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An Overview of Benefits and Challenges of Rare Disease Biobanking in Africa, Focusing on South Africa

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The North-West University's Centre for Human Metabolomics (CHM) is in the process of establishing the first rare disease (RD) biobank in South Africa and Africa. The CHM Biobank's main focus is on the collection of samples and information for rare congenital disorders. Approximately 72% of all RDs have a genetic origin, of which 70% have an exclusive pediatric onset. The need for such a biobank was identified by the CHM diagnostic laboratory. Feedback toward this initiative was overwhelmingly positive at the first stakeholder meeting in August 2019. However, gaining support from the public sector and recruiting of participants have proven to be challenging. Problems experienced to date include lack of support from government and clinicians; lack of knowledge on RDs (patients and clinicians); public health care focus not directed toward RDs; patients not returning for follow-up visits; and unwillingness to participate due to fear of exploitation. The CHM Biobank's vision and goals are aligned to address a national and international research need: it will provide a valuable resource for scientists to improve what is known about these diseases; to better understand the natural history and pathophysiology; to optimize diagnostic methods; and to potentially develop treatments. The genetic variability of the South African population provides added value to the RD biobank. This review provides a brief overview of the literature on the challenges and benefits of an RD biobank and how this relates to low- and middle-income countries (LMIC) like South Africa. The aim of the review is to draw attention to the potential benefits of such an undertaking and to create awareness, at both local and global level, toward some of the unique collective considerations that an RD biobank in LMIC (also unique South African challenges) faces on an operational, collaborate, and sustainability level.

Keywords: CHM Biobank, rare disease biobanking, rare disease challenges, South Africa biobanking

Introduction

With over 7000 ''individually rare, but collectively common'' rare diseases (RDs) known worldwide, awareness around this group of diseases has increased in some parts of the world.[1–8] A recent publication indicated that the majority (72%) of RDs are caused by genetic factors and are considered congenital disorders (CDs), defined as abnormalities in structure or function, including metabolic disorders, present from birth.[9–11]

Impact of RDs on children

While some RDs only manifest later in life in adulthood, for 70% of RD, onset is exclusively pediatric, which translates into the bulk of the ~300 million people affected by RDs globally being children.[11] Due to the progressive and life-limiting nature of many RDs, a third of affected children will not reach their fifth birthday, and those surviving often live with severe, lifelong disabilities.[10] In the absence of international consensus, the definition of an RD varies, ranging from 1 in 200,000 of the population in the United States to 1 in 2000 in Europe.[1,2] Since there is currently no official definition of RDs in South Africa, the European Union definition has been adopted by most stakeholders in the country. Approved treatments are currently available for only 2.5%–5% of RDs and their prohibitive cost may prevent access for many patients even when no alternative is available.[12,13] Many approved RD treatments remain unregistered for use in South Africa, creating challenges for reimbursement. Off-label drug use is often the only available option, with basic disease-specific treatment guidelines developed for only a

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few RDs.[4] RD research is challenging, with few patients available for research studies due to a combination of low prevalence, inadequate diagnostic capability, lack of comprehensive registries, and the high cost of research if it is not driven by incentives.[4,14]

Competing health priorities

While RDs are becoming a health priority elsewhere, in low- and middle-income countries (LMIC), particularly in Africa, the focus remains on persisting infectious diseases in parallel to the emerging burden of noncommunicable diseases as these countries transition epidemiologically.[1,2,15] This further exacerbates the challenges already facing RD patients, clinicians, and researchers, including delayed diagnosis, misdiagnosis and nondiagnosis, inaccessible care (if available), physical, emotional, and financial burdens placed on the patients and their families, and lack of clinicians with expertise equipped with clinical guidelines and other knowledge.[16] The required multidisciplinary care is often uncoordinated, placing an additional burden on the patient.[3,4,17]

A key challenge preventing RDs from being adequately addressed in LMIC is the slow development of RD diagnosis and research in the context of global collaboration.[16] The paucity of characterized local genetic variants and the often complex relationship between phenotype and genotype require attention in these LMIC. The average time for the diagnosis of an RD has been estimated between 5.5 and 7.5 years in high-income countries, with only 50% of patients treated at a clinic or genetic clinic being diagnosed.[3,14] In LMIC, including South Africa, where such specialized services are known to be extremely limited, the journey to diagnosis is likely further delayed.[18]

South Africa's response

As a part of the South African response to these identified challenges of the RD community, the North-West University's (NWU) Centre for Human Metabolomics (CHM) is in the process of developing the first RD biobank on the African continent. The vision and goals of the CHM Biobank address national and international research need: providing a valuable resource for scientists to improve what is known about these diseases; to increase understanding of the natural history and pathophysiology; to optimize diagnostic methods; and to potentially develop treatments. The genetic variability of the South African population offers added value to the RD biobank. As a resource, the CHM Biobank will serve as a biomedical resource for the global research community and also stands to benefit the wider South African community through the advancement of both medical and scientific knowledge, possible treatments, and technological advances through aligned studies.[19]

This review provides an overview of key literature on the limitations, challenges, and opportunities facing RDs and the proposed development of the CHM Biobank, including related ethical considerations in South Africa.

Socioeconomic Impacts of Health Research with Child Participants

The effect of social and economic standing directly impacts research activities in the country, particularly child health and RD research.[11,20,21] In sub-Saharan Africa (SSA), child-headed households* (CHH) are where the primary caregiver is a minor.† The HIV/AIDS epidemic has substantially impacted children in SSA, with a significant increase in orphaned children in the region, where an estimated 80% (14.9 million) of the world's AIDS-related orphans live.[22–28] While some may be fortunate to have other family members able to provide care oversight, for some, there are no other family members, near or extended (kinship care), or court-appointed guardians, and the eldest child takes responsibility for the younger siblings. CHH are prevalent in South Africa with an estimated 122,000 children living within ~60,000 CHH.[25,28–30] Many studies have found that the significant increase in orphans has overwhelmed kinship networks, government programs, and the community.[22,25,27–30] Children in CHH affected by RDs are potentially more vulnerable, remaining undiagnosed or unable to access relevant care, and their involvement in relevant research studies is more challenging. While socioeconomic aspects relating to CHH have been investigated, there is a gap with regard to the effect of CHH on health research and the access of CHH to relevant health care and genetic services, including diagnosis, biobanking, and care.

Socioeconomic Impacts Related to Discrimination and Exploitation

The HIV/AIDS epidemic has also created the very real fear of discrimination and that a person's sample will be used to screen them for HIV, or other potential disorders, which may affect their employment, careers, insurance services, and health care. The concept of anonymity is poorly understood and within the RD domain, anonymity is sometimes impossible to guarantee. The role of patient groups is also often underestimated. Local patient groups are critical in serving as advocates for the patients, explaining the potential risks and benefits, the consent process, and how the patients may protect themselves. To engage better with LMIC biobanks, it will be important to build collaborations that aim to develop local capacities and to offer academic credit to local scientists. Building trust with local communities are vital, along with improving infrastructure, educational opportunities, and fairness to allow patients to experience the benefit of their participation in research within their communities.

Ethics: Health Research with Child Participants

The minimum national ethical standards for research were published in 2015 by the National Department of Health (NDOH).[31] Research Ethics Committees‡ at tertiary academic centers in South Africa (SA) provide the ethical oversight for research, adhering to the 2015 guidelines.[31] These guidelines state that minors should only form part of a research study under the following conditions: (1) when their participation is of the utmost importance; (2) with only a minimum level of risk or harm for participants; and (3) that the research study must investigate a problem of

* *Child-headed households* are also defined as *orphaned households* or *orphan and vulnerable children* elsewhere.

† A minor is defined as a child younger than 18 years in accordance with standard legal designation of the term *child* within the South African legal framework.

‡ *Research Ethics Committees* is synonymous to *Institutional Review Boards.*

significant relevance to minors.[31] Where appropriate, children should also be approached for their assent to participate, in addition to, and after, permission from the parent/legal guardian before the research. If there is no parent, a guardian, foster parent, or a caregiver must provide consent in accordance with the specified proxy.[31] In situations where the caregiver is a minor and heading up a CHH, a trusted adult nominated by the minor must provide permission.[31] While compliance to relevant ethical requirements is essential, in some cases, access by CHH may be delayed or prevented entirely.

Ethics: Managing Various Consent Types

The collection and use of pediatric biobank samples have, historically, been hampered by ethical dilemmas related to the involvement of minors, resulting in an underestimation of their value. This has led to a variety of methodologies being developed to address these ethical concerns.[32] Progress has been made on developing model guidance for pediatric biobanks[33] and in developing standard assents for use with older children.[34] While most countries do not require re-consent to be obtained from children as they get older, in South Africa, it is required that participants be recalled at various stages during their development to obtain their assent and that participants have to re-consent at the age of 18 for participation in research or a biobank.[31]

Lack of Prioritization of RDs in South Africa

Burden of disease

While significant reductions in child mortality have been achieved in South Africa through the management of the HIV/AIDS epidemic and other infectious diseases as the country transitions epidemiologically, infant and under-5 mortality rates have stagnated since 2011.[35] The proportion of child deaths due to CDs and RDs continues to increase, as indicated by national efforts to quantify the burden of disease. Neonatal deaths due to congenital anomalies, which are obvious structural abnormalities (representing an estimated 50% of total CDs), increased to 11.6% by 2016.[36] In high-income countries, the total contribution of CD-related deaths under-5 averages almost 30%, with the majority of these deaths occurring during the neonatal and infant periods.[37] For South Africa to meet the Sustainable Development Goal, three targets by 2030, further significant reductions in neonatal, infant, and under-5 mortality are required.[18] As outlined in World Health Assembly Resolution 63.17,[38] for these to be achieved (just as for the Millennium Development Goals), CDs and RDs require prioritization as a health care issue. With an infant mortality rate of 25 per 1 000 live births,[35] South Africa is well past the point when genetic services for those affected and at risk of RDs should have been implemented.[39–41] In the absence of these services, many RD patients remain undiagnosed and die unnecessarily or achieve a much lower quality of life.[18]

Even though the proportion of RDs may appear smaller in South Africa, due to the persisting burden of communicable disease, the estimated 3.6 million South Africans affected cannot remain uncounted and unserviced. Late diagnosis, nondiagnosis, and lack of care for RD patients result in a significantly higher cost of care.[4,42] Faced with such a significant burden of disease and an already strained health budget, LMIC, including South Africa, require additional investment into assessing the impact of RDs and recommending actions for implementation. While dedicated funds have been promised by the government in the context of the National Health Initiative in South Africa (A Pillay, personal communication, October 3, 2019), a National RD Strategy is required to provide a framework and commitment to these activities.[43] As the proportion of mortality and morbidity due to RDs and CDs increases, following the trend of high-income countries, the need for this focused effort becomes even more imperative.

Lack of data and services

From a South African perspective, the centralization and standardization of accurate information related to RDs remain challenging.[44] Current inadequacies are resulting in the loss of valuable medical information relevant to future generations who may be carriers of these rare genetic disease variants. Repeat testing is a common occurrence due to the lack of a centralized patient database/registry with relevant clinical, biochemical, and genetic information in South Africa. This costly, *ad hoc* approach also extends the diagnostic time frame and limits accurate population-based statistics, which is detrimental to the patients, their families, and future siblings. An RD biobank will contribute to storage of genotype-phenotype descriptions, surveillance, and high-risk screening strategies urgently needed for different population groups.

While the RD burden of disease remains unquantified collectively in South Africa, recent work by Wakap et al.,[11] using a portion of Orphanet RD, estimated a global point prevalence range of 34.8–59.1 per 1 000 live births.[11,45] This equates to around 265–446 million people affected globally by RDs in 2018, including 3.6 million people in South Africa.[11,38] Due to the lack of empirical data and recent research data on CDs and RDs, as a collective means, little is known about the incidence and prevalence of the more common RDs in SA or an accurate contribution to the overall burden of disease.[44] This data vacuum prevents relevant services from being implemented in response.

Previous estimates of the incidence of two newborn screening (NBS) conditions suggest that South Africa, like any other country in the world, is not spared.[46,47] There is a cost associated with not addressing RDs that must be carried by individuals, the health care sector, and the economy in general.[42] RD patients are more likely to be admitted to hospital with longer and more expensive stays with a higher risk of an extended stay, palliative care requirement, and mortality.[4] This translates into a significant and disproportionate percentage of health care resource consumption.[12]

Small pockets of RD expertise exist in South Africa, although a cohesive approach toward diagnosis and treatment of RDs is lacking in most instances. A large discrepancy in the health service provided for public and private sector is evident.[48] Of 27 Health Professions Council of South Africa registered/practicing genetic counselors, based in only three out of the nine provinces of South Africa, seven are solely employed by the state, nine in the private sector, and 11 are working in both sectors due to the lack of allocated posts (Drs. Wessels and McCauley, personal communication, July 17, 2020). The number of practicing medical geneticists is similarly limited, with these specialists available in only Gauteng, KwaZulu Natal, and Western Cape.[18]

A key example of these service shortfalls is the lack of an NBS program in South Africa. In 2015, NBS was offered

almost universally in North America, Europe and in many countries in Latin America, Middle East and North Africa, and the Asia Pacific region. This equated to 37% of newborns globally receiving at least limited NBS, with many countries already offering or moving toward expanded screening.[49] Currently, in the South African public health care sector, screening for congenital hypothyroidism is offered to some newborns in the Western Cape.[50] The CHM offers a comprehensive NBS program on a fee for service base screening ~6000 (0.6%) newborns of the ~1,000,000 births in South Africa annually.

In the context of genetic testing, South African health care funders have expressed unwillingness to reimburse testing not undertaken locally, due to coding inefficiencies and the inability to assign the cost of the test against the International Statistical Classification of Diseases and Related Health Problems, 10th revision Code. Furthermore, transportation of genetic material can be a costly exercise and is not reimbursed by funders in the private sector.

Challenges Associated with Biobanks and RD Research in South Africa

Numerous studies have documented the limitations encountered within the ethical and legal regulations that guide biobanking activities in South Africa and elsewhere in Africa.[51–53] The literature highlights the need for a more standardized and unified approach to biobanking practices and creating a common approach on the governance of biobanks to ultimately promote valuable collaboration.[51–56] This is an ongoing challenge in South Africa, where legislation indirectly influences biobanking operations.[51,57]

Inadequate resources

Resources, including skilled human capacity, infrastructure, and financial allocation, relevant for biobanking are limited in South Africa, as in other LMIC, where competing health priorities place an additional burden on already limited capacity.[52,55,58] The limited and underdeveloped infrastructure cause LMIC to experience very unique challenges, for instance, when dealing with biological samples and sample collection logistics, which are not even considered in more affluent parts of the world. Postal services on the African continent and logistics are complex and must take into consideration the added challenges when collection occurs from remote sites.[52] This ultimately causes frequent delays in sample transportation from the collection site to the biobank and affects the viability of the samples. Usually, a simple approach to counteract the effect of the delay on the sample viability would be to centrifuge and separate samples before transportation. However, a simple centrifuge is not available in most remote areas in many LMIC, or only available in the private patient health care systems. Another logistical challenge that is frequently experienced in LMIC is that frozen samples must be transported for many kilometers, making use of various modes of transport. Even though this might sound simple enough to overcome by using dry ice or liquid nitrogen, it is very often impossible to get these mediums to collection sites in many LMIC.

A concerning challenge of the double burden of diseases faced by many LMIC due to ongoing epidemiological transition, is the shortage of skilled professionals and pathologists and other relevant medical specialties and subspecialties, which hampers effective biobanking in the sense of providing a correct diagnosis for patients and in collecting a high = quality specimen to bank.[59,60] Furthermore, very little has been published about the uniquely South African challenge of ''load shedding'' and its negative impact on biobanking practices in South Africa.[52,55] The term ''load shedding'' refers to regularly scheduled power outages, implemented since 2007, to reduce the energy demand placed on the South African national energy supplier. Consequently, load shedding has a substantial impact on the operational considerations for any biobank.[52,55] Many stakeholders in LMIC countries within Africa do not consider funding and development of biobanks as a priority, neglecting this diverse and rich resource and causing biobanks to be underutilized in research.[61] Consequently, these biobanks become heavily reliant on external funding for both initial implementation and sustainability, resulting in a short-term project-basis *modus operandi* to adhere to funder's goals,[52,61] rather than the biobank operating on its *fit for purpose* intended scope. It is therefore of vital importance for a biobank's sustainability to be supported by local government and the hosting institution in emerging countries.[61]

Standardization

In compliance with international and national obligations for all countries, South Africa is obligated to protect clinical, biochemical, and genetic information as associated with the biological samples of vulnerable communities. While South African legislation clearly defines the ethical use of biological samples and data generated from their use, in practice, this has not always been the case. Biobank custodianship provides the assurance that patients are protected at all times, by prohibiting the use of data and samples without permission and consent.[62–65] Recent studies illustrate the challenges surrounding the lack of a uniform approach in data sharing, the Protection of Personal Information Act,[66] and the import and export of biological materials and associated data for research purposes.[51,55,67,68]

To address some of these issues, a national material transfer agreement has been developed, which provides a framework of the minimum requirements that need to be adhered to before human biological samples may be exported or imported in South Africa.[63–65] Some studies have also been conducted to provide an indication of public perception of biobanking activities, how the public would like to be approached with regard to informed consent and trust, and on the development of community engagement models.[55,69–71] These studies inform the development of relevant, standardized approaches to engaging with and achieving the trust of patients and caregivers, as well as the wider public.

Benefits of an RD Biobank

One approach to breaking the perpetual cycle of inadequate services resulting from inadequate resources causing inaccurate and incomplete data is the implementation of a biobank offering a rational, evidence-based approach to underpin these efforts. Evidence indicates that RD biobanks, especially when linked to research registries, significantly improve the quality and quantity of epidemiological data, and local genotype-phenotype correlations, providing a more accurate evaluation of the burden of disease and the

required intervention to inform policy makers.[72] When managed through a comprehensive stakeholder model (involving RD community advisory boards, physicians & researchers, national government & other organs of state, and medical insurers and industry), evidence-based optimal decision making is likely to result. Structured appropriately, this can ensure skill transfer, bargaining, and broader access to specialized care. A similar undertaking has led to effective genetic counseling with the option for prenatal testing and preimplantation diagnosis for affected patients and families.[73]

RD biobank for South Africa

The CHM Biobank hosted the first comprehensive stakeholder meeting on the 15th of August, 2019, to launch the RD Biobank initiative, attended by 31 people. Participating stakeholders included Management of the NWU, National Government officials (from the Department of Science and Technology, the Department of Health, the Technology Innovation Agency and Diplomics), the National Biobank (National Health Laboratory Service), a specialist dietician, patient advocacy groups (Genetic Alliance South Africa and Rare Disease South Africa), and members from the private sector (Sanofi-Genzyme and Nutricia, Hamilton and Separations). Feedback toward this initiative was overwhelmingly positive and produced 11 letters of support toward the establishment of the CHM Biobank. However, support from the public sector and funding toward this initiative is still lacking.

The CHM Biobank is currently in phase 1 of a 10-year implementation strategy. The strategy is separated into three overlapping phases: Phase 1 (1–2 years) is currently underway, focusing on optimizing the infrastructure for the biobank and initiating participant recruitment and marketing. A suitable laboratory information management system according to International Society for Biological and Environmental Repositories Best Practice[74] recommendations was procured to aid in the governance of the CHM Biobank. Recruitment commenced in July 2019, with the first ''initial consent to contact'' obtained in August 2019. Currently, there are 12 participants in the CHM Biobank, of which 67% are pediatric participants. New strategies are currently being proposed to expedite the recruitment rate in 2021. Phase 2 of the strategy (years 3–5) includes initiating research projects to utilize the Biobank, increasing research outputs for IEM and research collaboration. To this end, a number of projects are currently in proposal stage. Proposed activities under phase 3 (years 6–10) of the strategy are focused upon obtaining ISO 20387 accreditation and the development of a university training course for Biobank Management and Curation in South Africa.

Benefits of biobanking for pediatric RD patients in Africa

A general misconception is that children are the same as their adult counterparts. However, most diseases often present differently in children compared to adults. Therefore, therapies for children need to be developed for their specific use by using pediatric biological samples and populations. For instance, cell turnover is much higher in pediatric tissues (representative of growth) compared to adult samples, which are static and there is much higher demand on cell repair and regeneration.[75]

The absence of comorbidities within pediatric samples, which sometimes interferes with interpreting adult samples, has promising advantages for health research, while simultaneously adhering to the requirements of the NDOH[31] regarding health research with minors. Furthermore, pediatric patients have not been influenced by lifestyle choices such as smoking and alcohol use, which are known confounders in adult samples.

Pediatric biobanking comes with benefits that are uniquely different to those from adult samples. Since many RDs are exclusively pediatric with death occurring before adulthood, progress on these disorders requires the use of pediatric samples. For example, the infantile form of Pompe disease was lethal before the development of enzyme replacement therapy. The infantile form is associated with a cardiomyopathy, which is not seen in the later onset forms.[76] This provides an opportunity to better understand the potential mechanism of cardiomyopathy, through the comparison of pediatric samples with adult samples. Cardiomyopathy in general is a significant cause of death in the adult African population.[77]

As more evidence is published on the impact of the microbiome on the health of nations, the African populations offer unique insights into very different diets with less complex and processed food. Sadly, it also includes samples showing the impact of malnutrition, which is becoming a significant problem in aging populations of high-income countries. In turn, this may be beneficial by providing insight into improved management of malnutrition and starvation.[78]

Conclusion

Awareness and interest toward RDs have steadily increased in some parts of the world, while in most LMIC countries, particularly in Africa and South Africa, the focus of the health care policies and support remains on communicable diseases. Some of the key challenges that affect this lack of support toward RD research collectively come down to a lack of knowledge and expertise in SA, slow development of RD research on a global level, and a lack of global collaboration.

As part of the South African response to local challenges associated with the RD community, the NWU CHM is in the process of establishing the first RD biobank on the African continent. The CHM Biobank aligned its vision and goals to address both national and international research needs that have been identified. Furthermore, the genetic variability of the South African population offers an added value to the RD biobank. This resource stands to benefit not only the local RD community but also the wider South African community and global research community, ultimately through the advancement of medical and scientific knowledge, the development of novel treatment options and technologies, and improvement of local expertise on RD, and to alleviate the high cost associated with diagnosis and treatment of RD patients.

Some of the more pertinent challenges associated with RD biobanks in South Africa include a lack of a comprehensive legal framework governing biobanking operations, a lack of support from stakeholders in terms of funding (leaving the resource underutilized), and a lack of support from local government. Furthermore, very little is known about the socioeconomic impacts relating to child health research and RDs in South Africa.

The lack of the prioritization of RD, as well as the centralization and standardization of information related to RDs in South Africa remain challenging, with no real indication of what the true burden of disease due to CDs and RDs in the country is. The lack of prioritizing actions toward RD research and support has spilled over to a serious shortage of genetic services to aid those affected and at risk of RDs in the country. Furthermore, this has also resulted in the loss of valuable information pertaining to RD carriers and the loss of valuable medical information for future generations.

The lack of RD policy in SA (also LMIC in general) has resulted in inadequate health care budget allocations, unnecessary repeat testing due to a lack of expertise, and an extended time frame to obtain a correct diagnosis, with dire effects for the patients and their families. There are only a few small pockets of expertise in South Africa and a lack of a standardized approach toward diagnosis and treatment. A key example of this shortcoming in services is the lack of national support toward an NBS program in South Africa. Currently, <1% of the newborns in South Africa has access to this service.

Even though the challenges listed are extensive, the overall benefits of having an RD biobank in South Africa are very promising and make the whole challenge worthwhile. Some of these benefits include an overall and significant improvement of the quality and quantity of available data on the local genotype-phenotype correlations, a more accurate estimation of the burden of disease, and the implementation of evidence-based required interventions. The ultimate goal of an RD biobank is to optimize the RD services that are offered on the African continent, but there are also numerous additional medium-term benefits that this initiative offers. For instance, several studies on RD patients in SA have exemplified how the country-specific ethnic findings may expand the international knowledge of RDs across various disciplines.

The local genetic variability may also not be the only benefit associated with the CHM Biobank that is hosted on the African continent but also the treatment-naive patient samples that offer the possibility of developing competitive treatments for RD, as well as the unique ability of RDs to help unlock some of the more complex biomedical answers to advance general disease research. The absence of comorbidities with pediatric RD samples also has exciting promises for health research and advancement of knowledge on these diseases.

The CHM Biobank, as a resource, thus holds enormous potential for the enhancement of the South African bioeconomy, given the desire and need that are based on the current global contribution that RDs offers within multiple sectors (including innovation, precision medicine, and international collaboration).

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