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Title

Enhancing inclusion of diverse populations in genomics: A competence framework

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Abstract

Genomic knowledge and technology have developed rapidly over the last decade and increased our capabilities to diagnose and manage rare diseases. However, current genomic datasets lack ethnic diversity as many genomic studies have focused on participants of white European ancestry. Studies, such as the Deciphering Developmental Disorders study, have been available to participants of any ancestry but have been unsuccessful in recruiting diverse populations. The inclusion of diverse populations in exome and genome sequencing is important to ensure that clinical benefits of genomics advances are equally shared amongst all populations and to advance scientific knowledge. Our clinical and research experience with the British Pakistani population (the largest ethnic minority in Yorkshire and Humber, accounting for 4.3% of the population) has fostered the development of an innovative cultural competence framework to enhance the inclusion of diverse populations in clinical genomic research and service provision. The application of this framework has the potential to guide healthcare professionals to develop a wide range of competences, so they are ready to embrace genomic advances in order to improve health outcomes for all patients. This practice model will inform precision medicine and improve access of diverse populations to genomic studies. Although based upon work with the Pakistani population in the UK, it is anticipated that the model would be broadly applicable to all underrepresented populations across the world.

Keywords:

Cultural Competence, Diversity, Exome Sequencing, Genome Sequencing, Practice Models, Underrepresented Populations

Introduction

Although independently rare, genetic disorders occur in almost 6% of the United Kingdom (UK) population (Genetic Alliance UK, 2018). These disorders have significant physical, emotional, social and financial implications for the patients and their families. Many rare disorders have a variety of complex phenotypes and pose a significant diagnostic dilemma, preventing access to therapeutic interventions, definitive recurrence risks, prenatal diagnosis and pre-implantation genetic diagnosis. Next-generation sequencing has revolutionized genetic testing in terms of speed, cost and improved diagnostic rates. In the UK, the national Deciphering Developmental Disorders (DDD) study utilized exome sequencing to identify the molecular basis for developmental disorders in approximately 13,500 children, achieving a diagnostic yield of approximately 40% with trio analysis (DDD, 2018). The DDD study was followed by the clinical 100,000 Genomes Project (GEL, 2017). The UK government recently announced its intention to sequence 5,000,000 genomes over the next five years through National Health Service (NHS) patients (GEL, 2018) and a new Genomic Medicine Service has been launched (NHSE, 2018). Exome and genome sequencing is now becoming routine in clinical practice and increasingly blurring the line between clinical practice and research. Likewise, the data from clinical testing is utilized in anonymized form in genomic databases. The increased availability of genomic testing has lead to 'mainstreaming' (moving the responsibility for organizing genomic testing and dealing with the results from specialist genetics services to mainstream specialties).

Within this context, the lack of ethnic diversity in current genomic datasets raises major concerns and restricts the clinical utility and benefits of genomic advances (Adeyemo & Rotimi, 2014; Sirugo, Williams, & Tishkoff, 2019). The inclusion of diverse populations in exome and genome sequencing is critical to ensure that clinical benefits of genomics advances are equally shared amongst all populations and to advance scientific knowledge (Bentley, Callier, & Rotimi, 2017).

Importance of ethnic diversity in genomic research

Interpretation of genomic variants is often difficult. Interpretation of variants is based upon databases such as ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), gnomAD (https://gnomad.broadinstitute.org/) and DECIPHER (https://decipher.sanger.ac.uk/) and *in silico* analyses to try to identify the effect on the protein. Variants may be benign polymorphisms, alter drug metabolism, be modifying factors, cause disease only in the presence of another pathogenic variant or be independently disease-causing. Interpretation of these variants increases our understanding of the pathology of the disease, supports accurate diagnosis and risk determination and informs clinical pathways. However, because genomic variants differ between populations, inclusion of diverse populations in genomic research greatly increases the interpretive power of genomic databases (Cornel & Bonham, 2017). Despite this, a recent review of genome-wide association studies (GWAS) showed that 88-90% of genomic studies to date have focused on white European ancestry (Mills & Rahal, 2019), which only accounts for 16% of the global population. This over-representation disadvantages other ethnic population groups, and contributes to existing health disparities (Curtis, 2018; Martin et al., 2019; Sirugo et al., 2019).

The Yorkshire Regional Genetics Service covers a population of about 4 million, with the largest ethnic minority population, British Pakistanis, making up 4.3% of the local population (ONS, 2011). Local data (unpublished) from the DDD study showed that the uptake by the British Pakistani population (69 accepted/ 166 invited = 42%) was significantly lower than the white population (560 accepted/ 662 invited = 85%) ($\chi^2 = 136.9$; df = 1; $p = 1.24^{-31}$). Consanguineous marriages are common in British Pakistani population, with 37.5% of babies of Pakistani origin born in Bradford being from first-cousin marriages (Sheridan et al., 2013). These unions lead to unequal distribution of founder pathogenic variants across populations, which contribute to a higher burden of rare, mainly autosomal recessive (AR) disorders (Hamamy et al., 2011). In the DDD study, only 3.6% of European ancestry patients were found to have an

AR disorder compared with 31% of Pakistani ancestry patients (Martin et al., 2018). Detection of the autozygous (identical by descent) pathogenic variants in consanguineous families is helpful for the individual family but also advances clinical and scientific knowledge by identifying new disease genes or proving pathogenicity of a specific genomic variant (Woods et al., 2006). The inclusion of patients with consanguineous parents aids research on genetic determinants of complex diseases such as diabetes and coronary artery disease, as homozygotes demonstrate stronger phenotypic effects than heterozygotes (Saleheen et al., 2017). Studies identifying non-disease causing autozygous genomic variants in probands or relatives also add to genetic knowledge by proving these genomic variants are polymorphisms (Narasimhan et al., 2016). The inclusion of populations practicing consanguinity, therefore, has direct clinical and diagnostic advantages.

The homogeneity of genomic data and lack of data from consanguineous populations restricts genomic knowledge and the ability to interpret variants for the whole population, thereby restricting diagnostic abilities. In addition, this prevailing trend in genomic studies (whether clinical or research) will further increase the existing health disparities (Martin et al., 2019). Therefore, an understanding of the factors leading to ethnic disparities in genomic studies, as well as an understanding of what drives and facilitates inclusion, is essential to improve access of underrepresented populations in genomics.

Barriers to engaging diverse population in genomic research

There are many barriers hindering engagement of ethnic minority populations in genomics, e.g. lack of knowledge amongst those at risk of genetic disorders, low uptake of genomic services, inadequately coordinated health services and lack of health policies to facilitate equity of access (Darr et al., 2015; Salway et al., 2019). Lack of ethnic diversity in genomics may be partially attributed to social structures and practical barriers such as financial constraints and transportation difficulties. Other barriers to the acceptance of genomic testing can be cultural values, family dynamics and religious beliefs, emotional and

psychological burdens associated with perceptions of genetic diagnosis and its implications for the wider family (Sanderson et al., 2013). In addition, perceptions of the research benefits, language difficulties, lack of understanding, fear of genomic information, mistrust in research, confidentiality concerns and social determinants of health may all create barriers (Skyers, 2018).

The British public's understanding of genomics is not keeping pace with genomic advances and there are uncertainties about the social, legal and ethical impacts of genomics (GEL, 2019). This may be more of an issue for ethnic minorities, who have specific cultural and communication needs, so more effort and investment is required to engage them. A study exploring the views of people from UK Black African and Black Caribbean communities showed a lack of organizational commitment, economic support, policies, practice, strategic vision and leadership in engaging these participants in the 100,000 genomes project (Skyers, 2018). Literature focusing on ethnic disparities in genomic research have shown the need for a global approach, strategic vision, funding, development of skilled workforce, community engagement programs promoting equitable access to genomics (Bentley et al., 2017; Mathew et al., 2017), but little progress has been made yet.

Equity of access and reducing health disparities are key areas of focus of the new NHS Genomic Medicine Service, so provision of culturally competent genomic care (CCGC) should be a priority for clinical commissioning to ensure all patients are well informed, educated and empowered to benefit from genomic advances. The importance of delivering genomic health services in a culturally competent manner is well recognized (Ahmed, Ahmed, Sharif, Sheridan, & Taylor, 2012; Kirk, Tonkin, & Skirton, 2014). However, there is no formal cultural competent training or specific guidance available for healthcare professionals (HCPs) facilitating access for these populations to genomic studies. Mainstreaming of genomic testing is already posing significant challenges for HCPs, whose genomic knowledge and clinical

skills need to be updated so that they can embrace the change in their clinical practice (Patch & Middleton, 2018).

Challenges of mainstreaming genomic testing

Many HCPs have graduated in an era in which genetic testing was very restricted and relatively simple, so struggle with the interpretation of new genomic results. They frequently choose to refer to genetics services to avoid having to make the choice of testing modality, or to explain genomic results that they do not understand or struggle to communicate to patients and families (Christensen et al., 2016). With the advent of mainstreaming, many health disciplines are recognizing the critical importance of genomic education for the entire continuum of nursing, midwifery and medical professions (Calzone et al., 2018; Kirk et al., 2014; Slade, Subramanian, & Burton, 2016; Tonkin, Skirton, & Kirk, 2018). However, a cross-professionals genomics training needs analysis showed that 84.9% of 2578 NHS HCPs felt in need of further training and 23% of them felt that they lacked the genomics knowledge required for their current role (HEE, 2017). This highlights the needs for continuing professional development to fill the skills and knowledge gaps in the workforce.

Integrating genomic education and training for a wide range of the healthcare workforce poses a significant challenge for genomic policy makers, health organizations and professional regulatory and training bodies (Slade et al., 2016). Health Education England was assigned to provide and commission genomic education and ensure that HCPs have the knowledge and skills to deliver genomic research and healthcare. A transformation strategy has been developed through the Genomics Education Programme in order to increase capacity and capability and to address genomic learning needs of NHS healthcare workforce (Simpson, Seller, & Bishop, 2019). A wide range of formal genomics training courses are now available in the UK for all clinical professional groups. Despite these training programs, educational

curricula are inconsistent in their approaches and need to be continually evolved to keep pace with the genomic advances.

Existing Frameworks of Cultural Competent training

Most widely used models of cultural competence in healthcare practice and research have not focused on genomics (Campinha-Bacote, 2002; Papadopoulos & Lees, 2002). A recent UK competence framework for consenting for clinical genomic testing refers to language, culture and effective communication (Genomics Education Programme, 2019) but there is no further guidance. Healthcare organizations and professional regulatory bodies in the UK including the NHS, General Medical Council, Nursing and Midwifery Council and Genetic Counselors Registration Board, have produced policies and educational standards promoting culturally competent clinical practice. However, a review exploring cultural competency training (CCT) for HCPs in the UK showed inconsistencies and a lack of 'institutional commitment' toward this training (George, Thornicroft, & Dogra, 2015) that may also reflect the political nature of the CCT strategy to reduce health inequalities rather than a clinically driven strategy, which could influence commissioning of CCT training to improve health outcomes more effectively. McGinniss, Tahmassi, & Ramos's 2018 review of CCT training in genomic education showed the limited evidence supporting the utility and efficacy of these training opportunities.

In order to enhance equity of access for diverse populations in genomic studies and to fill the training and knowledge gaps in the healthcare workforce, this paper presents the first cultural competence framework for genetic and mainstream HCPs, covering the cultural, genomic and research aspects. It is unique in illustrating the requirements for all of these skills and knowledge in synergy to provide CCGC.

Approach

This framework has emerged from the first author's evidence-based clinical and research practice over the last 20 years in Yorkshire Regional Genetics Service based upon the clinical need to identify rare genes responsible for AR disorders in the British Pakistani population. To achieve this through autozygosity mapping studies, recruitment and retention of the targeted group of patients, unaffected siblings, parents and second degree relatives, with blood samples being obtained from all, was fundamental. Previous research experience had highlighted that recruitment of British Pakistani families was difficult for the clinical team, with language and cultural differences being the most obvious barriers. Access to individuals and families was another challenge, as it was necessary to understand the family hierarchy and power balance in order to gain access to those responsible for making decisions. Therefore, a culturally competent approach to engage these families was required.

Families had been identified through local pediatricians and genetic HCPs. The first author then contacted the family to offer genomic research and organized a further clinic appointment or a home visit for those who agreed. Information about the studies and consent was explained in their preferred language (English, Urdu or Punjabi) to obtain informed consent, a detailed medical history, pedigree and family blood samples. Over 300 British Pakistani families were recruited for these studies. DNA samples were obtained from 362 affected individuals and 634 unaffected individuals, giving a total of 996 research samples. A total of 35 novel AR genes were identified and the findings have resulted in 59 publications (see Supplementary data). These research findings made carrier testing, prenatal and pre-implantation genetic diagnosis possible for multiple genes associated with AR disorders thus providing direct clinical benefits to patients in the UK and around the world.

Furthermore, a psychosocial study was performed looking at 222 British Pakistani participants (117 parents of children with an AR disorders and 103 of their relatives) and the findings enhanced understanding of the

attitudes of British Pakistani families toward prenatal diagnosis and termination of pregnancy (Ahmed et al., 2012).

Reflecting on the successful recruitment of a large cohort of British Pakistani families for research studies, Kolb's model of reflection (Kolb, 1984) was applied to identify the key factors determining this success. The four stages of this model are:

1. Concrete Experience: A new experience or situation or reinterpretation of an existing experience.

2. Reflective Observation: An understanding of the experience and identification of the issues.

3. Abstract Conceptualization: Reflection provides a new idea, or modifies an existing abstract concept (learning from the experience).

4. Active Experimentation: Application of theoretical knowledge to inform new practice.

The process of recruitment and engagement of the British Pakistani families in clinical genomic research provided the concrete experience and context which allowed identification of the key factors and challenges during this process. Initially this was done by reflecting upon the key HCP knowledge and skills that facilitated successful engagement (see supplementary table 1) and the factors impacting upon recruitment (see supplementary table 2). Further reflection and abstract conceptualization considering the chronology of research projects from design and set up, to recruitment and retention and then dissemination of results led to these factors being categorized under three main themes: culture, genomics and research. This reflection and conceptualization allowed the innovation of a simple, visual model (Figure 1), as well as a comprehensive set of competencies (Table 1). The framework provides an evidence-based guide for those offering genomic testing and/or managing genomic or mainstream services that do so.

Core concepts of the framework

The framework comprises of three core concepts: cultural competence, genomic competence and research competence. A Venn diagram was selected to visually represent the synergy between the core concepts (Figure 1). The area of overlap between three core concepts represents what is required for the safe, ethical and effective delivery of CCGC. Since none of the core concepts can be practiced successfully without effective communication, this is the central concept in this framework, in which the three core competences are embedded. The healthcare system is an encompassing and essential component for all of these core concepts since it plays multiple roles including developing culturally competent strategies that enhance the inclusion of diverse populations in genomics, enabling workforce training and providing resources for genomic education and cultural competence training. The core concepts are subdivided into a number of competence statements (highlighted in bold in Table 1).

The practice indicators provide a means by which these competences are demonstrated in practice. As genomic testing is offered by a wide range of genetics and mainstream HCPs, levels of current and required competence will depend upon area of practice, clinical knowledge and skills. Assessment of practice indicators can highlight the gaps in HCPs' training needs. The practice of the core principles of this framework will help HCPs identify their individual learning needs and develop the knowledge, skills and attitudes required to offer genomic testing in a safe and culturally competent manner for improved health outcomes.

Cultural Competence

Cultural competence is dependent on both the individual HCP, and the ethos, practice, policies and management of the individual organization. Cultural competence does not occur in a vacuum but in a setting that appreciates the cultural diversity of the population. The development of cultural competence approaches will depend on cultural desire (Campinha-Bacote, 2002). In the genomic context, what this

means is the willingness of the HCP and organization to appreciate genetic diversity and understand the tendency of some populations to specific genetic conditions and their significant emotional, cultural and social impact upon the individual and family.

A myriad of challenges exist that lead to lack of diversity in genomic studies. In view of the origins and histories of health disparities, a joint clinical and social science can be a powerful approach, working alongside communities to reduce and eliminates these disparities. Therefore, it is important that healthcare organizations and HCPs understand the impact of religious and cultural factors and other social and economic determinants of health, as these create barriers to accessing genomics health services and develop cultural competent strategies to improve access. Healthcare organizations must recognize that the increasing diversity of the nation requires a clear vision, economic and targeted strategic planning, leadership, education and research in order to support cultural competence practices and overcome these persistent cultural and organizational barriers.

In order to ensure that genomic datasets represent the diverse nature of the population it serves and to prevent bias, scientists and their funders must work in collaboration with healthcare providers and promote the inclusion of all ancestries in genomic research. Therefore, a more global cultural competent approach, dedicated organizational leadership, robust economic drive, investment from funding bodies and political willingness are all critical factors in facilitating access to genomics for all.

Cultural competence requires that both HCPs and health organizations have the cultural awareness, knowledge and skills to deliver genomic care in the cultural context of their diverse populations. They must understand the clinical and scientific imperatives of including diverse populations in genomic studies and play a key role in enhancing this inclusion, develop culturally competent strategies to eliminate

disparities and facilitate access to genomic healthcare. Therefore, genomic health policy makers and training bodies have a responsibility to ensure that cultural competence training for HCPs is a priority.

On an individual level, it is imperative that HCPs accept cultural differences (Kirk et al., 2014), understand how their personal beliefs are socially constructed and are willing to reflect upon these and their own stereotypical cultural assumptions (Campinha-Bacote, 2002; McGinniss, Tahmassi, & Ramos, 2018). This requires an intellectual curiosity regarding one's own culture and that of others, which can enhance one's knowledge of world views, health beliefs, social and religious customs, family dynamics, biological variation, as well as improving the healthcare provided. Further details of key cultural competences required by an individual HCP offering genomic studies are provided in Table 1.

Genomic competence

Genomic competence is the HCP's knowledge and understanding of genomics and ability to translate this clinical knowledge to inform precision medicine. Mainstream health disciplines will also become involved in pharmacogenomics, which involves analyzing genomic variants that influence drug metabolism, so an understanding of genomic diversity and the scientific and clinical imperatives of including diverse populations in genomic studies is essential. HCPs offering genomic testing, whether clinical or research, have key roles, including consenting, obtaining a detailed phenotype (observable characteristics) for patients and their families, sample collection, clinical interpretation of genomic variants and, most importantly, communicating this information to patients and families effectively. The process of gaining fully informed consent is already time-consuming and challenging for families but even more difficult for families with additional language and cultural barriers. Informed consent for genomic testing includes the possibility that variants of uncertain significance (VUS) and clinically significant secondary findings may be

reported back. Once genomic testing has been instituted, the family may need continual support and reassurance as results may take months or years to obtain.

Many results will be complex and require bioinformatics skills to interpret the potential significance of VUS. In some cases, where potentially pathogenic variants have been identified, the HCP may request extra samples, for example skin biopsies from an affected individual or blood samples from the extended family to prove, or disprove, pathogenicity. When diagnostic results or unexpected secondary findings are issued, the HCP needs genomic competence in order to understand and explain the diagnosis, prognosis, any specific management, inheritance pattern, recurrence risks, reproductive options and implications for family members in accordance with their language ability and family dynamics.

Research competence

Those planning to recruit patients must understand the research aims, protocol and eligibility criteria so they can identify suitable patients. All UK HCPs involved in research should have undergone Good Clinical Practice training, which provides ethical, scientific and practical guidance and standards for conducting genomic research. Genetics HCPs are likely to be involved in research recruitment but may not have wider research experience and the same will apply to many senior HCPs and trainees in mainstream specialties. HCPs require a good understanding of research and genomics to enable them to explain how testing will be performed, what is expected of the families and the timescale of the results. When creating a genomic research protocol, it is essential to recognize potential ethical dilemmas such as significant secondary findings, carrier data for other disorders, non-paternity or undisclosed/ unknown consanguinity. These ethical issues should also be detailed in patient information leaflets and discussed at recruitment, so it is clear what information will be revealed to HCPs and families.

For rare diseases, blood DNA samples will be required from patients and often their parents, and from cancer patients, their tumor sample alongside their blood DNA samples. HCPs must be aware of

professional codes of practice and ethical guidelines and ensure appropriate consent for storage of DNA and human tissue samples. They should be familiar with the consent process and information required for potential participants to make informed decisions. It is the HCP's responsibility to reassure families about the utility, anonymity and security of their stored data. HCPs may have to contact a family to encourage compliance in providing further blood samples, to re-establish contact if there is an extended period of time before results become available or to seek consent for publication, which may include photographs of a dysmorphic individual.

Communication

Effective communication plays a significant role in achieving a therapeutic relationship, bridging cultural gaps and effectively addressing health disparities. Each of the three concepts in this framework is reliant on communication and it is the synergy of these central concepts with communication that facilitates CCGC. Communication skills are an essential component: they cannot be viewed as a discrete entity but as all-encompassing. Communication is complex and goes beyond merely the use of language, indeed it is a whole package in relation to interpersonal communication. Effective communication skills are much more than just conveying the complex genomic information through written or spoken words but it is about considering languages and linguistic, cultural, psychosocial and religious aspects of the communication. Communication is a transferable skill which guides HCPs to effectively engage with families and understand the communication strategies required to deliver complex genomic information in cultural context of the patients and families (Ahmed, 2013; Tonkin et al., 2018).

Healthcare system

The implementation of this framework cannot be achieved without the support of the local healthcare system. It is, therefore, seen as an overarching concept of this framework. Researchers have indicated that HCPs' training needs are inadequately met and the need for genomic education remains challenging

(Crellin et al., 2019; Simpson et al., 2019; Slade et al., 2016). This necessitates further guidance and genomic training for HCPs so that they can embrace the unprecedented scope of genomics in their clinical and research roles and develop a wide range of competence across multiple areas. Organizations should ensure their workforces have the competence to deliver genomic care in the cultural context of the diverse populations. Organizational policies, strategic vision and leadership, educational standards and curricula will play a fundamental role in the implementation and practice of this framework. Healthcare organizations must provide resources (time and funding) for HCPs to develop genomic, cultural and research competence. Training should also be designed using culturally responsive and discipline-specific learning outcomes and practice indicators.

Conclusions

This competence framework sets out the requirement for HCPs to have genomic competence, cultural competence and research competence to provide equitable access to genomic testing, whether on a clinical or research basis, in a genomics service or a mainstream specialty. The knowledge and skills at each competence could be developed separately but all three must be applied synergistically. As this whole process is dependent on the practice of effective communication skills and governance of healthcare system, deficits in any of these concepts would influence the safety of CCGC and would exacerbate health disparities. The framework needs to be fully tested in practice to ensure it is applicable to all minority ethnic groups. It is anticipated that this framework will improve equity of access to clinical genomic testing and lead to increased diversity in genomic studies by encouraging researchers and funders, as well as recruiting HCPs to consider cultural competence in their genomic research. It should guide genetics HCPs, trainees and HCPs in mainstream specialties to identify their knowledge and/or skill gaps and to develop further.

Author contributions

The framework was developed by SMS for her PhD with the guidance of supervisory team from University of South Wales (MK, ET, RS, JY) and Yorkshire Regional Genetic Service (MB, MA, ES). All authors have been involved in drafting the work or revising it critically for important intellectual content and have approved the submitted version.

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Conflict of interest statement

SMS, MK, ET, RS, JY, MB, MA and ES declare that they have no conflict of interest.

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Figure Legends

Figure 1: Visual representation of competence framework

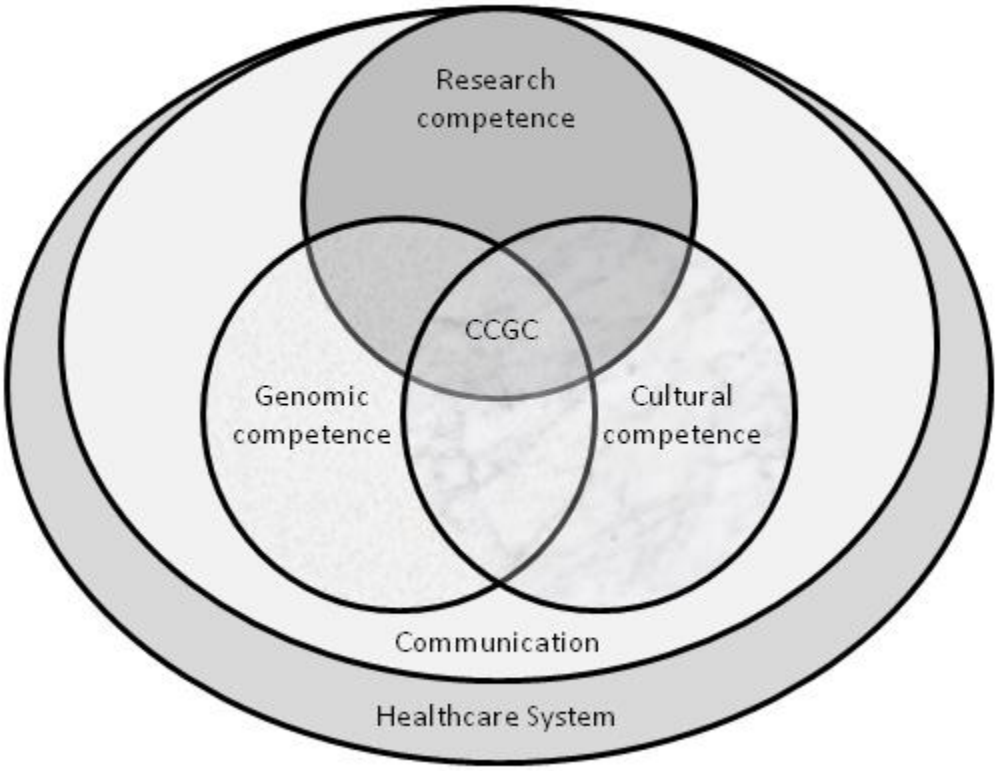

Table1: Key competences (bold) and practice indicators of competence framework for clinical genomic care and research

Cultural Competence	Genomic competence	Research competence
Study preparation phase: Research protocol, funding, approvals; Research infrastructure; Patient information		
Promote equity of access for under-represented diverse populations in clinical genomic research – Understand factors contributing to disparities – Ensure inclusion criteria appreciate diversity of population and protocol will achieve stated aims – *Engage diverse populations in research protocol development and throughout the research process* – Consider ethical, legal and cultural issues with regard to consent, data storage and publication, especially in view of consanguinity and potentially relevant information for the wider family **Develop strategies to improve access to clinical genomic research** – *Identify cultural practices, preferences and language needs of local population* – *Seek guidance and input from culturally competent HCPs to develop strategies to improve access* – Seek funding for research staff who speak required language(s) +/- interpreting services – Understand cultural and religious perspectives – *Ensure patient information leaflets and consent forms are in accordance with likely language ability and translated appropriately* – Ensure funding for cultural competency training for recruiting HCPs if required	**Demonstrate knowledge and understanding of the underpinning scientific principles of genomic testing that inform clinical practice and impact patient clinical pathways** – Recognize training needs e.g. advances in genomics, change in practice and ensure access to appropriate programs – Understand disease mechanism, biological variation, clinical manifestation, variability of genetic disorders and interpretation of new genomic results – Understand the increased frequency of certain genetic disorders in specific ethnic population and scientific imperative for ethnic diversity in genomic research – Consider various modalities of genomic testing and availability of clinical and research testing – Appreciate the clinical/pharmacogenomics benefits of clinical genomic research – Identify potential participants who would be eligible and benefit from clinical genomic research – Understand scientific and ethical issues underpinning clinical practice – Understand principles of mental capacity laws – Recognize potential for secondary findings and ensure policies are in place to feed these back if appropriate – *Design patient information leaflets and consent forms covering relevant genomic concepts, limitations of genomic testing and possibility of secondary findings*	**Contribute to protocol development in line with organizational policies and governance framework of clinical genomic research** – *Identify and apply to relevant funding agencies* – Obtain research and ethical approvals – Consider ethical and legal issues with regard to consent and DNA/tissue sample storage – Review any potential barriers to participation (e.g. requirements to provide clinical photographs if this could be an option) – *Ensure patient information leaflets and consent forms are in language that will be understood by lay people* **Identify training and educational needs of the HCPs undertaking the recruitment process - capacity building and infrastructure** – Identify who will recruit: HCPs as part of routine clinical and/ or dedicated research staff? – Ensure access to research skills training – *Make all relevant HCPs aware of research aims, protocol, inclusion & exclusion criteria, expectations of participants and process of recruitment*
Recruitment phase: Participants recruitment, informed consent; Phenotyping and DNA sample collection, Phenotyping entry and Data Storage		
Promote effective communication and ensure adequate translation – Consider literacy levels of local diverse population – Promote communication skills (e.g. paraphrasing and	**Identify potential participants who would be eligible and benefit from clinical genomic research** – *Be able to explain research aims, protocol, inclusion & exclusion criteria, expectations of participants and routes of*	**Understand research process** – Understand professional codes of practice and legislation – Know aims, protocol, inclusion & exclusion criteria,

reflecting back) – Provision of interpreters – Provision of appropriate patient information leaflets – Maintain confidentiality **Demonstrate cultural desire, sensitivity and cultural knowledge in understanding the impact of psychosocial issues on decision-making** – *Examine and challenge personal values and beliefs* – *Understand societal influence on personal values and beliefs and other social determinant of health* – *Recognize impact of family hierarchy, religion, health beliefs and values on decision-making* – *Avoid stereotypical assumptions or cultural imposition* – *Show cultural sensitivity and show respect for cultural differences e.g. consanguinity* – *Understand family dynamics and potential for head of household (etc) to make decisions for, or influence, others, while ensuring that valid consent is provided* – *Promote and facilitate individual's autonomy in decision-making* – *Understand motivations/perspective of patients/families and impact of timing e.g. during active treatment, bereavement*	*recruitment when seeing patients in clinic* – *Explain potential benefit of research to individual patients/ families and to genomic knowledge* ***Explain relevant genomic information in an appropriate and sensitive manner*** – Collect accurate phenotyping data and draw detailed pedigrees – *Utilize diagrams for genomic concepts e.g. genes, chromosomes and pattern of inheritance* – *Describe benefits, limitations and uncertainty of genomic testing and enhance patients genomic literacy* – *Understand patients' perspective and concerns* – *Delineate potential timescales for results* ***Remember dual role and put patient care before research*** – Emphasize the implications of diagnostic results for the patient, immediate family and wider family – Develop therapeutic alliance and offer on-going emotional support – Balance families' hopes and expectations from genetic testing, as result may be inconclusive – Explain the possibility of secondary findings and potential implications of diagnostic results or secondary findings for patients, children and family – Explain potential impact of genomic results on insurance	expectations of participants and routes of recruitment – *Identify and approach potential participants* ***Explain all information required for a fully informed consent process*** – Understand key principals of informed consent**,** including the right to withdraw – *Provide patient information leaflets and be prepared to answer queries and to give potential participants time to fully consider and discuss the study with others before recruitment* – *Allow adequate time and space for a consent appointment, including time for questions* – *Recognize and respond to non-verbal clues that family are confused, upset etc* – *Utilize diagrams for difficult research concepts* – *Be non-directive, non-judgmental and respect decisions to decline participation* – Gain informed consent in accordance with good research practice guidelines and reassure families about confidentiality of stored data – Obtain DNA samples from participants, with on-going consent and further DNA samples if required. – Arrange transportation of samples and notification of laboratory
Retention phase: Genomic analysis and result interpretation and validation		
Establish therapeutic relationship and continuity of care – Maintain effective communication with the family depending upon their level of literacy, knowledge and age – Respond if families have questions during study – Establish rapport with family – Establish patients understanding and expectation of genomic testing – Maintain ability to return to wider family to seek further samples if helpful to confirm/ refute findings – Be mindful of social circumstances influencing consent	**Understand the importance of genomic result for families** – *Identify needs of participants and families while awaiting results* – Recognize circumstances when results should be chased up e.g. to offer prenatal diagnosis for at risk pregnancy – Recognize when further diagnostic testing should be organized, even if this is detrimental to research – Contribute to MDT discussion for interpretation of primary & secondary findings – Arrange confirmation in accredited diagnostic laboratory	**Maintain on-going support and contact with family** – Provide contact details (ideally more than one route) – Reassure about timescales for results – *Encourage patients to comply with study e.g. if further samples needed* – *Offer support if have any concerns* – *Manage patients expectations, remaining aware of limitations of genomic testing and not giving false hope* – Remain aware of ethical dilemmas of dual roles as researcher and HCP

process and hindering retention – Consider welfare and support needs of participants that may impede retention – Maintain professional boundaries – Remain mindful and put in place (where applicable) information and disclosure pathways for extended family	– *Ensure families are aware of timescale for accredited results* – Recognize limitation of one's own genomic knowledge and ask for help or refer to colleague with expertise for further clinical input	– Maintain confidentiality – Respect autonomy and right to withdraw from study – Remain aware of individual learning needs and request further training – Contribute to MDT meetings and maintain contact with Genomic Laboratory and referring clinician.
Results phase: Feedback for clinicians and patients; Personalized management; Publications		
Recognize significance of genomic information in cultural context of the family – *Consider cultural or language barriers to communication* – *Use interpreters as required and maintain family confidentiality* – *Offer psychological support and be aware of their mental, physical and social well-being* – *Refer to support agencies and liaise with school etc if required to tailor services* – *Offer follow-up to help family understand results and implications* – *Encourage disclosure of genomic information to at-risk family members* – Understand patient concerns about disclosure of genomic information and facilitate the disclosure process – *Offer support to at-risk family members and explain referral pathway if carrier testing requested* – *Sensitive discussion about consanguinity and risks for subsequent generations* – Recognize the impact of genomic result on personal values, religious concerns and family dynamics – *Offer support if genetic testing did not provide a clear answer and discuss options for possible future testing* – *Provide information on patient resources/ support groups* – *Maintain continuity of care and provide point of contact*	**Understand utility and implication of genomic results for individual patient and family to guide clinical management** – *Explain diagnostic results, clinical implications and secondary findings to families* – *Disseminate results to patient's referring physician, primary care and other HCPs* – Consider any specific management plan or targeted therapeutic interventions and clinical pathways – *Offer details of genetic counseling and describe genetic concepts e.g. mode of inheritance* – *Delineate family risks and discuss reproductive options e.g. prenatal or pre-implantation genetic diagnosis* – *Provide support to deal with the personal, emotional and psychosocial aspects of genomic information* – *Provide access to family for carrier or predictive testing* – *Be aware of principles of childhood testing.* – *Encourage disclosure of genomic information to at-risk family members* – *Demonstrate evidence based practice and contribute to publications/presentations* – *Obtain up-to-date phenotype if required* – *Request consent and organize additional clinical photographs if required* – *Encourage laboratories to offer testing for newly discovered genes, so that testing will be available for other families*	***Provide summary of research findings and disseminate genomic knowledge*** – *Ensure results are provided to HCP responsible for patient's care* – *Prepare publications to disseminate research findings* – *Seek consent from families for the inclusion of identifiable information e.g. clinical photographs or detailed pedigrees in publications* – *Understand data protection principles and assure families of anonymity* – *Understand social factors and family dynamics that may influence participant's choice to consent for publication* – *Respect autonomy and right to decline* – Provide copies of relevant articles to families – *Provide a written summary of research findings to participants*

Some items fit exclusively on one list, some mainly on one list and equally between two lists. The latter group is shown in italics for clarity.

MDT: multi-disciplinary team

Supplementary table 1: Key factors that facilitated successful engagement of the British Pakistani population in clinical genomic research

Communication skills	**Cultural understanding**	**Genomic knowledge**	**Research skills**
· Development of therapeutic alliance · Limited English language skills and education - need *appropriate strategies to explain complex genomic concepts in simple manner* · *Detailed consent forms and participant information leaflets* · Ability to communicate at inter-generational level · Offer family-centered approach · Effective use of interpreters - need to confirm with the family · *Explain results to families and inform referring physicians* · *Encourage and promote disclosure of genetic results to at risk relatives* · Provision of psychological support	· Social and cultural aspects of consanguinity · Impact of rare genetic disorders on entire family · Appreciates religious beliefs, cultural values & their influence on decision making · Perceived healthcare models · Complex family dynamics - influence on decision making · Cultural sensitivity to overcoming family dynamics and, in turn, facilitating women's autonomy · Understand practical and financial difficulties and other social determinants of health	· Clinical /diagnostic importance of inclusion of British Pakistani families in genomic research · Provision of genetic counseling · *Appropriate strategies to explain complex genomic concepts in simple manner* · Discuss potential benefits and limitation of genomic testing · *Confidentiality and ethical considerations, including family disclosure* · *Understand timescale of results* · Recognize testing may not provide answers · Implications of possible secondary findings · Balancing hope and expectations · *Explain results to families and inform referring physicians* · *Encourage and promote disclosure of genetic results to at risk relatives* · Coordinating clinical referrals · Recognizing need for pursuing urgent results for e.g. for prenatal testing · Training needs of mainstream HCPs · Wider community engagement and education	· *Detailed consent forms and participant information leaflets* · Ability to explain the aims and process of research study · Family ascertainment and data collection · Facilitate informed decision making process · *Confidentiality and ethical considerations, including family disclosure* · Safeguarding and utility of data · *Understand timescale of results* · *Maintain on-going follow up and point of contact*

Supplementary table 2: Factors impacting upon recruitment of the British Pakistani population for clinical genomic research

Factors affecting the patient/ family	Factors affecting the HCP	Factors affecting the patient/ family and the HCP
Higher incidence of consanguineous marriages · Increase risk of AR disorders · Relatives are at risk of having an affected child **Burden of undiagnosed rare AR disorders** · Fear, uncertainty and lack of clinical pathways · Emotional, psychosocial and financial **Communication barriers** · To access genomic services and utility of information · Challenge of understanding genomic concepts that have no direct translation in native language · Expect HCPs to provide direct advice **Strong religious beliefs** · Families are less likely to accept genetic causation or consider ToP, so may not see utility of a diagnosis · Lack knowledge of the Islamic *fatwā* (Islamic Verdict) regarding ToP · Seeks advice from family or religious leaders **Family dynamics** · Influence on decision making for carrier testing, reproductive options and research recruitment · May compromise women's autonomy **Non-disclosure of genomic information** · Impact on family marriages practice **Practical barriers** · Additional appointments - time consuming, work pressure and financial implications · Multiple blood samples from affected individuals, their parents and wider family	**Diagnostic odyssey** · Lack of molecular diagnostic techniques and inability to guide patient clinical pathway and manage family expectations, e.g. treatment and prenatal testing **Communication barriers:** · Inability to speak relevant language and difficulty in explaining genomic information in cultural context · Need communication strategies that help explain genetic condition, inheritance pattern, recurrence risk and reproductive options · Understanding cultural framing of this group **Ethical considerations** · Families expect HCPs to provide direct advice · Reliance on family members to interpret and convey Information; risk of withholding clinical information · Appropriate use of interpreters- risk of withholding clinical information; maintain confidentiality · Confidentiality of data storage and sharing · Implications of possible additional findings **Family dynamics and cultural beliefs** · Cultural sensitivity in overcoming religious and cultural beliefs, family dynamics and its influence on decision making e.g. ToP **Non-disclosure of genomic information** · Challenging for HCPs if caring for other relatives · Patient confidentiality versus family right to know **Practical barriers** · Lengthy genetic counseling session - time pressures · To manage additional hospital appointments and ascertainment of multiple biological samples · Families need on-going support	**Diagnostic odyssey** · Lack of clinical diagnosis - challenge for both · Limitation of genetic testing - impact on carrier testing and reproductive options **Communication barriers** · Complex genomic information to give/understand · A detailed research process and requirement · Perception that HCPs oppose consanguinity · Power dynamics - HCPs and families perspectives · Implications of possible additional findings e.g. cancer risk **Strong religious beliefs** · Acceptance of genetic diagnosis and utility of genomic information - pressure of meeting the deadline of the *fatwā* in prenatal genetic · Pressure to incorporate advice from family members and religious leader **Family dynamics** · Influence on decision making for carrier testing, reproductive options and research recruitment · May compromise women's autonomy **Non-disclosure of genomic information** · Confidentiality versus family right to know **Practical barriers** · Lengthy genetic counseling session - time pressures for families and HCPs · Ascertainment of multiple biological samples **Timescale of research finding and follow up care** · Frustration due to uncertain timescale of time · To manage family expectations, e.g. treatment, prenatal testing and maintaining follow up

ToP: termination of pregnancy

Supplementary data: Publications resulting from the genomic research with the British Pakistani population

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