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OPPORTUNITIES FOR PRECISION MEDICINE AND PRECISION PUBLIC HEALTH IN SAUDI ARABIA

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Abstract:

Precision approaches in health stem from innovations in basic sciences and -omic technologies and rely on individuals' genomic structure to develop tailored treatment and prevention opportunities. Saudi Arabia has recently shown increasing interest in implementing precision approaches to improve healthcare and tackle its major health challenges. This study investigated opportunities, requirements and barriers in the implementation of precision approaches in health in Saudi Arabia.

A narrative literature review included resources published in English and Arabic after 1995 if identified by search terms.

Opportunities for implementation of precision approaches were identified in the context of the main local health issues. Requirements for precision medicine implementation were identified, including the ability to collect and process data. In addition, barriers and challenges, as lack of awareness of the field amongst health staff, were pointed out.

The outcome offers relevant information to implementation attempts in the field and may help guiding policymaking efforts.

Keywords: *Precision medicine, Precision public health, Genomics, KSA.*

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INTRODUCTION:

Precision medicine refers to the modern approach in medicine aiming at enhancing the effectiveness of disease prevention, diagnosis, and treatment (1). Precision medicine involves the analysis of the diversity in the individual genetic information, lifestyle and environment a person is exposed to. As a result, it may provide medical practitioners with the ability to anticipate the best prevention, diagnosis, and treatment approaches for a certain disease occurring in different patients (1).

Overall, precision medicine is important in the future of healthcare and public health, and is the approach increasingly invested on in high-income countries. The Kingdom of Saudi Arabia (KSA) is one such high-income economy, whose aim is also to improve care and increase the use of new innovative technologies and approaches for the benefit of its citizens' health (2).

However, to date, there is very limited research investigating the opportunities for precision public health and precision medicine approaches in KSA (3). Therefore, the aim of this study was to investigate opportunities and challenges in the future implementation of precision medicine and precision public health in the Kingdom of Saudi Arabia. To be more specific, this study first maps individual and population health challenges in KSA where precision medicine and precision public health may play a role. Then, it identifies requirements for implementation of the precision approach in healthcare and public health in KSA. Finally, it investigates barriers and challenges to the implementation and successful use of precision medicine and precision public health in KSA. The results may inform the design of guidelines for future implementation of precision medicine and public health in KSA. Furthermore, they may offer relevant and useful information to policymakers and stakeholders involved in precision medicine and precision public health implementation in KSA.

MATERIAL AND METHODS:

A comprehensive narrative literature search was conducted between April 2017 and May 2018 to identify articles containing information related to opportunities and challenges for the implementation of precision medicine and public health in the Arab countries, particularly in the Kingdom of Saudi Arabia. The following databases were used: PubMed, the Cochrane Library, and Google Scholar. Other websites and databases were also accessed, such as: governmental websites of KSA (Ministry of Health, MoH), the global and regional WHO websites, the Public Health Genomics Foundation, the Personalized Medicine Coalition and the Saudi Center of innovation in Personalized Medicine.

The following search terms were used in the online engines: personalized and precision medicine, genetics/genomics, (whole) genome sequencing, pharmacogenetics/pharmacogenomics, pigenetics/epigenomics, microbiomics, proteomics, metabolomics, transcriptomics, -omic sciences, individualized medicine, and precision public health; along with: Saudi Arabia, the Kingdom of Saudi Arabia, KSA, the Gulf Countries, the Middle East, and Asia.

Full-text articles were included if written in English or Arabic. Articles were excluded if they did not include genetic or genomic information and if published before 1995.

Individual and population health challenges in KSA where precision medicine and precision public health may play a role

According to the report by Institute for Health Metrics and Evaluation, the most prevalent health challenges in Saudi Arabia in 2015 were non-communicable diseases (4). The table below shows the leading causes of mortality and disability in Saudi Arabia in 2015 (4).

The top 10 leading causes of mortality (both genders) in Saudi Arabia in 2015 were:								
Ischemic heart diseases (21.53%)	Road injuries (10.2%)	Stroke (9.86%)	Lower respiratory infection (5.59%)	Chronic kidney disease (4.89%)	Alzheimer disease (4.49%)	Congenital birth defects (4.35%)	Neonatal preterm birth complications (2.45%)	Diabetes mellitus (1.96%) and other cardiovascular and circulatory diseases (1.6%).

In females among the top 10 causes there were also:			
stroke (11.78%)	neonatal preterm birth complications (3.06%)	other cardiovascular and circulatory diseases (2.27%)	and breast cancer (2.25%).

Among under 5 years old the following were also in the top 10 causes of deaths:				
Neonatal sepsis and other neonatal infections (11.8%)	Neonatal encephalopathy (5.47%)	Other neonatal disorders (3.68%)	Sudden infant death syndrome (1.54%)	Diarrheal disease (1.45%) and drowning (0.98%)

In 15 - 49 years, among the top 10 causes of mortality there were also:			
Self harm (4.51%)	Falls (3.2%),	Exposure to mechanical forces (2.38%),	HIV/AIDS (2.11%)

Finally among over 70 years in the top 10 causes of mortality there were also*:	
chronic obstructive pulmonary disease (2.14%)	and cardiomyopathy and myocarditis (1.22%)

The top 10 leading health causes of disability in KSA in 2015 were:								
low back and neck pain (13.54%)	depressive disorders (8.43%)	migraine (6.66%)	skin diseases (6.45%)	sense organ diseases (6.34%)	diabetes mellitus (5.32%)	anxiety disorders (4.1%)	other musculoskeletal diseases (3.9%)	iron deficiency anemia (2.6%) and asthma (2.43%).

Among under 5 years in the top 10 causes were also:			
skin diseases (21.82%)	protein energy malnutrition (14.24%)	diarrheal disease (9.98%)	and congenital birth defects (8.22%).

Among the causes of disability in over 70 years also Alzheimer disease (AD) was reported (8.67%)

Table 1: Leading causes of mortality and disability in Saudi Arabia in 2015 (from Health data-Saudi Arabia, 2015)

Out of those health issues, many have the potential to benefit from innovative scientific discoveries at the core of precision approaches. Indeed, personalized approaches are for example already being tested and implemented in the field of **cardiology**. Tests are available to determine whether people have a genetic predisposition for risk factors of ischemic heart diseases, such as familial hypercholesterolemia (5). Moreover, pharmacogenomic tests are being used for commonly prescribed medications in the field, including antihypertensive medications (6), simvastatin (7), warfarin (8), and clopidogrel (9).

The application of precision medicine in the diagnosis, prevention, and treatment of **stroke** is achieved through exome sequencing, genome wide genotyping, and gene expression studies. An example is exome sequencing studies identifying genes associated with a high risk of stroke (10). Indeed, exome sequencing has established the presence of protein-coding variants of PDE4DIP and ACOT4 genes that are linked to the rising cases of stroke in Africans and Europeans (11). Furthermore, the use of pharmacogenetic studies has influenced the prescription of stroke medications, taking into account the genetic differences across individuals suffering from stroke, or at high risk of it (12). One such medication is warfarin, whose response varies according to genetic variants in CYP2C9 and

VKORC1 genes. Likewise, the response to clopidogrel is reduced in individuals with specific variant alleles (CYP2C19*2 and *3) of CYP2C19 gene, so the dose must be increased to avoid thrombotic events (13).

Furthermore, gene variants have been associated with the development of **congenital heart defects** (CHD), and multiple gene defects have been detected in patients with CHD via exome sequencing (14). For instance, MYH6 Ala290Pro, a variant of the cardiac myosin heavy chain 6, has been found in individuals with CHD (14).

The use of precision approaches has also provided useful insights on the underlying genetic and hereditary interplay of **back and neck pain**, as well as **headache** (15)**.** Recent studies showed that heritability accounts for approximately one third (35%) of neck and back pain cases and for about 46% of headache cases (15,16). For instance, a variant of the voltage-gated potassium channel codified by the KCNS1 allele rs734784 is responsible for increased pain, among others in headache and low back pain patients (16,17).

Precision medicine can also play a role in the management of **chronic kidney diseases**. Currently, genetic tests exist that can be done before starting anti-rejection therapy for kidney transplant recipients. For example, before prescribing thiopurine (an immunosuppressive agent), genetic variants of thiopurine methyltransferase (TPMT) can be investigated (18). When patients have gene variants codifying for TPMT with reduced activity, the dose of thiopurine should be reduced to avoid severe myelosuppression (18).

Alzheimer's disease is currently ranked as one of the leading types of dementia in the kingdom of Saudi Arabia. However, the complex nature of the disorder has resulted in only few effective drugs being developed to manage it (19). Through the application of precision approaches, researchers have been able to accurately determine the risk profile of individuals that are likely to be vulnerable to AD (19). For instance, the E4 allele of apolipoprotein E has been found to possibly predispose individuals to the development of AD (19). Research indicates that individuals having one copy of the allele have a two to fourfold higher chance of developing the disease. On the other hand, those with two copies have up to a tenfold higher risk of developing it. Drugs like the nuclear retinoid-X receptor (RXR) agonist which induces clearance of B-amyloid, by target ApoE4, have been developed and utilized in a mouse model of AD and results have been remarkable (20).

Precision medicine evidence has also shown a role in the **mental health** field. Indeed, variants of CYP2D6 and CYP2C19 have been shown to play a crucial role in the variability in response and tolerance to drugs used to treat several mental health problems (21). For example, the dose of tricyclic antidepressants - including clomipramine, amitriptyline, imipramine, doxepin, and trimipramine- should be reduced if patients carrying CYP2D6*3–*6 *or* CYP2C19*2–*3 variants (22). Moreover, it was found that carrying the high-expression L allele of the serotonin transporter-linked promoter region (5-HTTLPR) polymorphism of the serotonin transporter gene may significantly impact an individual's response to selective serotonin reuptake inhibitors (SSRIs) (23).

Precision approaches offer likewise a contribution in the field of **dermatology.** For instance, studies of the human leukocyte antigens (HLAs) have determined a variant, HLA-Cw6, which is highly associated with the early onset type of psoriasis (24). Moreover, microarray analysis of differently expressed genes in psoriasis has indicated an up-regulation of cytokines pathways including TNF, IL-23/IL-17, and interferon type 1 (25). Identifying these pathways may lead to improving psoriasis therapy by targeting the upregulated cytokines by, for example, IL-17 targeted therapy (26).

Precision medicine approaches have also shown a role in the management of **Diabetes**. For instance, the common allele variants of cytochrome CYP2C9, CYP2C9*2 and CYP2C9*3, were associated with a decrease in sulfonylureas oral clearance and impaired metabolism (27,28). Moreover, it was also noticed that polymorphisms of the organic cation transporter 1 (OCT1) gene were also associated with a decreased efficacy of metformin (29,30).

Several investigations have also been conducted on **COPD** (Chronic Obstructive Pulmonary Disease) complex phenotypes (31). For instance, Alpha-1 Antitrypsin deficiency (AAD) is a genetic disorder that results in reduced production of Alpha-1 Antitrypsin leading to early-onset emphysema and liver disease (32). So, Alpha-1 Antitrypsin deficiency is one of the best examples of COPD phenotypes that can simply be diagnosed with a biomarker in the serum, and requires in some cases a particular supplementation therapy (32).

Concerning precision approaches and **asthma**, research showed that the response of asthma patients to drugs varies regardless of their similarities in clinical characteristics (33). According to such studies, interindividual variations to inhaled

corticosteroids, beta-2 agonist, and modifiers drugs of oral leukotriene have been demonstrated (33–35). In asthmatic subjects, 49 ADRB2 genetic polymorphisms, which encode for the beta-2 adrenergic receptor, have been identified (36). It was also found in another study that another ADRB2 variant (rs1042713, Arg16Gly) was linked to the downregulation of beta 2 receptors after in vitro treatment with beta-2 agonist (37).

Host genetic biomarkers are also providing a more precision treatment for **cancer**. In **breast cancer**, women with BRCA 1 or 2 mutations have a higher risk to develop breast cancer in the future (38). Thus, , they should considser BRCA 1 or 2 mutations genetic testing using next generation sequencing , and early and frequent breast cancer mammogram screening (38). Moreover, overexpression of receptor 2 of human epidermal growth factor gene (HER2), which has been associated with poor prognosis, should be analyzed and then treated using anti-HER2 therapy for all invasive breast cancers (39–41). Breast cancer patients that earlier had poor prognosis have now their health improved significantly via anti-HER2 therapy, which has a 44% decrease in risk of mortality for HER2 positive invasive breast cancers, compared to HER2 negative invasive breast cancer patients (42).

In regards to **colorectal cancer metastasis,** patients with mutations at codons 12, 13, 61, 117, and 146 in exons 2, 3, 4 of RAS proto-oncogene fail to benefit from anti-epidermal growth factor receptor therapy (panitumumab) (43). Therefore, for patients considered for the anti-epidermal growth factor receptor therapy, the recommendation is to undergo testing for RAS mutations (43). Moreover, there has been a poor prognosis in patients who have colorectal tumors that contain a point mutation, V600E, in the oncogene of BRAF (which encodes for B-Raf protein) (44). These additional biomarkers could be harnessed to offer better prognostic information.

Precision approaches can also play a role in **neonatal preterm birth complications.** According to multiple studies, various single nucleotide polymorphisms (SNPs) in 190 candidate genes showed a strong association with the risk of preterm delivery (45). For instance, it was established that SNPs in the tissue inhibitor of metalloproteinase 2 gene (TIMP2; rs2277698 gene) may play a critical role in preterm delivery. The aforementioned SNP was not only linked to increased risks of the premature rupture of membranes (PROM) but also preeclampsia (45–47) as it induces the metabolism of collagen IV by inhibiting the enzyme activity (47).

Precision approaches can also play a role in **sense organ diseases**. The strategy of molecular diagnosis is successful in about 70% of cases of inherited eye disease in the Middle East due to consanguinity as the main underlying cause (48). Knowledge of genetic makeup and specific biomarkers then enables more personalized treatments. For example, retinoblastoma, the most common malignant ocular tumor, occurs in both heritable and phenotypic (sporadic) forms (48). Inherited retinoblastoma accounts for about 25-40% of all cases and is caused by mutations of both RB1 alleles. Identification of genetic mutations facilitates screening and timely treatment of at-risk family members.

Precision approaches can also play a role in **Hemoglobinopathies and hemolytic anemia**. Several genetic mutations associated to inherited hemolytic anemias, have been identified using next generation sequencing (NGS) and may allow to early prediction of the condition. Such relevant mutations include: hereditary spherocytosis (ANK1, SPTB, SPTA1, SLC4A1 and EPB42), hereditary elliptocytosis (EPB41, SPTA1 and SPTB), hereditary pyropoikilocytosis (EPB41, SPTA1 and SPTB), hereditary stomatocytosis and ovalocytosis (PIEZO1, KCNN4, RHAG and SLC4A1) and red blood cell enzymopathies (G6PD, PKLR, ENO1, AK1, GPI, NT5C3A, GCLC, GPX1, GSR, GSS, HK1, BPGM, PGK1 and TPI1) (49). Improved definition of individual genetic makeup can only better determine prognosis, guide clinical decisions, and facilitate family counseling. However, not all anemias are genetic in nature (50).

Precision approaches can also play a role in **Epilepsy.** The International League Against Epilepsy (ILAE) Consortium on Complex Epilepsies conducted a comprehensive meta-analysis of data from 12 cohorts of 8,696 individuals with epilepsy using genome-wide association matched with 26,157 ethnically equivalent controls (51). The group aimed at identifying risk loci for genetic generalized epilepsy and focal epilepsy. Some of the following loci with genome-wide significance were identified: 2q24.3, identified as a voltage-gated sodium channel gene SCN1A that is associated with some monogenic epilepsies. Moreover, 4p15.1 that included the 3′ end of the protocadherin gene (PCDH7), associated with generalized epilepsy. VRK2, a serine-threonine protein kinase, located at 2p16.1 and involved in signal transduction and apoptosis, is another gene that was associated with genetic generalized epilepsy (51).

Autism spectrum disorder (ASD) is not a single entity and its etiology and pathogenesis are currently unclear (52). However, the Longitudinal European Autism Project (LEAP) study included a variety of neurocognitive measures and genetic markers were included to identify ASD-risk genes in families with two or more individuals with ASD (52). Further, the study by Gandal, et al. (2018) utilized transcriptomic profiling with the objective of evaluating the distinct and shared gene expression perturbations in ASD. The complex polygenic architecture of ASD was found to partly overlap with other major psychiatry disorders, demonstrating pathways of molecular convergence (53).

Requirements for the implementation of precision approaches in healthcare and public health in KSA

The key requirements for the success of precision medicine include the systematic collection of relevant data and their processing using appropriate tools, storage and retrieval systems and powerful analytical tools, regulation that permits the use, processing, storage and sharing of health data and analytical outputs, security and privacy safeguards, and the willing and active participation of individuals (54). The Saudi Genome Program prospectively intends to sequence at least 100, 000 human genomes within a timeframe of five years with the core objective of initiating genomic oriented biomedical studies for the Saudi population (55). This would make the KSA Genome project one of the top-ten genomic projects in the world. It is believed, that this project would have major implications for the improvement of public health in KSA including reducing the use of chemotherapy to treat breast cancer as much as 34%, reducing strokes by at least 17,000 cases per year, and more (55). However, stable funding and dedicated resources are needed before it can meaningfully move forward.

The collection and analysis of data from electronic health records (EHRs) is an essential condition of high-quality data input in the system, but is an area in which KSA lags behind the Western world (56). While there is growing interest, implementation of EHRs at hospitals and other service providers in KSA is slow (56). Saudi Association of Health Informatics (SAHI) provides a regulatory framework to develop scientific knowledge related to health information (57). SAHI exhibits the capacity and scope for developing scientific information, and facilitates the exchange of scientific information between various healthcare entities within and outside KSA to facilitate the development and promotion of precision medicine.

Training and certification of specialists in clinical genetics is an essential requirement of efforts to implement precision medicine approaches on a wider scale (54). More than thirty certified clinical geneticists in KSA effectively practice across the state-funded tertiary healthcare facilities. The population of physicians who practice in various clinical genetics disciplines is increasing day-by-day in KSA (58).

Finally, quality standards at all levels have to be agreed by all stakeholders, starting with validation of biomarkers, considerations for informed consent and protection of privacy (59). In KSA, as the Genome project is developed, it is critical that stakeholders come together to specifically establish a quality control process, which sets clear objectives and ways to evaluate progress toward them.

Barriers and challenges to the implementation and successful use of precision medicine and precision public health in KSA

Considering the tranlsation of precision approaches in KSA is still limited, the country can learn from the implementation of precision medicine approaches elsewhere in the world. In Europe, the barriers for the implementation of precision medicine and pharmacogenomics can be identified at all levels, from scientific and operational to economic. Scientific barriers arise from the difficulties to translate vast amount of disparate molecular data into clinically meaningful information (54). Health assessment approaches assess the cost-effectiveness and utility of diagnostic and therapeutic approaches based on information retrievable from information systems. Lack of consistency in the available evidence introduces uncertainties in clinical practice in the terms of validity of used biomarkers and their clinical utility (54).

In KSA, one of the main barrier is the lack of knowledge and awareness of personlaized medicine amongst health staff.(60) Additional challenges in KSA stem from the limited research-based data coming from KSA electronic health systems (2). The implementation of EHRs in KSA is still limited to a few facilities and regions and slowed by a variety of delays and negative beliefs about EHRs (2).

DISCUSSION:

Conditions like epilepsy, autism, ischemic heart disease, stroke, chronic obstructive pulmonary disease, skin disease, headache, Alzheimer's disease, congenital birth defects, preterm birth complications, breast cancer, diabetes mellitus, depression, congenital birth defect, and a variety of others, all

have the potentional to be more accurately diagnosed and treated, upon the basis of genomic research and treatment targeting. However, as shown in this paper, this requires the expansion of Saudi genetic and genomic research, in order to build up the precision medicine field.

The key requirement for the implementation of precision medicine and precision public health is the ability to access innovative biomedical techniques as they evolve, and the continuous assessment of their benefit (61). Clinical implementation of personalaized medicine is based on more than a decade of research, but is still rapidly evolving, so taking a front-line approach, which stays on the cutting edge of medical evolution, is critical (62). KSA can take advantage of experiences from implementation of large data collection and analysis systems in other countries and avoid some of the pitfalls when designing and implementing precision approaches in the healthcare and public health systems (63).

As seen in many countries, barriers for the implementation of precision medicine approaches may occur at all levels, from scientific to operational and economic (62). Personalized medicine is still a very young field, and so the barriers are emphasized, including extensive review of current implementation and testing, questions about ethics and legal issues tied to genetic research and the implementation of reimburse, or pay for, the implementation of these new methods (62). Further, studies indicate that the clinical utility of the most recent scientific evidence in the precision health field are often unclear and difficult to quantify. The available evidence is often inconsistent, introducing uncertainties to clinical practice. Economic barriers include limited reimbursement for biomarkers and pharmacogenetic testing (54). As a result, solutions must be contructed which build a secure infrastructure for the implementation of new technologies, and regulation and clinical evidence should be improved in favor of precision medicine, to break down barriers and increase active implementation of personalized medical solutions (62).

In KSA, however, there are additional challenges which must be addressed, in order to grow the field of precision medicine. The main challenges include the shortage of qualified professionals and dependence on the foreign workforce, whose language and culture differences may contribute to misunderstandings (64). Recently, there has been new hope for removing these barriers, as the government has shown interest in supporting research that is focused on imporving the treatment of common diseases, through personalized medicine (3). Finally, the lack of awareness on the health risks of consanguineous marriages and the lack of accurate data can hinder precision approaches to tackle this issue, and make implementation of precision medicine approaches in KSA especially challenging.

In conclusion, many health precision approaches have been implemented, or are currently under development, that may be relevant for medicine and public health in KSA. Precision medicine options in KSA are, to date, limited, althought the amount of options is expected to greatly increase in the future. Overall, effective precision medicine approaches require appropriate data collection systems, quality control, integration platforms and analytical tools, storage and data retrieval and sharing systems to be effective. A broad consensus within the Saudi Arabian society is therefore essential to make such vast collection systems practicable. In addition, a clear regulatory framework needs to exist to distinguish between research and care and to protect the privacy of data subjects. Finally, multidisciplinary expertise across many clinical and non-clinical disciplines needs to be developed to make large-scale precision medicine projects practicable.

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