

# Need of Countrywide Genetic Risk Scores (GRS) or Polygenic Scores (PGS) for Type-2 Diabetes Mellitus

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The recent surge in the cases of type-2 diabetes mellitus (T2DM) needs to be intervened with short and long-term guards and much needful preemptive explorative efforts. Unfortunately, the existing efforts still fall short. As per WHO data, Pakistan has climbed up the world diabetes ranking with a prevalence close to 15%. The factual position may be even worse due to the lack of undiagnosed cases in the poverty-stricken country with limited resources.<sup>1,2</sup> This will burden not just diabetes therapeutics, but additional workload in ophthalmology for retinopathy, cardiac centres for atherosclerotic cardiovascular diseases, neurology for neuropathies and nephrology for early-onset chronic kidney diseases. While resource bound in every possible way, human productivity will be at a loss and money will be wasted if preventive strategies will not be evolved and implemented with full-thrust. Though primary preventions stand as the key intervention, still lessons can be learnt from the various evolving concepts by doing risk profiling especially the genetic risk scores (GRS) which can highlight the prevailing genetic predispositions among our much-varied racial population.<sup>3</sup>

GRS, also sometimes termed with different nomenclature like polygenic score (PGS) implies a numerical count calculated by the adding the presence of certain specified alleles which can lead to genetic predispositions for a given medical condition or trait in a biological creature at the time of birth.<sup>4</sup> Central to the concept is to understand that GRS does not include epigenetic changes which appear after birth due to environmental factors in life. Evaluation of genetic trends as GRS implies measurement of various genetic alterations like single nucleotide polymorphisms (SNPs), which can help geneticists calculate the wholesome risk by adding the risk of individual variants in a numerical manner.<sup>5</sup> The technical methods leading to the development of a disease-specific GRS or PGS incorporates number of associated genetic alleles, effect size, and statistical significance, which allow the final mathematical and statistical calculation of numerical scores.<sup>6</sup>

It is believed that an appropriate and optimal utilisation of GRS data may surface as the new norm in the field of medicine. There are studies which signify the utility of GRS and PGS scores in translational research and slowly and steadily the system is creeping into the mainstream medical system. A multicentre study utilising 400 genome wide association studies identified 400 genetic variants, which could not only help in prediction of T2DM but also provided insight into the subgroups / phenotypes *i.e.*, phenotype-genotype linkage into clinically different T2DM subtypes. However, the authors highlighted multiple limitations in the widespread personalised screening and therapeutic usage.<sup>7</sup> Another small-scale Mexican study utilised a GRS based upon 10 single nucleotide polymorphisms (SNPs) in children less than 18 years to highlight that T2DM prediction can be improved.<sup>8</sup> Similarly, Parna *et al.* developed a strengthened GRS scoring method, called doubly-weighted GRS (dwGRS) which enabled better incident T2DM risk prediction along with the guidance on T2DM phenotypes.<sup>9</sup> There are other studies which have shown the use of such scores to be more predictive with pharmacogenomic targeting and in future may become the cornerstone of precision medicine in T2DM.

GRS or PGS while seems like future genetic modes to predictive and individualised medicine, still remain evolutionary with South Asian countries struggling to adopt preliminary genetics into the system. While the aforementioned discussion establishes the dire need for these genetic techniques, we remain barricaded with the mammoth burden of T2DM at one end and then poverty-ridden population at the other. Both these dimensions need some preemptive diagnostic, lifestyle, and therapeutic measures starting from today to address the metabolic pandemic. While we plan to adopt GRS or alike system in the local diagnostic care pathways, certain limitations also need to be understood. Polygenic risk scores or GRS only provide relative risk scores due to the multiple external influences like accidental deaths and exposure to certain epigenetic triggers, which add to the risk contribution in different ways for the development of a specific trait or disease.<sup>4</sup> Different countries have evaluated their own population and apparently, it appears that there are genotype differences in T2DM leading us to place more emphasis on local data addressing the region's racial differences.<sup>10</sup> Technical issues posing as obstacles for ensuring uniformity of GRS adoption include differences in methodology, number and types of SNPs included, algorithmic variations, and deep learning techniques especially in pruning causing differences in threshold definitions.<sup>11</sup> Another situation which can

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affect GRS is linkage disequilibrium (LD), where SNPs for their independent evaluation compromise the predictive capability of the score.<sup>12</sup> However, various bioinformatic and statistical tools have been evolved to address these technical issues like using a specified software for detection.

The current understanding of Genetic Risk Scores, resource constraints related with molecular lab development and limited molecular sciences experts is evident from paucity of data about GRS evaluation in the Pakistani population. However, there are some work being done on the Pakistani population. Shabana *et al.* have developed a GRS for coronary heart disease by identifying SNPs among IL-6, ITGB3, PON1 and ALDH2 genes to suggest specific genetic risk scores for Pakistani population.<sup>13</sup> Rana *et al.* have worked on certain obesity genes like MC4R, FTO and TMEM18 to identify certain specific variants in the Pakistani population predisposing to weight gain.<sup>14</sup> A recent study on T2DM Pakistani patients identified that 16 SNPs were in equated prevalence among our population in comparison to SNPs identified in T2DM patients from European ancestry.<sup>15</sup> This trend highlights for Pakistani molecular sciences community to acknowledge the importance of developing race-specified GRS in general, T2DM, and obesity in specific. However, these efforts seem insufficient and more data is needed for specific diseases, especially T2DM.

The way forward for Pakistan is to develop a real-time consensus-based GRS for T2DM with various racial groups and relate their genotypes within phenotypes to help out decipher the heterogeneity of disease, providing predictive tools for the pharmacogenomic intervention and most importantly to guide the possible association with short and long-term complications. The end-points from this communication may allow researchers, diabetologists, diagnosticians, healthcare policy-makers and experts in the healthcare economy to curb the evil in the budding stage. While primary preventions remain central but deep-down data from genomics and molecular pathology will allow diabetes prevention and management thus providing the final punch to this growing pandemic in our population. Genetic epidemiology assessed via GRS scoring in T2DM in various racial groups can emerge as a valuable primary intervention guide and later on in therapeutics.<sup>10</sup>

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