangladeshi and British-Pakistani populations in East London, UK. ELGH has already recruited over 30,000 participants and aims to recruit 100,000 participants by 2023 [58]. To date, 9681 (33%) of the ELGH participants have been British-Pakistani. The Pakistani population living in east London has a significantly higher risk of common diseases, such as type 2 diabetes and cardiovascular disease, compared with the local population of European descent [59, 60]. Similarly, 35–44% of South Asian children (10–11 years old) in East London are obese or overweight, compared with the UK average of 33% [61]. Therefore, the main focus of research for ELGH is to address the burden of type 2 diabetes and cardiovascular disease [59, 60].

To date, 3781 ELHG participants have undergone whole exome sequencing. Genotyping of 50,000 is in progress. By 2023, 100,000 participants will have their whole exome sequenced. The ELGH project can link genomic data with real time electronic health record data, and perform recall-by-genotype studies, with associated follow-up in the future [58].

Large cohort studies involving Pakistani participants may help fill the current knowledge gaps in human genetics resulting from poor representation of non-Caucasians [62]. However, population-scale genomics studies will be difficult to conduct in Pakistan, due to the inadequate medical infrastructure, limited research funding and limited genomic literacy. If the Pakistani government formulates a policy where the Health Ministry, NGOs and Universities can collaboratively work together with international projects such as ELHG, this will assist greatly in initiating population-scale genomic research in Pakistan.

Roadmap for genomics policy in Pakistan

Resources allocated towards precision health initiatives in developed countries reflect the current promise of genomics for population health. These initiatives are involving collection of human genetic, medical and environmental data on thousands, or even millions, of individuals, and implementation of genomics into routine healthcare [6, 63]. For most developing countries, such as Pakistan, consideration of a genomics initiative at this scale does not currently seem feasible. Genomics and precision medicine must first be identified, and formalized in policy, as a national health priority. This has not yet happened in Pakistan. For example, in the National Health Vision Pakistan 2016–2025 report, there was mention of new strategic priorities including non-communicable diseases, but no mention of genomics [64].

Investing in national funding for research, as well as prevention, diagnosis and treatment of genetic conditions, could lead to significant health benefits in Pakistan. A policy development and action plan, taking into account the goals set out below, could assist with the translation of genomic research into clinical practice for public health benefit. The prevalence of certain genetic conditions in Pakistan is particularly high, in part due to the high rate of inter-family marriages. Investment in genomics may assist in addressing these health burdens. The federal and provincial governments in Pakistan, the Pakistan Medical and Dental Council, research institutes, universities and international collaborators, such as WHO, could work together to help achieve progress.

As a starting point, Pakistan could consider a program comparable to the Human Heredity and Health in Africa (H3Africa) initiative [65]. H3Africa has been successful in helping focus efforts towards developing research and clinical genetic services in African countries. It provides a pathway towards developing infrastructure, resources, training, ethical guidelines, and epidemiologic/clinical research in human genomics for developing regions. H3Africia is funded by the Wellcome Trust (WT) (United

Kingdom), and the National Institutes of Health (NIH) (United States) [66, 67]. Pakistan's unique population structure and increased autozygosity create considerable opportunities for human genetics research and improvements to medical services [57].

To facilitate the successful translation of genomic research into public health benefit in Pakistan, the government must begin to integrate genomics into public health policy. We acknowledge the limitations of the Pakistan federal health budget and the significant burden of other pressing public health concerns; however, we propose an achievable, staged approach for the implementation of PHG, which includes setting short term (3–5 year) goals, followed by longer term (10–15 year) goals.

Short term public health genomics goals in Pakistan (3 to 5 years)

1. Invest in capacity building and professional training. Consider scholarships for Pakistani nationals to study clinical genetics and genetic counselling at overseas institutions, followed by six months of clinical training, before returning to Pakistan to serve clinical positions.
2. Upskill the current genetic health workforce, including medical doctors/physicians and other health care providers. Consider implementing a genomics education programme into medicine.
3. Establish a newborn screening (NBS) programme to diagnose treatable genetic disorders at birth. Initially, this programme could be piloted through existing laboratories and hospital infrastructure, to minimize costs. Consider partnering with foundations to expand already established programmes to government hospitals, and pilot the use of testing for home births, through partnering with local maternal health support networks in each district. This initiative would also assist with the establishment of a national disease registry.
4. Establish a national genomics advisory committee to provide evidence-based recommendations to the Secretary of Health on genetic conditions (which can be modelled on the extensive work already conducted by developed countries on NBS guidelines). Consider expanding the Punjab Thalassemia Prevention Programme to the entire country, and consider new screening programmes for pre-natal chromosomal and neural-tube development disorders.
5. Build strategic partnerships with the US, UK and Australian governments, to establish guidelines for appropriate use of genomic information, as well as for the accessibility, effectiveness and quality of genomic testing and services. Partnering with such countries, where there are established medical genomics services and significant Pakistani migrant communities, could help to aid Pakistan in developing and implementing genetics services and translating genomics research locally.
6. Incorporate genomics into federal and provincial Health Department portfolios, with a focus on public health, prevention and job creation. Establish an advisory panel of expert Pakistani researchers (including Pakistani researchers working abroad), who can advise government on relevant issues related to genomics in Pakistan, as recently suggested [68]
7. Begin to allocate funds from the federal and provincial health budgets to genomics, including a public awareness programme to build a basic understanding of clinical genomic testing and its implications for health. Seek funding partnerships with NGOs.

Long-term public health genomics goals in Pakistan (10–15 years)

1. Develop a national public health genomics policy framework through consultation with medical and genetics experts, government representatives (federal and provincial), health departments, stakeholders, community members, and the public, to identify strategic priorities and challenges for genomics in Pakistan.
2. Establish an advanced training programme in clinical genetics, to bolster the medical genetics workforce.
3. Invest national funds into genomic research and clinical genetic testing. Initially, the focus could be on pre-natal testing for common autosomal recessive diseases in Pakistan, such as β-thalassemia. This could progress toward increased access to genetic testing for high-risk families affected by inherited cancer syndromes, with a pathway towards risk surveillance, risk-reduction, and timely cancer treatment.
4. Establish a national genomic service platform funded by the federal government, including a clinically accredited national genomic testing laboratory to work in collaboration with universities and other institutions conducting genetic research.
5. Establish a national data platform in partnership with universities and other genetic research institutions for the collection, storage and sharing of genomic data at scale. This could involve establishing data collection

systems, such as rare disease registries, which would be invaluable. This will ensure efficient, effective and ethical use of data for public health benefit.

Developing countries like Pakistan have the opportunity to improve public health outcomes by adopting new and emerging technologies, such as genomics. There are opportunities for Pakistan to utilize the knowledge gained from international studies involving Pakistani populations, to improve local public health outcomes. However, the government must begin to develop and prioritize public health genomics policy to achieve these goals.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Khoury MJ, Burke W, Thomson EJ. Genetics and public health in the 21st century: using genetic information to improve health and prevent disease. New York: Oxford Studies in Historical T; 2000.
2. Sirisena N, Sumathipala D, Wettasinghe K, Dissanayake V. The provision of medical and health genetics and genomics in the developing world. Medical and Health Genomics: Amsterdam: Elsevier; 2015. p. 285–94.
3. World Health Organization. Advisory Committee on Health Research. Genomics and world health: report of the Advisory Committee on Health Research. World Health Organization. http://www.who.int/iris/handle/10665/42453. 2002.
4. Thong M, See-Toh Y, Hassan J, Ali J. Medical genetics in developing countries in the Asia-Pacific region: challenges and opportunities. Genet Med. 2018;20:1114–21.
5. Pang T, Oestergaard M. Creating policy frameworks for public health genomics to benefit developing countries. Pers Med. 2014;11:487–96.
6. Khoury MJ, Bowen MS, Clyne M, Dotson WD, Gwinn ML, Green RF, et al. From public health genomics to precision public health: a 20-year journey. Genet Med. 2017;20:574–82.
7. House of Commons Science and Technology Committee U. Genomics and genome editing in the National Health Service. https://publications.parliament.uk/pa/cm201719/cmselect/cmsctech/349/349.pdf. UK. 2018.
8. Council of Australian Governments (COAG) Health Council. National Health Genomics Policy Framework 2018-2021. Report No.: 11905. Australia. 2017.
9. Australia B. Genetics in family medicine: the Australian handbook for general practitioners. Canberra: Commonwealth of Australia; 2007.
10. Metcalfe SA, Bittles AH, O'Leary P, Emery J. Australia: public health genomics. Public Health Genom. 2009;12:121–8.
11. Health CoAarbtDo. Newborn Bloodspot Screening National Policy Framework. Australia department of Health, Health; Canberra ACT, Australia. 2018.
12. World Health Organization(WHO). Grand Challenges in Genomics for Public Health in Developing Countries: Top 10 policy and research priorities to harness genomics for the greatest public health problems. https://www.who.int/rpc/grand_challenges.pdf. 2011.
13. Mehboob B, Safdar NF. Zaheer S. Socio-economic, environmental and demographic determinants of rise in obesity among Pakistani women: a systematic review. J Pak Med Assoc. 2016;66:1165–72.
14. Saleheen D, Zaidi M, Rasheed A, Ahmad U, Hakeem A, Murtaza M, et al. The Pakistan risk of myocardial infarction study: a resource for the study of genetic, lifestyle and other determinants of myocardial infarction in South Asia. Eur J Epidemiol. 2009;24:329–38.
15. Meo SA, Zia I, Bukhari IA, Arain SA. Type 2 diabetes mellitus in Pakistan: current prevalence and future forecast. Pak Med Assoc. 2016;66:1637–42.
16. Lixian Zhong MZOaRT. Mapping of WHO collaborating centres related to public health genomics. Geneva: The World Health Organization Cooperation DoRP; 2010.
17. Afroze B, Humayun KN, Qadir M. Newborn screening in Pakistan—lessons from a hospital-based congenital hypothyroidism screening programme. Ann Acad Med Singap. 2008;37(12 Suppl):114–3.
18. Yaqoob M, Gustavson KH, Jalil F, Karlberg J, Iselius L. Early child health in Lahore, Pakistan: II. Inbreeding. Acta Paediatr. 1993;82(s391):17–26.
19. Ajaz M, Ali N, Randhawa G. UK Pakistani views on the adverse health risks associated with consanguineous marriages. J Commun Genet. 2015;6:331–42.
20. Joint WHO. Management of birth defects and haemoglobin disorders: report of a joint WHO-March of Dimes meeting. World Health Organization. Geneva, Switzerland, 17–19 May. 2006.
21. Watson MS, Mann MY, Lloyd-Puryear MA, Rinaldo P, Howell RR. Newborn screening: toward a uniform screening panel and system—executive summary. Pediatrics . 2006;117(Supplement 3):S296–S307.
22. Foundation Z. The ZB foundation. 2013. http://www.thezbfoundation.com/. Accessed 27 Mar 2018.
23. Khan MH, Noman N, Hashmi G, Gul S, Ali A, Babar KS. Essential newborn care practice in hospital versus home deliveries. Gomal J Med Sci. 2004;4:1–9.
24. Ansari SH, Shamsi TS, Ashraf M, Farzana T, Bohray M, Perveen K, et al. Molecular epidemiology of β-thalassemia in Pakistan: far reaching implications. Indian J Hum Genet. 2012;18:193.
25. Ahmed P, Shamsi TS, Adil SN, Satti TM, Chaudhry Q, Mahmood S, et al. Hematopoietic stem cell transplantation in Pakistan-country report. Hematol/Oncol stem cell Ther. 2017;10:303.
26. Punjab Go. Punjab Thalassemia Prevention Programme. 2015. https://ptpp.punjab.gov.pk/. Accessed 5 Sep 2018.
27. Jafri H, Hewison J, Sheridan E, Ahmed S. Acceptability of prenatal testing and termination of pregnancy in Pakistan. J community Genet. 2015;6:29–37.
28. Ahmed S, Saleem M, Modell B, Petrou M. Screening extended families for genetic hemoglobin disorders in Pakistan. New Engl J Med. 2002;347:1162–8.
29. Ghani F, Maniac S, Khilji Z, Azim M, Khurshid M. Diagnosis of genetic defects by chromosomal analysis. J Pak Med Assoc. 1995;45:295.
30. Paksitan Go. The College of Physicians and Surgeons. 1962. https://www.cpsp.edu.pk/about-cpsp. Accessed 15 Jun 2018.
31. Ashfaq M, Amanullah F, Ashfaq A, Ormond KE. The views of Pakistani doctors regarding genetic counseling services–is there a future? J Genet Couns. 2013;22:721–32.
32. Ahmed S, Jafri H, Rashid Y, Mason G, Ehsan Y, Ahmed M. Attitudes towards non-invasive prenatal diagnosis among obstetricians in Pakistan, a developing, Islamic country. Prenat Diagn. 2017;37:289–95.

33. De Vries J, Bull SJ, Doumbo O, Ibrahim M, Mercereau-Puijalon O, Kwiatkowski D, et al. Ethical issues in human genomics research in developing countries. BMC Med ethics. 2011;12:5.
34. WHO. Health systems profile- Pakistan. Pakistan: regional health systems observatory—EMRO. Eastern Mediterranean Region: World Health Organization; 2007.
35. Warsy AS, Al-Jaser MH, Albdass A, Al-Daihan S, Alanazi M. Is consanguinity prevalence decreasing in Saudis?: A study in two generations. Afr health Sci. 2014;14:314–21.
36. Shanti H, Chouchane L, Badii R, Gallouzi IE, Gasparini P. Genetic testing and genomic analysis: a debate on ethical, social and legal issues in the Arab world with a focus on Qatar. J Transl Med. 2015;13:358.
37. Alkuraya FS, Kilani RA. Attitude of Saudi families affected with hemoglobinopathies towards prenatal screening and abortion and the influence of religious ruling (Fatwa). Prenat Diagn. 2001;21:448–51.
38. Alsulaiman A, Al-Odaib A, Rijjal A, Hewison J. Preimplantation genetic diagnosis in Saudi Arabia: parents' experience and attitudes. Prenat Diagn. 2010;30:753–7.
39. Abotalib Z. Preimplantation genetic diagnosis in Saudi Arabia. Bioinformation. 2013;9:388.
40. Hessini L. Abortion and Islam: policies and practice in the Middle East and North Africa. Reprod health matters. 2007;15:75–84.
41. Al-Matary A, Ali J. Controversies and considerations regarding the termination of pregnancy for foetal anomalies in Islam. BMC Med Ethics. 2014;15:10.
42. Memish ZA, Saeedi MY. Six-year outcome of the national premarital screening and genetic counseling program for sickle cell disease and β-thalassemia in Saudi Arabia. Ann Saudi Med. 2011;31:229.
43. Dhabi HA-A. Premarital screening and counseling. In: DHABI DoHA, editor. (Abu Dhabi Govt, UAE), 2005.
44. Alfadhel M, Al Othaim A, Al Saif S, Al Mutairi F, Alsayed M, Rahbeeni Z, et al. Expanded newborn screening program in Saudi Arabia: incidence of screened disorders. J Paediatr child health. 2017;53:585–91.
45. QATAR biobank. QATAR. 2013. https://www.qatarbiobank.org.qa/. Accessed 4 Feb 2019
46. Saleheen D, Natarajan P, Armean IM, Zhao W, Rasheed A, Khetarpal SA, et al. Human knockouts and phenotypic analysis in a cohort with a high rate of consanguinity. Nature. 2017;544:235.
47. Pollin TI, Damcott CM, Shen H, Ott SH, Shelton J, Horenstein RB, et al. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection. Science. 2008;322:1702–5.
48. Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjærg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. New Engl J Med. 2014;371:32–41.
49. The T, of the Exome HWG, Project S. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. New Engl J Med. 2014;371:22.
50. Khor CC, Do T, Jia H, Nakano M, George R, Abu-Amero K, et al. Genome-wide association study identifies five new susceptibility loci for primary angle closure glaucoma. Nat Genet. 2016;48:556.
51. Aung T, Ozaki M, Lee MC, Schlötzer-Schrehardt U, Thorleifsson G, Mizoguchi T, et al. Genetic association study of exfoliation syndrome identifies a protective rare variant at LOXL1 and five new susceptibility loci. Nat Genet. 2017;49:993.
52. Ajmal M, Khan MI, Neveling K, Khan YM, Azam M, Waheed NK, et al. A missense mutation in the splicing factor gene DHX38 is associated with early-onset retinitis pigmentosa with macular coloboma. J Med Genet. 2014;51:444–8.
53. Maria M, Ajmal M, Azam M, Waheed NK, Siddiqui SN, Mustafa B, et al. Homozygosity mapping and targeted sanger sequencing reveal genetic defects underlying inherited retinal disease in families from pakistan. PLoS ONE. 2015;10:e0119806.
54. Ahmed W, Whittall R, Riaz M, Ajmal M, Sadeque A, Ayub H, et al. The genetic spectrum of familial hypercholesterolemia in Pakistan. Clin Chim Acta. 2013;421:219–25.
55. Riazuddin S, Hussain M, Razzaq A, Iqbal Z, Shahzad M, Polla D, et al. Exome sequencing of Pakistani consanguineous families identifies 30 novel candidate genes for recessive intellectual disability. Mol Psychiatry. 2017;22:1604.
56. Rebbeck TR, Friebel TM, Friedman E, Hamann U, Huo D, Kwong A, et al. Mutational spectrum in a worldwide study of 29,700 families with BRCA1 or BRCA2 mutations. Human Mutation. 2018;39:593–620.
57. Minikel EV, Karczewski KJ, Martin HC, Cummings BB, Whiffin N, Alfoldi J, et al. Evaluating potential drug targets through human loss-of-function genetic variation. bioRxiv. 2019:530881. https://doi.org/10.1101/530881.
58. Finer S, Martin H, Hunt KA, MacLaughlin B, Ashcroft R, Khan A, et al. Cohort profile: East London Genes & Health (ELGH), a community based population genomics and health study in people of British-Bangladeshi and-Pakistani heritage. bioRxiv. 2018:426163. https://doi.org/10.1101/426163.
59. George J, Mathur R, Shah AD, Pujades-Rodriguez M, Denaxas S, Smeeth L, et al. Ethnicity and the first diagnosis of a wide range of cardiovascular diseases: Associations in a linked electronic health record cohort of 1 million patients. PLoS ONE. 2017;12:e0178945.
60. Mathur R, Noble D, Smith D, Greenhalgh T, Robson J. Quantifying the risk of type 2 diabetes in East London using the QDScore: a cross-sectional analysis. Br J Gen Pract. 2012;62:e663–e70.
61. Meic G. Public Health Profile of north east London for NE London sustainability and transformation plan. 2016. http://archive.eastlondonhcp.nhs.uk/wp-content/uploads/2017/06/NEL-STP-JSNA-2016.pdf. Accessed 5 Nov 2018.
62. Popejoy AB, Fullerton SM. Genomics is failing on diversity. Nat News. 2016;538:161.
63. Nimmesgern E, Benediktsson I, Norstedt I. Personalized medicine in Europe. Clin Transl Sci. 2017;10:61–3.
64. Health Department GoP. National health vision Pakistan 2016–2025. Pakistan: Health Department; 2016.
65. Mulder NJ, Adebiyi E, Alami R, Benkahla A, Brandful J, Doumbia S, et al. H3ABioNet, a sustainable pan-African bioinformatics network for human heredity and health in Africa. Genome Res. 2016;26:271–7.
66. Adoga MP, Fatumo SA, Agwale SM. H3Africa: a tipping point for a revolution in bioinformatics, genomics and health research in Africa. Source Code Biol Med. 2014;9:10.
67. Group HAW. Harnessing Genomic Technologies Toward Improving Health in Africa: Opportunities and Challenges. https://h3africa.org/wp-content/uploads/2018/05/h3africa_whitepaper.pdf. 2011.
68. Editorial Nature. Pakistan's prosperity needs independent experts. https://www.nature.com/articles/d41586-018-06659-9. 11 Sep. 2018.
69. Ballantyne, Angela, Goold, Imogen, Pearn, Amy & WHO Human Genetics Programme. Medical genetic services in developing countries : the ethical, legal and social implications of genetic testing and screening. World Health Organization. http://www.who.int/iris/handle/10665/43288. 2006.
70. Ahmad FKaW. State of Health Sector in Pakistan. Pakistan: Monetary Policy Department, at SBP; 2018.