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REVIEW ARTICLE

A Strategic Research Framework for Defeating Diabetes in India: A 21st-Century Agenda

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Abstract | Indian people are at high risk for type 2 diabetes (T2DM) even at younger ages and lower body weights. Already 74 million people in India have the disease, and the proportion of those with T2DM is increasing across all strata of society. Unique aspects, related to lower insulin secretion or function, and higher hepatic fat deposition, accompanied by the rise in overweight (related to lifestyle changes) may all be responsible for this unrelenting epidemic of T2DM. Yet, research to understand the causes, pathophysiology, phenotypes, prevention, treatment, and healthcare delivery of T2DM in India seriously lags behind. There are major opportunities for scientific discovery and technological innovation, which if tapped can generate solutions for T2DM relevant to the country's context and make leading contributions to global science. We analyze the situation of T2DM in India, and present a four-pillar (etiology, precision medicine, implementation research, and health policy) strategic research framework to tackle the challenge. We offer key research questions for each pillar, and identify infrastructure needs. India offers a fertile environment for shifting the paradigm from imprecise late-stage diabetes treatment toward early-stage precision prevention and care. Investing in and leveraging academic and technological infrastructures, across the disciplines of science, engineering, and medicine, can accelerate progress toward a diabetes-free nation.

1 Why is Diabetes Research Important for India?

Within India, 74 million people (of the total population of 1.4 billion) currently have diabetes. This represents 14% of the global burden of diabetes (95% of which is type 2 diabetes [T2DM]), and making India an epicenter for the disease, along with the USA and China. Furthermore, the diabetes epidemic in India is accelerating across all geographic and socioeconomic groups, and it is projected that there will be at least 124 million people with diabetes by 2045.[1,2] Yet, India currently contributes to 1% or less of the world's peer-reviewed diabetes research output.[3] This represents a major potential opportunity for scientific discovery to impact public health, led by researchers across India and their international collaborators.

Opportunities for innovative research into different facets of diabetes in India are immense (Box 1). For example, Indians are highly susceptible to T2DM at younger ages and lower body weights relative to other world populations. Several intriguing and understudied factors may drive this unique, heightened risk: first, Indians have a high propensity for innate deficiency in insulin secretion or function and for hepatic fat deposition.[4] Second, the increase in overall prevalence of adult-onset diabetes (from 2% in 1972 to 9% in 2018) across all strata of Indian society

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- Understanding contributions of genetics, environment and gene-environment interactions, and the pathways through which they lead to higher incidence of diabetes at younger age and lower body mass index
- Stratifying the population by clinical and genetic characteristics for tailored prevention, diagnosis, treatment, and prognosis strategies to realize the goal of precision medicine in diabetes
- Leveraging public-private partnerships and India's strengths in information technology, pharmaceuticals, and other sectors to develop innovative solutions tailored to local communities to realize the goal of precision public health in diabetes

Box 1: Research opportunities

(age, gender, socioeconomic, urban/rural) has coincided with rapid economic development and rise in overweight.[5] India's population is also experiencing dramatic changes in lifestyle and environmental factors—notably: food, nutrition, and activity, air pollution, and stress—but their relative contributions are understudied.[6–8]

Although T2DM is largely a polygenic disease, current genetic knowledge explains only 10–20% of etiological variability in incidence globally. Furthermore, available data are predominantly from European populations, and a recent study indicated that only 22% of diabetes gene associations identified in European populations were replicable in Indians.[9] Unidentified genes and gene–environment interactions and their accompanying epigenetic changes are also likely to be important drivers for the rapid rise in diabetes prevalence across all strata of Indian society.

The emerging question of diabetes phenotypes, and resulting implications for precision medicine and public health, is of great topical interest worldwide.[10] Well-conducted research in Indian populations—in which some phenotypes are more widely prevalent and novel phenotypes may manifest—can provide ground-breaking and widely generalizable findings with global impact.[11] Yet, gradients in risk of complications across phenotypes as the diabetes epidemic evolves, coupled with the vast population diversity, offer contextual opportunities to explore important questions regarding gene–environment interactions in diabetes causation and in the differences manifest in disease phenotypes and pathophysiology.

Given India's large and growing population, there are opportunities for scalable and affordable high-quality innovations in diabetes technologies, medications, and delivery of care of models tailored to local contexts. Many advances in diabetes prevention and care currently come from high-income countries and are thus cost-prohibitive for large swaths of the Indian population, which may seriously limit the ability of such advances to benefit those living in the Indian subcontinent.

Beyond research on etiology, precision approaches, and technology-enabled innovations, there ought to be emphasis on developing and evaluating cost-effectiveness of policies that enable prevention and better care management. For example, policies that encourage healthy diets (such as supply- or demand-side subsidies) and more physical activity may have implications for both diabetes prevention and control.[12,13] Research reports that half of those with diabetes in India are unaware of their condition, more

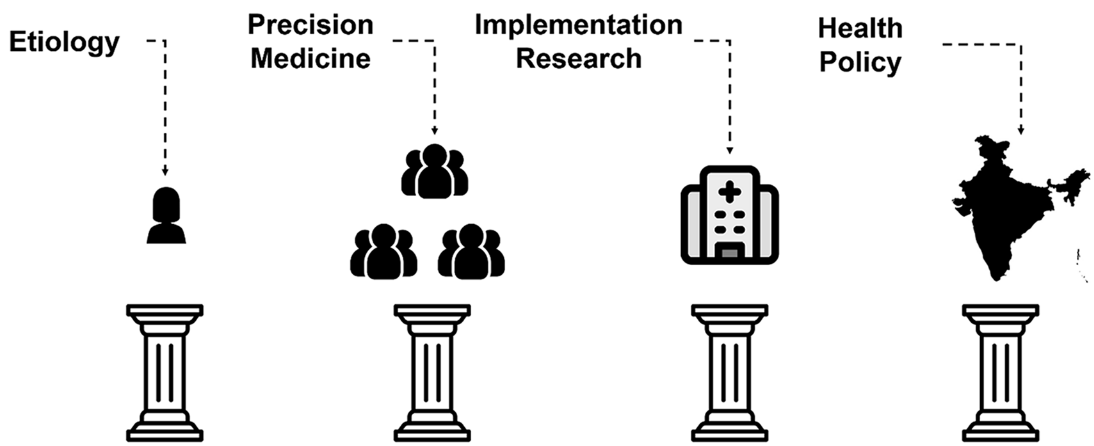

Figure 1: Four thematic pillars of the strategic framework.

than half of those diagnosed are not currently taking medication, and nearly two-thirds of those diagnosed do not have their diabetes under control, with substantial between-state and within-state disparities.[5,14] Innovative national and regional policies, tailored to local settings, along with decentralized monitoring (i.e., precision public health), to improve management of diabetes must become a priority area for research in India.[15]

India is thus a fertile environment for shifting the paradigm of diabetes management, away from imprecise late-stage treatment toward precision early-stage prevention and care. In this regard, the environment in India offers notable and unique advantages to accelerate scientific progress. The country has strong foundations and skilled personnel in information technology, bioinformatics, biotechnology, engineering, and analytics, and reputable industries specializing in affordable technologies and scaling challenges.[16] Previously, India has leveraged these resources in areas such as vaccine research and development, and the potential for similar interdisciplinary work in diabetes and related diseases is enormous.[17,18]

2 A Strategic Research Framework for Diabetes in India

In the section below, we describe four thematic pillars that can form a strategic research framework for defeating diabetes in India: etiology, precision medicine, implementation research, and health policy (See Fig. 1). We also provide suggested key research questions for each pillar (Table 1), as well as infrastructure needs and improvements for each.

2.1 Pillar 1: Etiology

As described above, the reasons for rise in diabetes prevalence across India is likely multifactorial (Fig. 2)—a combination of genetics and environment, and coincides with dramatic shifts in lifestyle due accompanying economic development, namely, wide availability of processed foods high in refined carbohydrates, fat, and sugar; mechanized transport labor; and increase in sedentary behaviors, driven by television and digital technologies.[1,19] In combination, these changes in food and in activity lead to an imbalance in energy metabolism, thus increasing the risk of non-communicable diseases, such as diabetes.[6] These are modifiable factors that could be tackled with the appropriate actions in individual, societal, and policy arenas; yet, more research is needed on how to facilitate effective modification across multiple levels. Further, India is known for its substantial diversity in terms of culture, languages, faiths, and socioeconomic groups; hence, a diversity of factors—varying from social norms to gut microbiota, which can influence the function of the host's metabolic phenotype—offer opportunities for investigation. Several large and complex questions remain: What is the role of the environment in dictating the mechanism of action in diabetes? How do gene–environment interactions increase susceptibility of Indians to diabetes? Do microbiota, pollution, or other environmental toxins alter biochemical or biological pathways in the body increase the risk of diabetes?

Despite the established overweight/obesity link with diabetes, substantial data show increasing occurrence of T2DM in Indians at low body mass indices and young ages. Some have postulated the thin-fat Indian phenotype, characterized

Table 1: Key research questions.

Pillar 1: Etiology of diabetes	
1	How is diabetes in Indians different from other populations? What is the importance of understanding the difference in terms of prevention, detection, treatment and prognosis? Is the etiology of diabetes similar across different population subgroups of India?
2	What is the genetic map of diabetes in Indians? Is genetics of diabetes related to the alleles expressed in the person or is it related to DNA modifications (post-translational modification in histones, activation of microRNA, DNA methylation…) transmitted through germline and hence creating phenotypic changes? How can multi-omics help in a deeper understanding of diabetes in India?
3	How does the thin–fat Indian phenotype play a major role in diabetes risk in India? Is the capacity for insulin secretion compromised in Indians? If so, how can this be investigated more thoroughly? Is fat distribution in specific organs and the low lean mass and stature important players in diabetes development? How can we assess lean mass and fat deposition accurately?
4	What is role of food and activity and other lifestyles in diabetes in Indians? How can we improve measurement of these variables?
5	What is the role of environmental pollutants and contaminants in risk for diabetes, and is there population heterogeneity in this relationship? Further, how are those contaminants interacting with genes and how might this alter the risk of diabetes?
Pillar 2: Precision medicine	
1	What are the statistical and machine learning methods that need to be developed for multi-modal data integration, and population segmentation (phenotypical classification)? How do we translate data-driven phenotypes into clinical practice?
2	How do we leverage government–industry–academia partnerships to develop ambitious precision medicine research programs in institutes of national importance?
3	How do we leverage secondary datasets, especially the National Health Stack, for precision medicine?
4	How do we ensure benefits of precision medicine are available to all stakeholders irrespective of their socioeconomic position?
Pillar 3: Implementation research	
1	How do we design and deploy technological solutions targeting frontline health workers?
2	Can voice be used as the fundamental data entry method for mobile applications used by frontline health workers?
3	Can we design a transparent payment system that leverages the digital payment infrastructure, and interfaces between traditional government systems and frontline health workers?
4	Can secure models of data aggregation and learning systems be developed for healthcare, where patients and providers contribute to a common pool for clinical and public health decision support?
Pillar 4: Health policy	
1	How can existing nutrition programs and policies like ICDS and MDMS be improved to address those at risk for diabetes/gestational diabetes and other chronic conditions?
2	What are the relevant food supply chain policies and how can they be leveraged to increase availability and affordability of healthy foods like fruits and vegetables, whole grains, and legumes?
3	How can sustainable cold chains be developed to reduce the amount of food loss/waste and ensure nutritious foods get to rural populations that need them?
4	What role can local food systems (small distribution networks) play in increasing availability of fresh fruits and vegetables and reducing food waste?
5	What infrastructural changes are needed to promote population physical activity and active transport? What challenges remain?
6	Can front of package labeling help direct consumers to healthier products?

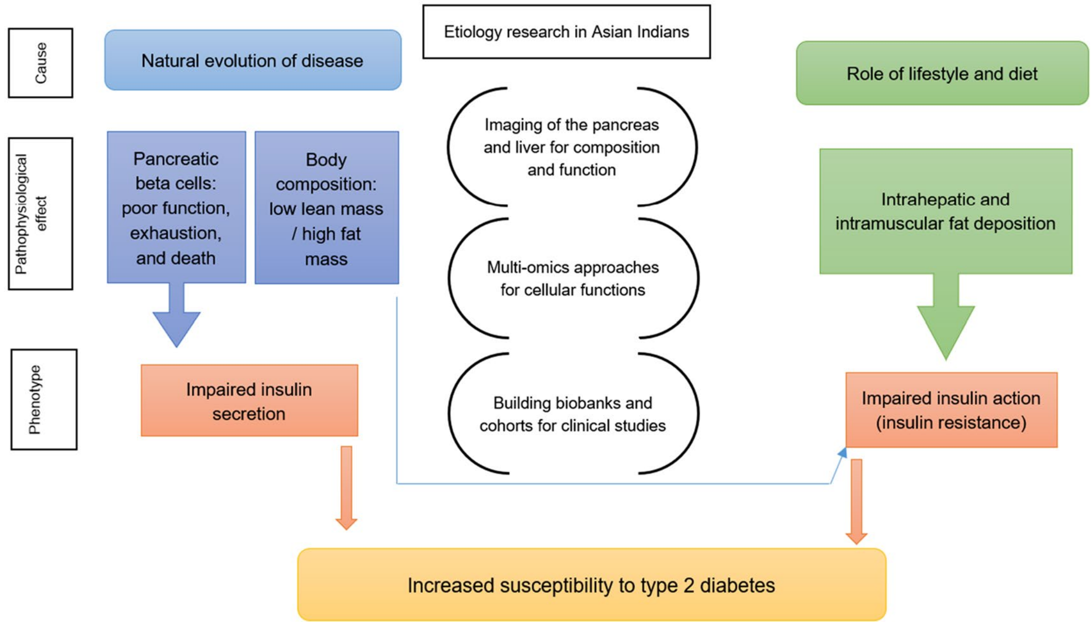

Figure 2: Research framework for diabetes etiology. The figure above (modified from Narayan and Kanaya, 2020) proposes a pathophysiological pathway connecting both common causes leading to diabetes in Asian Indians. The natural evolution leads to the poor beta cell function and hence an impaired insulin secretion; while the intrahepatic and intramuscular fat accumulation caused by lifestyle and inadequate body composition leads to impaired insulin action. Further, the diagram summarizes the proposed areas for research to better understand the etiology of diabetes in Asian Indians to curate a more targeted treatment and prevention.

by small body size and thin lower limbs but high visceral fat, to cause metabolic obesity.[4] However, recent data from several independent sources have offered additional potential but unexplored explanations for the risk of T2DM in Indians, especially, in non-obese and young people. Studies comparing diabetes pathophysiology in Indians with that of the Pima Indians of Arizona—two high-risk populations differing substantially in body weight—have suggested that innate defects in insulin secretion may be the primary driver in Indians, while insulin resistance may be the dominant influence in Pima Indians, suggesting different diabetes phenotypes.[21,22] In fact, Indian men 20–44 years old with a body mass index (BMI) <25 kg/m^2 have a five-fold incidence of diabetes compared to Pima Indians, while those with a BMI >30 kg/m^2 have approximately the same incidence as Pima Indians.[21] One study showed Pima Indians have four-fold greater insulin resistance compared to Indians, while Indians secreted half to a third of insulin than Pima Indians.[22] Further, studies comparing T2DM among Europeans (the UK and the Netherlands) to Indians have shown that Indians had lower insulin secretion, lower beta cell reserves, and poorer beta cell adaptation.[4]

The notion of multiple phenotypes has gained popularity with time. Intriguingly, the frequency of insulin-deficient phenotypes is far more common in Indians than in other ethnic populations.[11,23,24] In an investigation of young onset T2DM (<45 years of age) in Pune, India, 53% were of the insulin-deficient phenotype.[25] Furthermore, recent meta-analysis on diabetes phenotypes reported that Asians in general (including Indians) may have poorer insulin secretion across all reported phenotypes.[26,27]

Understanding the distribution of fat in the abdominal area may be critical to understanding the etiology of diabetes in Indians. The main culprit may be hepatic fat—fat accumulated inside the liver—which has been shown to be higher in Indians compared to Europeans and Pima Indians.[21] One possible explanation to this increased hepatic fat is the high intake of carbohydrates and high concentration of saturated fat in traditional Indian foods.[28] Indian carbohydrate intake that traditionally comprised healthier cereals (millets) is now predominantly from rice and wheat, with an increasing intake of sugar (free sugar as well as from beverages and desserts), often reinforced by government subsidies and child feeding programs.[29–31] Moreover, Indian diets are low in high-quality protein.[32] Very few studies have examined the association between hepatic fat and the risk of diabetes,[33,34] although the Chennai Urban Rural Epidemiology (CURES) study found that hepatic fat was associated with progression from pre-diabetes to diabetes.[35] As recent data suggest that Indians are at high risk of hepatic fat deposition, and overall visceral adiposity is higher in Indians than in Europeans,[36,37] suitable methods are needed to clearly discriminate between ectopic, visceral, and hepatic fat deposition—opening avenues for imaging and artificial intelligence research.

Data also point to low muscle mass in Indians.[36,38] Some have postulated that the increased risk of diabetes is related to long-term intergenerational influences that inflicted negative effects on women of childbearing age and their offspring during early childhood, causing a diminished metabolic capacity.[39] The latter is reflected as short stature, lower lean muscle mass, and increased risk to diabetes due to poor pancreatic development.[38,40] Lean muscle mass plays an important role in glucose metabolism, as skeletal muscle is responsible for the clearance, uptake, and metabolism for the majority of glucose in the circulation. Furthermore, Indians have, on average, a diminished beta cell capacity and lower insulin secretion, compared to European and most other populations.[41] Hence, peripheral insulin resistance could cause beta cell exhaustion over time, which has greater implications when insulin secretion is not optimal at baseline.[4] It may be that the nexus of innate defects in insulin secretion, ectopic hepatic and pancreatic and muscle fat deposition, along with low lean muscle mass conspire in an evolutionarily susceptible population to drive high diabetes risk.

This warrants a closer look at pancreatic islet cells, requiring advances in imaging technologies and creation of pancreatic biobanks. Imaging of the pancreatic islet cells can assess the existence of apoptosis or differentiation to aid in diabetes prevention or treatment or enable a precision medicine approach. In fact, both magnetic resonance imaging (MRI) and computed tomography (CT) have been widely used to diagnose pancreatic tissue heterogeneity and fat distribution and accumulation in various pancreatic disorders.[42] Several studies have favored MRI over CT, as MRI has been shown to be very useful in the identification of internal lesions and inflammation in the pancreas specifically, such as in pancreatic cancer, which gives insight to cell functionality.[42] Further, MRI can help assess tissue infiltration, namely ectopic fat, which helps assess progression toward diabetes or reversal after treatment.[43] CT has been shown to be useful in identifying cell heterogeneity and fat distribution, although to a lesser extent than MRI.[43] Hence, it is worth further investigating both methods to adopt the best practices for assessing diabetes development and prevention in Indians. Additionally, the creation of a pancreatic and organ biobank could be a major resource for diabetes research, as it would offer ways to identify the fundamental causes of diabetes, as well as cancers and genetic disorders. For instance, a recent study utilized the UK biobank to predict risk of pancreatic cancer among those with T2DM.[44]

Genome-wide association studies (GWAS) have garnered attention from a large number of researchers interested in understanding the genetic etiology of diabetes. The most recent and largest GWAS studies included 228,499 T2DM cases and 1,178,783 controls from five ancestral groups and reported 568 associations and 318 novel risk loci for T2DM,[45] and over the last decades, GWAS studies have identified over 700 genetic variants associated with T2DM.[45] One study identified six variants (*GRB14*, *ST6GAL1*, *VPS26A*, *HMG20A*, *P3S2*, and *HNF4A)* unique to the South Asian population, also noting their absence in European populations[46]. However, the large number of currently known variants explains less than 20% of the cases of diabetes, leaving unanswered questions as to how to explain the remaining 80%, especially with recent studies suggesting data-driven subtypes of newly diagnosed T2DM that require different treatments and having different risks of complications.[47] Furthermore, where do genes stop and epigenetics takes over? What are the differences in gene expressions in Indians compared to Pima Indians, Europeans, and other races/ethnicities?[48] How do we understand the mechanistic and cellular actions of the variants discovered by GWAS?

Answering these complex questions requires the integration of multi-omics modalities, including metabolomics, proteomics, transcriptomics, and metagenomics, driven by recent advances in technology. For instance, transcriptomics and proteomics are essential to map gene expression, which helps understand transcriptional and post-transcriptional regulation.[49] Further, it is important to complement such studies with other methods such as single-cell RNA sequencing, a novel approach that provides insights on cellular mechanisms at the epigenetic level. Single-cell RNA sequencing can reveal complex and rare cell populations, uncover regulatory relationships between genes, and track trajectories of distinct cell lineages in development.[50]

In summary, it is important to channel resources to answer crucial scientific questions with interdisciplinary research teams across the spectrum of basic, population, and clinical research, as well as policy sciences and engineering. Examples of research questions may include: Why are Indians innately more insulin-deficient on average than other ethnic groups, what upstream factors are involved (e.g., intergenerational influences, genetics, epigenetics, nutrition, and environmental toxins), and how can approaches to prevention, diagnosis, and treatment be tailored for different diabetes subtypes that may be present in the population? Why are Indians more prone to ectopic fat deposition and low lean muscle mass than Europeans? How do genes, lifestyle, and environmental factors interact in a rapidly transitioning society to manifest differences in diabetes phenotypes and pathophysiology? This integration of different scientific disciplines will require funding and infrastructure to: (1) develop new imaging techniques to understand baseline function of the pancreas and fat distribution; (2) integrate multi-omics modalities to understand the etiology of diabetes; (3) create organ biobanks (e.g., pancreas, liver, muscle); and (4) build and retain diverse deep phenotype cohorts to facilitate clinical and translational studies.

2.2 Pillar 2: Precision Medicine

Precision medicine and prevention involves identifying subgroups for whom some particular sets or sequence of interventions, either preventative or therapeutic, may be more effective.[51] Personalized medicine is similar, but we disambiguate it as the clinical translation of precision medicine after considering each patient's clinical and socio-demographic profile. Current approaches to precision medicine for diabetes mainly involve diagnosis and treatment. Recently, researchers characterized subgroups of diabetes beyond existing classifications such as type 1 diabetes (T1DM), type 2 diabetes (T2DM), latent autoimmune diabetes in adults (LADA), and maturity onset diabetes of the young (MODY). T1DM and T2DM are complex polygenic diseases, while MODY refers to types of monogenic diabetes (with an unknown prevalence among Indians).[52] An important advancement in precision treatment was the identification of differential treatment responses of monogenic forms of diabetes. For example, MODY 1, 3, and 12 are responsive to sulfonylureas (hypoglycemic agents), while MODY 2 may not require treatment.[51,52] However, research on prevention on an individual- or subgroup-level, and understanding the cost-effectiveness of current precision medicine strategies to improve diabetes care, are lacking in India.

Precision medicine for diabetes may involve population segmentation for prevention, diagnosis of disease, treatment choice, and prognosis of complications, with tailored monitoring (using wearables and smartphones) incorporating anticipated cost–benefits and risk of complications (Fig. 3).[10] Data modalities typically used for such segmentation in diabetes include both routinely collected clinical data (laboratory and anthropometry) and deep phenotyping data (biological samples for multi-omics, sensor data to monitor health-related behaviors, and sociodemographic factors). Recently, data-driven subtypes of newly diagnosed T2DM were identified in Indian populations using routine clinical data.[11,53] Among these novel subtypes, those characterized by insulin deficiency constituted a higher proportion of newly diagnosed T2DM in Indians than among their European counterparts.[27] Beyond clinical and biological characteristics, environmental exposures (such as air pollution and enteric pathogens) may have moderating influences. These factors must be integrated in precision medicine research,[54] or studies may end up with poor generalizability from unmeasured effect modification.[55] There is also growing interest in studying psychosocial phenotypes, using cognitive and behavioral attributes of the patient, to tailor interventions for long-term behavioral change and adherence to interventions.[56,57]

Collaborations between clinicians, epidemiologists, computer scientists, and statisticians to pursue approaches, such as multi-modal data integration and population segmentation, may be useful to characterize phenotypes for prevention, diagnosis, treatment, and prognosis.[58] Data fusion techniques to combine heterogeneous data from various sources, coupled with data analytics and machine learning algorithms, have significant potential to capture patterns and nuances in the phenotypes that may not be visible in the initial raw data extraction phase.[59,60] This would enable stratification of patients and could extend the paradigm of precision medicine and prevention for diabetes. For instance, unsupervised data mining or machine learning techniques, including deep learning, such as clustering and auto-encoders, can be used to learn features as a basis for building effective clinical decision support systems.[61] However, this requires assessing

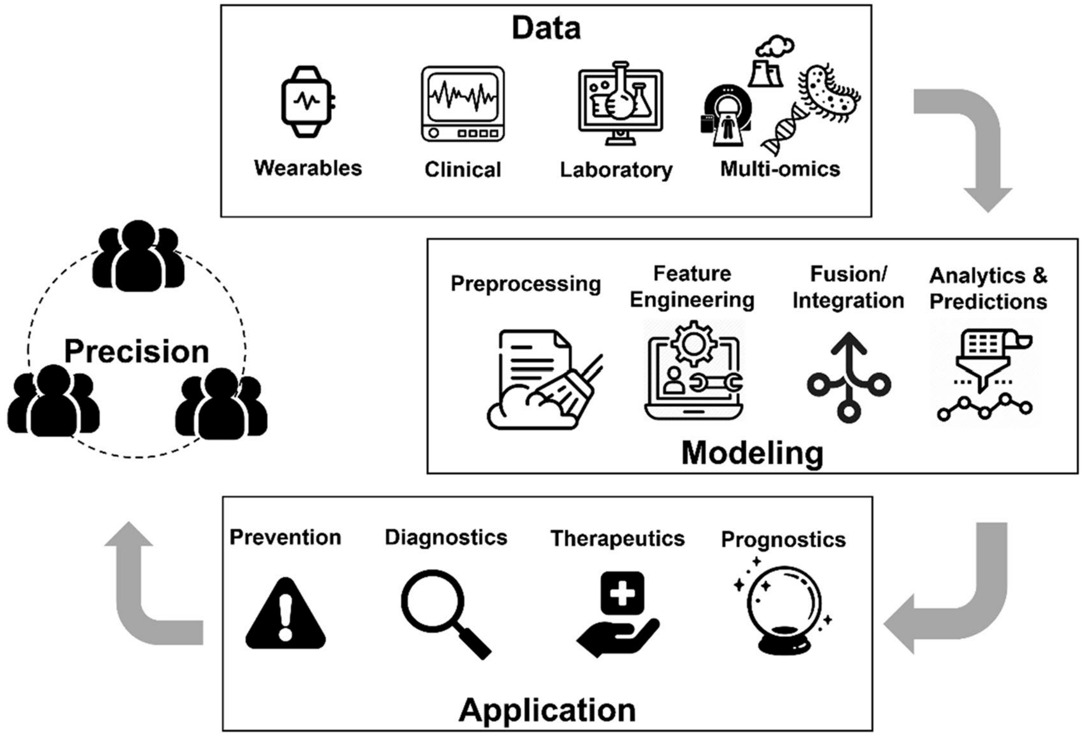

Figure 3: Research framework for precision medicine.

model performance in external datasets and validating explainable aspects before implementing the model in clinical settings.[62,63] Going forward, interpretable (and explainable) artificial intelligence, and causal inference approaches have important roles to play.[64–66]

By its very nature, precision medicine initiatives must be localized and their benefits be made available to the population on which the studies were based.[67] This implies either calibrating existing models for local settings using secondary data or developing models for prevention, diagnosis, treatment and prognostics using primary data.[68–71] A research agenda for India should consist of both these approaches.

Results from studies using secondary data for precision medicine face challenges of causal inference from disparate data sources via data fusion methods, which then need to be validated via randomized trials or additional high-quality observational studies. First, data fusion is expected to be hard in practice in India, where data integration concerns and challenges are prevalent at organizational, departmental, and even household levels. For example, studies of mobility and user interaction with mobile applications may present issues when multiple users in a family share a smartphone. Second, analysis of electronic health records (EHRs) from different care providers present challenges, such as harmonization of variables, varying laboratory standards, missing data, and fragmentation of care.[72,73] Third, integration of health records and other sensitive information across providers present not only the aforementioned implementation challenges but also concerns of data security and privacy.[74,75] The National Health Stack (NHS), proposed in September 2021 as a part of the National Digital Health Mission (NDHM), is a significant initial step toward a solution to address some of these issues in India.[16] The NHS aims to provide unique person-level health identifiers and an application programming interface (API) for submission and retrieval of sensitive health data to authenticated providers. This initiative presents opportunities for large-scale clinical data research, such as developing prediction algorithms for diagnosis, treatment response, and prognosis. However, concerns with storing sensitive health data remain, such as standards for anonymization, data migration from legacy systems, cybersecurity and fraud control risks, and must be abated.

The primary data approach is an expensive endeavor that should be supported by a mix of government and industry funding. The U.S.

government is launching an ambitious high-throughput research program for healthcare as part of the Advanced Research Projects Agency for Health (ARPA-H).[76] This initiative is designed along the lines of the Defense Advanced Research Projects Agency (DARPA) that gave rise to technologies, such as the internet, global positioning system (GPS), and micro-electro-mechanical system (MEMS) sensors.[77] Recent initiatives of industry–academia collaborations, such as the Innovative Medicines Initiative in Europe ($5B), the Accelerating Medicines Partnership in the U.S. ($215M), and the Precision Medicine Initiative in China ($9.2B), are parts of larger strategies with expected long-term benefits.[78–80] These initiatives invest in basic science and biomedical research capabilities in universities. India could leverage its strength in pharmaceuticals and information technology by undertaking a similar initiative. For example, India's National Health Mission, in partnership with a health-focused non-profit (Piramal Swasthya) and a technology services company (Cisco), is implementing an integrated health technology platform for early diagnosis of chronic disease and high-risk pregnancy.[81] Moreover, partnering with technology companies may add another dimension—user behavior—to tailor precision medicine interventions, that is presently underexplored except by companies like Google (FitBit + Android), Amazon, and Apple.

India experiences high levels of undernutrition and poverty, and previous research has shown how early life undernutrition may confer higher risk of cardio-metabolic disease in adulthood.[39,40] As a result, there is a constant struggle to balance the priorities of the most impoverished billion with initiatives to tailor care for the more affluent 400 million who are at higher risk of diabetes.[82] It is important to replicate successful research models from other countries and tailor these for Indian settings. One potential approach may be to provide "freemium" services (free with fewer features than paid services) to government health facilities to facilitate digital inclusion with respect to both data and solutions. As internet connectivity has grown rapidly across the country, there is a tremendous opportunity to facilitate further digital onboarding by investing in Health Information Management Systems (HIMS) nationally and identify trained personnel to support this initiative.[83] That India's young population is digitally adept provides an added benefit. Initiatives such as the Deen Dayal Upadhyaya-Grameen Kaushalya Yojana (part of the National Rural Livelihood Mission) as well as National Skills Development Mission, which upskill young Indians, could facilitate this process.

Representative sampling of the national population, and oversampling of those at higher risk, for biobanks may provide long-term benefits in prevention and management of diabetes. Such initiatives may present opportunities to design tailored prevention strategies (precision prevention). At a global level, there is increasing recognition of ethnic variability in predisposition to diabetes. A recent study reported that only 22% of the loci in Europeans were replicated and only 33% (9 out of 27) of causal genetic loci were shared by those of South Asian (Pakistani and Bangladeshi) descent.[9] India has experienced high geographic genetic isolation for the last 1900 years, with inter-caste marriages continuing to occur infrequently.[84,85] Moreover, there is substantial variability in environmental exposures, providing opportunities to study gene–environment interactions.[86,87] Therefore, a precision medicine approach that would benefit the nation as a whole must incorporate the geographic, ethnic, and socio-demographic diversity that characterizes India.

2.3 Pillar 3: Implementation Research

In 2020, 700,000 Indians died of diabetes, hyperglycemia, kidney disease, or other complications of diabetes. At-home, community-based, and primary care facilities for early diagnosis, appropriate care, and ethical treatment have not grown to address diabetes early and adequately, whereas tertiary care services dominated by procedure-driven care have grown exponentially. The result is detection at a late stage and treatment at a very high cost, often unaffordable to much of the Indian population, both in terms of money and mortality. To access diagnosis and detection services, patients have to go to established hospitals, lose wages, and incur out-of-pocket expenses, which disproportionately affects the most vulnerable in the society and consequently, results in neglect at initial stages of the disease.

As early identification of those at risk reduces lifetime treatment costs,[88] there is a pressing need for affordable solutions that both individuals and communities can access regularly for timely screening and diagnosis.[89–94] The paradigm of diabetes care delivery in India has traditionally been provider-centric; however, given the magnitude of the diabetes epidemic and long-term need for management, a shift to a patient-centric

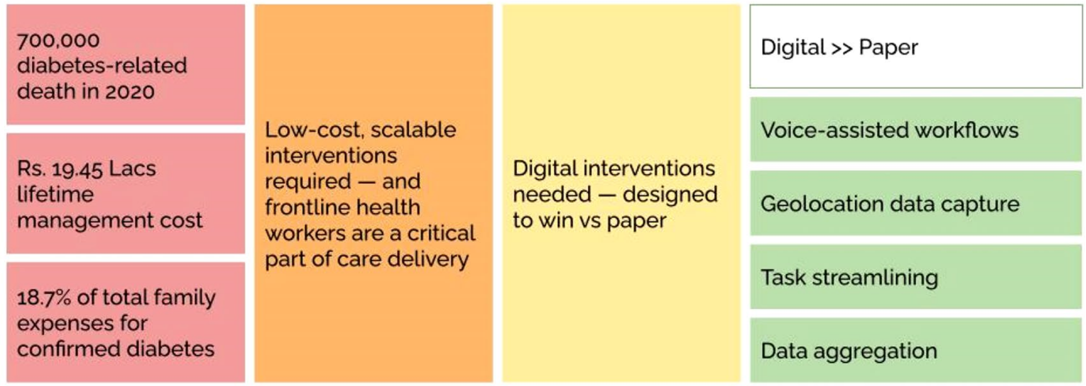

Figure 4: Research framework for implementation research.

paradigm is needed. This requires both process and technology innovations, targeting patients and providers.

Frontline health workers (FLHWs) are often the target of new digital initiatives, but are chronically underserved among providers [95–97] Consider the wave of mobile applications targeting FLHWs, deployed for data collection or decision support, with the hope of systemic benefits.[98] Systemic benefits, however, have to be accompanied by value for the user.[99] From the user's perspective, immediate benefits gained from using the application often do not outweigh the effort required to do so. Care providers accustomed to paper records find it hard to transition to an English language keyboard or handheld devices.[100] Although the latter offers benefits of data storage and retrieval for a trained provider, the former does not run out of battery or memory, and crash from unforeseen technical bugs in the middle of a patient interaction. Hence, digital transformations not only need to minimize costs of transition, but also provide benefits that paper cannot provide.[101] By exploring the dimensions on which digital interventions offer markedly greater value than paper, we can deliver on the promise of technology.[102] We propose five areas for exploration to improve the value generated by digital initiatives targeting FLHWs (Fig. 4): voice, direct benefit transfers, geolocation, task streamlining, and digital systems for aggregation of data from both patients and providers.

2.3.1 Voice

Voice may be useful for both data capture and communication. Can we use voice as the fundamental data entry method for a community health app? WhatsApp's voice messaging system sends billions of messages a day, breaking barriers of both language and literacy. Visualize a future where a community health app "gets out of the way" and quietly listens to the interactions between an FLHW and a patient. The FLHW looks at the patient, not at their phone, and the app works in the background—where it generates a transcript, fills forms, provides cues to the FLHW, helps refer the patient to primary care facilities, and triggers reports for administrators to consume.

2.3.2 Direct Benefit Transfers

Direct benefit transfers can provide immediate and secure access to funds for FLHWs, who often have to wait for months' before receiving compensation for their fieldwork. Reports (on paper) have to wind their way through the administrative system before they are approved and processed. Can we design a transparent payment system that leverages the UPI infrastructure, and interfaces between traditional government systems and FLHWs?

2.3.3 Geolocation

Geolocation or the ability to track 'where' and 'when' is now possible with a smartphone. Can this geolocation data be used to develop an understanding of how location (and consequently food habits, occupations, movement and migration patterns) correlate with health indices? Geolocation has to be managed judiciously, with strong privacy controls that only allow information to be reported in aggregated form.

2.3.4 Task Streamlining

Task streamlining is the idea that beyond digitization of the provider experience, there needs to be a greater emphasis on improving patient agency. Greater agency for patients can be viewed from Amartya Sen's capabilities approach by deconstructed into two steps: (1) knowing what to do (information) and (2) having the means to do it (resources). The third step—taking action (or functioning)—follows attainment of agency. "Knowing what to do" requires access to the right information at the right time. COVID-19 demonstrated that traditional and digital media could be harnessed to emphasize simple, but actionable messages. However, there ought to be further research into how tailored communication for diabetes management, a more long duration intervention, should be operationalized. Unless we frame diabetes as the pandemic that it is, communication may not match the urgency that the situation demands. "Having the means" has to be driven by cost reduction, since the majority of cost of care continues to be out-of-pocket (> 60%).[103(p. 202),104] India has attained substantial progress in reducing glucometer strip costs from Rs. 22.7 (in 2016) to Rs. 13.6 (in 2022), a 63% reduction in real terms.[105(p. 1),106] Similar focus on cost reduction and ease-of-use is required for other tests like HbA1c, and essential medication like insulin.[107]

2.3.5 Digital Systems for Data Aggregation

Finally, digital systems enable us to combine information that has traditionally been siloed—such data self-reported by patients, observed and recorded by FLHWs, and captured in a healthcare facility during treatment. While data from healthcare facilities has high fidelity, it has low coverage. Conversely, self-reported data may be low fidelity, but has wide coverage. Integrating hitherto disparate data sources gives us the ability to combine scale with precision. A powerful example of such an initiative is the use of smartphone accelerometers to detect earthquakes and alert users.[108] Though far less precise than seismographs, a large network of devices has the potential to eliminate localized noise, and provide alerts at little to no incremental expense. Can similar models be developed for healthcare, where patients and providers contribute to a common pool, and gain more than they invest?

Furthermore, how can such a paradigm help up prioritize disease surveillance, and help identify which communities are at higher risk? A localized approach that examines the cascades of care (screening, diagnosis, treatment, control) may provide some insights[5,14,109]. Infectious diseases have a location-based risk paradigm (tuberculosis or Cholera). Are there similar paradigms for diabetes, such as risk clustering within families or communities, which can help optimize surveillance efforts?[110]

Use of self-reported data requires intermediaries to guarantee a strong layer of data security and privacy. Contributors must have the ability to restrict access and remove their data, similar to the framework proposed by the National Digital Health Mission.[16] Such a system should either be enabled by trusted intermediaries (for instance, banks in the case of financial transactions), or by removing intermediaries altogether. The latter approach has been attempted using public blockchains in Syrian refugee camps set up in Jordan, which has enabled identity information to be isolated from (and made inaccessible to) authentication systems. Another key issue in any large-scale public health intervention is interoperability. The adoption of FHIR as a standard for data exchange can greatly increase information motility. These and many other technological developments may pave the way for better delivery of diabetes care.

2.4 Pillar 4: Health Policy

While health services research and quality of care improvement frameworks can help to address important aspects of patient self-management of diabetes, equally important is creating an environment in India that promotes health and well-being to facilitate T2DM prevention.[111] Policies and practices relevant for T2DM prevention can include those promoting good nutrition through (a) improved availability and affordability of healthy foods, such as agricultural policies to encourage production of healthier crops; (b) improved distribution of, and access to, foods that encourage proper nutrition for all, in terms of caloric and macro- and micronutrient needs; (c) ensuring sustainable production practices that consider both human and planetary health; and (d) nutrition-labeling regulation to ensure the population is empowered with the tools to choose healthier foods and promotion of increased physical activity through urban planning policies to ensure walkable, inclusive cities and other initiatives. In this section, we focus on these policies that lie outside of the healthcare sector (Fig. 5).

Currently, India's National Health Policy (adopted in 2017) aims to attain the highest possible level of good health and well-being for the entire population through preventive and promotive health care orientation in all developmental policies, with universal access to good quality, affordable health care services.[112] A specific goal

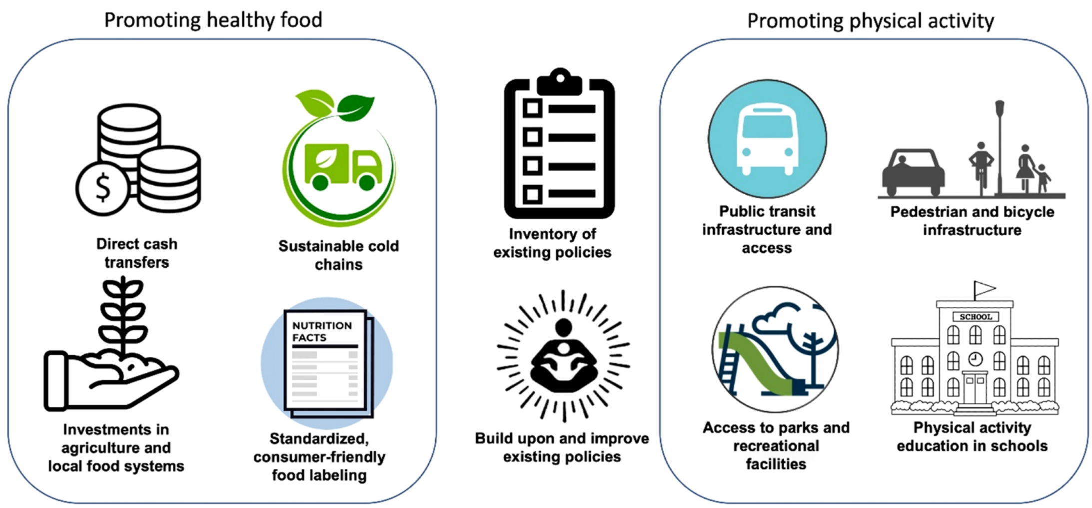

Figure 5: Research framework for health policy.

is to reduce premature mortality from cardio-metabolic diseases by 25% by 2025. To accomplish this, the Indian government launched the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDCS).[113] The objectives are to: (1) prevent and control common NCDs through behavior and lifestyle changes; (2) provide early diagnosis and management of common NCDs; (3) build capacity at various levels of health care for prevention, diagnosis, and treatment of common NCDs; (4) train human resources within the public health system; and (5) develop capacity for palliative and rehabilitative care. Although the choice to eat healthy foods or to increase physical activity is made at the individual level, there is also responsibility at a country level to encourage these behaviors. The NPCDCS can be more effective in this regard with an additional objective to create and redesign environments to prevent T2DM, and by conducting a needs assessment to determine what gaps currently exist in this space.

As a first step, an inventory of relevant policies and programs that currently exist in India and that could be leveraged for creating health-promoting environments must be created. Such an inventory could also help to identify potential gaps and/or duplication of efforts across departments and sectors. In a previous study that could provide a roadmap for such inventories, researchers analyzed the policy environment related to fruit and vegetable supply in India. The analysis included 29 policies across the supply chain (including production, distribution, processing, retailing, and demand in consumer level) and 55 interviews with stakeholders at the national and state levels.[114] Results suggested growing government support for agriculture over the past decade, with an increasingly diversified fruit and vegetable supply chain. The study also identified the need to better integrate nutrition and improve coordination across stakeholders, especially at central government and state levels, to avoid duplication of efforts.[115] Specific strategies for improving consumers' external food environment for fruit and vegetables in India included development of strategic public–private partnerships to increase access to diverse expertise across the supply chain; linking health, economic, and agricultural policy agendas; strengthening surveillance of policy impacts on consumer access to fruit and vegetables; and leveraging public health actors to advocate for 'consumer oriented' fruit and vegetable supply policies. This study demonstrated the usefulness of 'policy learning'-oriented qualitative policy analysis in identifying 'points of entry' for food policy change and research, and extended the understanding of political dynamics in engendering agricultural policy change for nutrition.[116] Similar studies could be performed for other sectors of the food supply chain (grains, legumes, meat, and dairy), and implementation research can help to identify ways to address gaps or insufficiencies.

In addition to an inventory of existing policies, research into how to build upon and improve pre-existing policies is also needed. For example, the government's Integrated Child Development Services (ICDS) program provides nutritional meals, preschool education, and primary healthcare (including immunizations, health check-ups, and referral services) to children under six years of age and their mothers.[117] The program also provides rations for all pregnant women; however, these rations are given without any consideration of the mother's risk for gestational diabetes or other high-risk conditions.[118] Moreover, the rations are typically cereal-based and include more calories than are needed. No screening is currently in place to suggest discretionary use of dry rations for a woman with diabetes or prediabetes compared to a healthy woman without diabetes; this is an important area for future research and one that could help to address inter-generational causes of T2DM.

One current major obstacle to healthy food availability and safety is the large amount of food loss and waste at all levels of the food chain. Globally, 40–50% of root crops, fruits, and vegetables are wasted each year, perishing during harvest, storage, transport, packaging, and distribution.[119] In India's warm climate, where fruits and vegetables are prone to spoiling before reaching their market destinations, the lack of adequate distribution systems may lead to supply-side wastage and disincentives for their production—in fact, United Nations Environment Programme estimates 50 kg of food wasted per capita per year in India.[120] A sustainable solution to the lack of cold chains that can link producers to markets in India is urgently needed and could potentially prevent up to one-quarter of food waste.[121] This is an area in which clean technology, powered by renewable energy, could help tremendously—again highlighting the need for cross-sector partnerships. Local distribution systems can also play a role here, as well as initiatives to bolster local food systems through community gardens. Some of the authors were working with the Karnataka State Horticultural Department and Panchayat Raj Department to create such an initiative, and estimate that it could have the potential to provide up to 50 g of vegetables to each child per day (or 1 kg/day to an Anganwadi that serves 20 children). Current challenges to implementation include working across multiple sectors and departments, as well as securing land, seeds, fertilizers, organic pesticides, and labor.

Greater investments in research aimed at reducing production costs for fruits, vegetables, and other healthy crops could greatly benefit population health by helping to lower prices and make these foods more accessible to the populations that need them. While this is a long-term endeavor, shorter- or intermediate-term research can examine ways to improve availability, such as direct cash transfers. Ongoing research in Bihar, India is examining whether direct bank transfers mitigate the impacts of food insecurity (specifically in the context of the COVID pandemic) on household food quality (consumption of foods like pulses, green leafy vegetables, and milk) and modeling the potential impact of such cash transfers on stunting in India.[90,91] This is an area of research with large potential for expansion. For example, what would be the impact of these cash transfers in combination with nutrition education?

The cost-effectiveness of nutrition interventions also remains a relatively understudied area, both in India and globally. In the India-specific context, a better understanding is needed to determine whether provision of fruits and vegetables in meal schemes for children is cost-effective. For example, is an approach to provide more vegetables and fruits through the Integrated Child Development Scheme (ICDS) and the Mid-Day Meal program cost-effective in terms of the resulting health benefits, including adequate growth? Ongoing efforts with the Karnataka government ICDS to provide an additional 50 g ration of fruit and vegetables plus 100 ml of milk per day per child (including encouraging the Panchayati Raj Department to provide funding for additional high-quality foods) has a very high cost of four rupees per day, 50% more than is currently spent. Partnerships between agriculture, education, health, and finance sectors must address such questions jointly to provide cost-effective nutrition health solutions.

Policies to promote physical activity among the population are equally important as those promoting better nutrition. Physical activity policies may include providing support for comprehensive physical activity programs in schools or even requiring physical activity education in schools as part of a comprehensive health education curriculum to support an active lifestyle.[124] Educating the next generation of children can help to create a cultural shift that understands and views these issues as urgent. Additionally, and of particular importance, are research and efforts to design cities and towns that are conducive to physical activity. Without suitable policies and infrastructure to manage India's recent urban population growth, urban sprawl and traffic congestion has occurred, made worse by inadequate quality and safety of public transport and non-motorized transport infrastructure. Pedestrians and cyclists are most vulnerable to poor urban planning; pedestrians account for more than 40% of road traffic fatalities in New Delhi. In most Indian cities, barely 30% of streets have pedestrian pathways, and even where they do exist, they are often taken over for parking or driving. There are encouraging signs of improvement, however: Chennai has drafted non-motorized transport policies to create footpaths along 80% of its streets, along with infrastructure such as cycle lanes, with the promise that they will begin prioritizing people over vehicles.[125] Research evaluating the impact of such initiatives, as well as how to implement similar initiatives in other Indian cities, is needed. This could include experimental research to examine how the initiatives impact behavior (walking and cycling over driving), community engagement, and ultimately health. Community-engaged research could also uncover remaining obstacles/barriers to successful implementation, enabling such initiatives to fully realize their potential.

While many of the policies mentioned in this section are universal and are being implemented in countries around the world, there are unique features to implementation in the Indian context. For example, 176 million (13.4%) of India's population lives in poverty.[126] Designing cities and societies in which health-promoting attributes — whether these are screening initiatives, access to medicines, access to healthier food options, or safer walking paths—are either low-cost or free is essential. Additionally, the adverse effects of malnutrition in utero (due to a high burden of maternal malnutrition) means that metabolic conditions appear in younger ages in those exposed to malnutrition in utero.[20] This also has implications for screening and prevention services, which need to start at younger ages in India, and underscores the importance of health promotion across policies and sectors.[127]

3 Infrastructure Needs for Diabetes Research

Infrastructure needs for diabetes research in India should support deep dive physiological and molecular mechanistic research with animal and human models, tissue (like cadaveric islet, liver, and adipose tissue) biobanks, and the development of well-phenotyped cohorts that allow for developing risk models and disease progression. The needs can be summarized as four inter-related "C's"- cohorts, collaboration, capacity building, and community engagement and empowerment.

3.1 *Establishing Cohorts for Research and Learning*

India has always had an excellent clinical infrastructure (and patient load) to conduct high-quality clinical trials, validating approaches toward clinical care of established patients. However, these trials should move toward prevention at an early stage, perhaps even in childhood, and evolve toward a paradigm of precision in care and prevention across the lifespan. This will require the careful building of cohorts. Early age cohorts may be a good place to start, as the finding of an extraordinary burden of chronic disease biomarkers in a cross-sectional survey of Indian children between 5 and 19 years, including those who were underweight or stunted, suggests that the rapid increase in diabetes in the Indian population has its origins in early childhood.[20] This includes establishing representative and large cohorts of normal young individuals to understand the natural history of beta cell function, risk factors for development of diabetes, and development of diabetes-related complications. One can go further with nested trials to evaluate risk reduction efforts to prevent the development of insulin resistance and the deterioration of beta cell function. Cohorts of individuals (young and older) with and without existing diabetes and prediabetes are also required to understand the clinical course of the disease in Indian populations, which will also shape treatment outcomes. The last will also require nested trials of different risk reduction efforts and treatments for established disease, with long-term follow-up of these trial participants. As a starting point, existing Indian cohorts should be identified and collated, such that cross-cohort analyses are possible, simultaneously resulting in the creation of a network of investigators.

3.2 *Collaborative Skills and Approaches in Sciences, Humanities, Engineering, and Precision Medicine*

Beyond etiology, both public health and implementation science would benefit from interdisciplinary research, such as learning systems deployed in healthcare settings, and novel technologies for integrated care of comorbidities. Precision is fast becoming a buzzword, related to both clinical care and public health. Collaboration with engineering sub-disciplines, such as biomedical engineering and computer science, to produce wearables, develop artificial intelligence systems and validate predictive algorithms requires infrastructure to support computing needs and engineering R&D. A more ambitious infrastructure need relates to the development of biobanks, which would exist with the population cohorts as well as with human cadaveric islet banks, to enable molecular investigations to understand mechanisms of development of functional deterioration of beta cell function. Other banked tissues could include liver, skeletal muscle, and adipose tissue samples. This ambitious task includes multidisciplinary efforts to access human islet and liver in cadavers as well as muscle and adipose tissue in cohorts, with large implications for specimen management and tracking to facilitation efficient utilization of these assets in research while adhering to data privacy and cybersecurity policies. India has developed biobanks for diseases, such as cancer, brain disorders and liver diseases, but a biobank for diabetes research is lacking, and there is limited spare capacity beyond the needs of studies that receive funding to set them up.[128] Integration of such biobanks with electronic health records may provide an avenue for novel insights into disease etiology among Indians. This requires an extensive effort for transdisciplinary research and collaboration across medical and basic biological institutions. Barriers can include the siloed way in which research is often conducted, with separate siloes for basic and clinical science. Facilitating horizontal interactions between siloes and developing a new cohort of multidisciplinary researchers would be transformative in this area. Additionally, current resources are either not shared or are ineffectively shared. Sharing of resources developed under the proposed research framework, such as cohort data, HIMS data, banked specimens, and clinical trial information will not only allow for testing of new hypotheses, but the cross-pollination will also generate new hypotheses.

3.3 Human Capital Investments

Human capital, i.e., skills, knowledge and training, is important and must be specifically deployed for transdisciplinary research; no investment in infrastructure is complete without this component.[129] Research that spans transdisciplinary cell-to-society approaches must include intentional building of individuals as well as transdisciplinary teams that span institutions. Essentially, borders between institutions must become much more porous than their current state, and access and availability of resources (cohort or HIMS data, biobanks, etc.) should be widely advertised, such that multidisciplinary grants utilize these resources. This requires opportunities for training across different disciplines, including basic biology and whole-body physiology to measure insulin sensitivity and beta cell function, as well as innovations in monitoring individuals through precise measurements of functionality. Fields, such as computational biology, statistical genetics, engineering, nanotechnology, imaging, medical informatics, bioinformatics, mathematics, and social sciences, are also key toward building sufficient capacity to address India's diabetes research challenges. Although it will take time to build transdisciplinary human capital, this needs to begin by inserting these principles into curricular teaching and mission statements of colleges and institutions and used to develop opportunities for post-medical or post-doctoral training—to develop human capital for innovation interdisciplinary and intersectoral collaborations.

3.4 Community Engagement and Empowerment

The general public—both patients and non-patients—is critically important to advance diabetes research in India. They are not simply valuable resources as volunteer participants for studies, but also as drivers of research, as user-inspired research is becoming increasingly important to funding agencies. Public engagement is thus a critical part of infrastructure development, and the public, healthy or otherwise, should be educated and engaged as enthusiastic participants in cohorts, trials, and basic physiological research, and empowered as voices that can call for more research in specific areas.

4 Concluding Remarks

Diabetes represents a major public health and economic challenge for India, and its solution requires an ambitious and innovative interdisciplinary research agenda. Implementing such an agenda can propel science in India toward approaches to solve diabetes, and can also be an exemplar for other areas and problems.

Data availability

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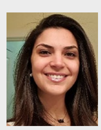

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