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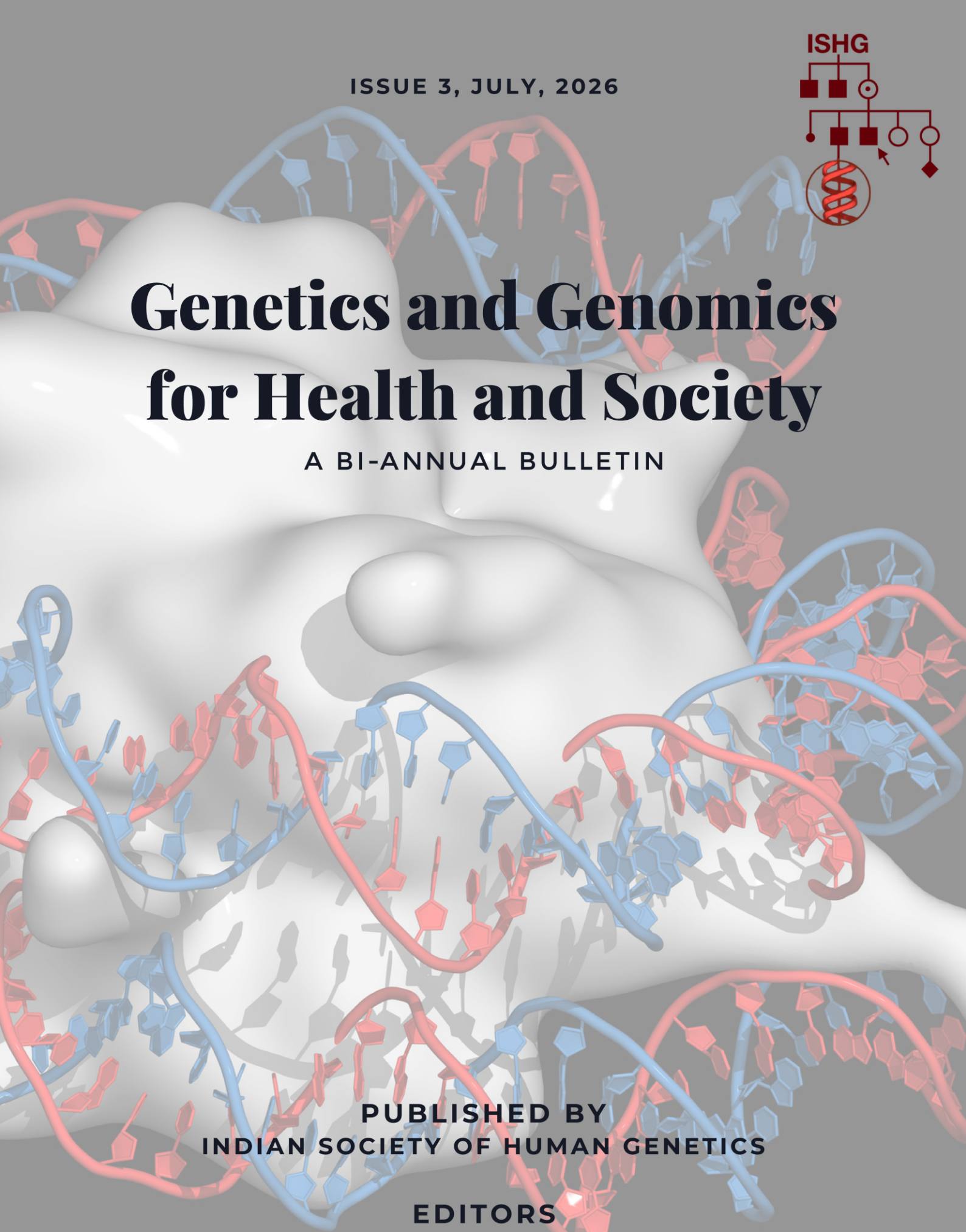

Genetics and Genomics for Health and Society

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Message From **EDITORS' DESK**

Prof. B.K. Thelma

Prof. Monojit Debnath

"Dear Readers,

Greetings to you!

Over six decades have flown by since the visionaries of yore- both basic research scientists and clinicians put their hearts and souls for laying the foundations for a non-profit making society with an aim to spread the necessity for conducting human genetics research in India. Their early focus of research was anthropocentric, particularly population studies, but such initiatives motivated fellow scientists and clinicians to expand them into genetic studies relevant to human health and disease. The ideation was in Pune, at B J Medical college, with Dr G. S. Mutalik a clinician, and Prof. K C Malhotra at Deccan College; followed by active involvement of several like-minded colleagues in Pune and Mumbai and a few more from other parts of the country, to achieve the above goal. Discussions continued, years passed, and, eventually, the Indian Society of Human Genetics (ISHG) was established and formally registered in Pune in 1973. Dr L D Sanghvi was the first President and Dr G.S Mutalik was the founder Secretary. The fledgling organisation was nurtured, and gradually transformed into a vibrant society under the stewardship of renowned geneticists across India, navigating different challenges. Over the decades, the ISHG has made its strong and purposeful presence among the Indian researchers, and continues to engage in the contemporary pursuit of genomic science and carry forward its ethos with the successive generations of young researchers. As we celebrated 50 glorious years of the ISHG's annual meetings at PGIMER, Chandigarh, in February 2026, the attendees had an opportunity to hear from four senior most members namely Prof. Partha Majumder, Prof. Jai Rup Singh, Prof. Kanjaksha Ghosh and Prof. Ramesh Bamezai of the society, who reflected on the history and growth of the society, as well as the contribution made by them and their fellow scientists to human genetics in India. They recounted the challenges, the triumphs, and, the vision and relevance of the initiatives of the ISHG over the decades. They also made recommendations and shared their wisdom for the future and formulated a task list that encompassed the work required to keep up with global trends. This wonderful celebration of the ISHG and its journey evoked joy and appreciation in the members, both Juniors and seniors, and will be cherished as an important milestone in the journey of ISHG. The four doyens who spoke at the meeting also captured the essence of their talks in the four articles included in this issue of the Bulletin. It is heartening that all of them continue to be active in their respective arenas- including mentoring, sharing their considered opinions and imparting their wisdom to their next generation of colleagues. The society is indeed very fortunate to have Prof. KC Malhotra, from amongst the founding members and the third President of ISHG (who sadly could not be present in person during the golden jubilee celebrations), who continues to share with great pleasure and enthusiasm, his precious memories of the genesis, vision and journey of the ISHG with interested members who have followed him into the society.

The early field-based biological anthropology studies were soon strengthened by an increase in laboratory-based research activities, largely biochemical genetics and human cytogenetics with diagnostic implications. Such developments attracted several clinicians throughout India to join the ISHG fraternity. With advances in molecular genetic analyses tools, some members of the society made major strides in various domains of human genetics and also established national and international collaborations.

This may sound like reminiscences of a bygone era, but the strong foundations laid during those early years empowered subsequent generations with the skills to leap into biomedical genetics. It would not be inappropriate to mention that a large number of cytogeneticists in diagnostic settings in the USA until late 1990s were of Indian origin and received their early research training in different cytogenetics labs across the country. It is important to remember that Cytogenetics and Molecular cytogenetics with newer molecular tools and improved precision remain integral to contemporary genetic diagnosis. An interesting note, what were considered basic chromosomal or genetic diagnostic tools in a clinic, over the years, were increasingly applied to prenatal diagnosis and subsequently pre-implantation genetics, which has now carved its own big niche involving clinicians and geneticists, in their efforts to predict and prevent genetic/chromosomal anomalies and offer help in the completely different setting of assisted reproduction. This not only changed the focus from science to commerce but, as all of you know, has made significant strides towards the cure or treatment of genetic conditions with the magic wrought by CRISPR-based gene editing technology.

It is not surprising that as times have changed, the nature and depth of the work in science have also changed, but it is important to revisit the old principles while staying relevant. With technological advances bringing with them the threat of misuse, especially in the area of biomedical genetics, and consequent ethical issues, governance is of critical importance. Regulations in clinical practice and work in laboratory settings are essential to help us continue to fulfil our responsibility towards society at large.

Conforming to the principle of continuity that underlies scientific progress, a seamless integration of science currently being done by the ISHG fraternity, with the old paving the way for the new, with all the excitement and promise it holds, has been witnessed at each ISHG annual conference over recent years. While tools and technologies are evolving and being refined at an overwhelming pace, the transformation of fundamental understanding of the core aspects of the genetic regulation of the life processes are occurring only incrementally. The time spent from the conception of the central dogma of molecular biology and its revision in the 1970s and emergence of yet another revolutionary paradigm in the Omics era revolving around RNA biology has though not been a long period, a magnificent progress is witnessed. The shift from DNA centric to RNA centric

research is very evident. The unravelling of the important facets of RNA biology has made it a crucial candidate for dissecting the complex trajectories of human diseases including rare diseases as well as for developing next-generation therapeutics. In literally a volte-face from the concept of junk DNA to regulatory implications, RNA of different kinds, with multitude of biological functions, and big time use in RNA therapeutics has emerged in the last decade. The power and progress including global efforts and opportunities in our understanding of the non-coding RNA; and impact of this new science on precision medicine and personalised therapy, with success stories and challenges are effectively reflected in the other articles in this issue of the bulletin.

Finally, it is imperative that the ISHG (as also indicated by RNKB in his article here), as an important body of human geneticists/biomedical scientists, should engage actively with the relevant national bodies in the formulation of policy, governance, prioritisation of research funding for growing Public Health issues, guidelines for data sharing etc, for which models abound globally. Nothing is static but the direction in which progress is made is the responsibility of the respective players and ethics will be the most important element in today's fiercely competitive science. To quote from Roy T. Bennett's The light in the Heart "The past fades into shadow, offering lessons to heed; the future stretches before us, a promise yet to be fulfilled; the present unfolds as a gift, asking only to be embraced".

Warm regards,

Prof. B.K. Thelma
Prof. Monojit Debnath

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Report of the 50th Annual Meeting of the Indian Society of Human Genetics (ISHG 2026), Postgraduate Institute of Medical Education and Research, Chandigarh, 5–7 February 2026

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The 50th Annual Conference of the Indian Society of Human Genetics (ISHG 2026) held from 5th to 7th February 2026 at the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, marked a historic milestone in the journey of human genetics in India. Celebrating the Golden Jubilee of ISHG, this landmark conference was organized by the Departments of Hematology and Pediatrics, PGIMER, and brought together leading clinicians, scientists, researchers, and trainees from across the country and abroad.

The theme of the conference, "Golden Jubilee Celebration of Decoding Genetics: Transitioning to Translational Genomics," aptly reflected the field's evolution from fundamental genetic discoveries to its growing application in clinical medicine. Over five decades, human genetics has transformed from a niche discipline into a cornerstone of modern healthcare, influencing diagnosis, prognostication, and therapeutic decision-making across specialties. ISHG 2026 served as both a celebration of past achievements and a forward-looking platform to discuss the integration of genomics into routine clinical care.

The conference was held under the chairmanship of Prof. Reena Das and Prof. Inusha Panigrahi, whose leadership and meticulous planning were central to its successful execution. The organizing team received strong and enthusiastic support from Prof. B. K. Thelma, President of ISHG, and Prof. Monojit Debnath, Secretary of ISHG, as well as from the Society's Executive Committee, all of whom played an instrumental role in shaping the scientific and organizational framework of this landmark event.

The conference witnessed robust participation, with over 120 faculty members, 350 registered delegates, and a dedicated organizing team of around 60 members ensuring seamless execution. A total of 259 abstracts were received, reflecting the growing depth and diversity of research activity in human genetics across India.

The conference commenced with an inaugural ceremony graced by Prof. K. K. Talwar, former Director of PGIMER and former Chairperson of the National Medical Commission. A special Golden Jubilee reminiscence session titled "The Journey of Human Genetics in India" brought together pioneers of the field, including Prof. Partha Majumder, Prof. Jai Rup Singh, Prof. Kanjaksha Ghosh and Prof. R. N. K. Bamezai.

The scientific program was thoughtfully curated to balance foundational knowledge with cutting-edge advances, and basic science with clinical translation. Spread over three days, the conference featured plenary lectures, keynote talks, symposia, concurrent sessions, oral presentations, poster discussions, and stimulating panel discussions.

Sessions began with a presidential address by Prof. B. K. Thelma, who delivered a lecture titled "Revisiting Principles of Ancient Medical Wisdom: Obtaining New Insights into Complex Disorders," focused on ayurgenomics. The plenary sessions featured internationally renowned experts. Dr. Danny Miller (University of Washington, Seattle) delivered an insightful lecture on the future of human genetics, emphasizing the transformative potential of long-read sequencing technologies. Another highlight was the plenary lecture by Dr. Samuel Chong (Singapore), who elaborated on the role of pre-implantation genetic testing (PGT) in reproductive medicine.

The second day featured a special spotlight session on the application of artificial intelligence (AI) in genetics and oncology. Dr. Jatinder Lamba (USA) discussed the development of digital atlases for cancer diagnosis, while Dr. Debarka Sengupta (IIIT Delhi) discussed the application of AI in modeling drug response and accelerating oncology drug development. This was followed by another plenary session where Dr. Naval Daver (MD Anderson Cancer Center, USA) highlighted advances in targeted therapies for acute myeloid leukemia, including emerging strategies

such as FLT3 inhibition and combination molecular therapeutics, underscoring the transition toward precision oncology.

The third day further strengthened the meeting's translational focus with three important plenary lectures. Dr. Bushra Ateeq (IIT Kanpur) discussed the molecular underpinnings of genetic complexity in prostate cancer and their implications for targeted therapy. This was followed by Dr. Mark Fleming (Boston Children's Hospital), who emphasized the challenges and opportunities in translating genomic discoveries into clinical practice in pediatric genetic disorders, with a focus on sideroblastic anemia. The concluding plenary by Dr. Indumathi Mariappan (inStem, Bengaluru) addressed the current status and future readiness of gene therapy for inherited genetic diseases, highlighting its promise as a transformative therapeutic modality.

Beyond the plenary sessions, the scientific program featured a wide range of concurrent thematic sessions covering functional genomics, disease modeling using induced pluripotent stem cells (iPSCs), epigenetic regulation, RNA biology, genome integrity, and clinical genomics. These sessions included discussions on diverse topics such as neurodevelopmental disorders, cancer genomics, mitochondrial biology, CAR-T cell therapy, pharmacogenomics, and rare genetic diseases, reflecting the breadth and translational depth of contemporary human genetics research.

Two panel discussions added significant value to the scientific discourse. The first panel focused on targeted therapy for lysosomal storage disorders, bringing together experts to discuss emerging therapeutic strategies and the translational challenges in this specialized area. The second panel, titled "Advances in Genomic Medicine: From Diagnosis to Personalized Therapy," was moderated by Prof. Binay Panda and drew a distinguished panel comprising clinicians, laboratory scientists, and industry representatives. This wide-ranging discussion spanned a broad spectrum ofissues, from ethical considerations in genomic medicine to quality control in laboratory testing reflecting the multidisciplinary nature of modern genomics and the collective responsibility of all stakeholders in advancing its responsible clinical applications.

The program also incorporated industry sessions on next-generation sequencing and multi-omics, emphasizing the role of emerging technologies in bridging the gap between discovery research and clinical applications.

A major highlight of the conference was the ISHG Young Scientist Award (YSA) session, which showcased nine outstanding research presentations from early-career investigators. The first prize was awarded to Tahseen Ahmed (BRIC-NIBMG, Kalyani), followed by Madhubala Sharma (second; PGIMER, Chandigarh) and Chitra Bharadwaj (third; PGIMER, Chandigarh). The Next-Generation Investigator session, comprising five shortlisted researchers, showcased cutting-edge research, with Ravina Taak (PGIMER, Chandigarh) adjudged the best presenter.

The conference also featured 17 free oral paper presentations across multiple themes, including cardiovascular genetics, oncology, and rare diseases. Poster sessions were a vibrant component of the conference, with 228 posters presented over two days, spanning topics such as bioinformatics, pharmacogenomics, hematology, neurology, endocrinology, and medical genetics.

The conference also recognized excellence through prestigious awards. The Prof. I. C. Verma Lifetime Achievement Award was conferred upon Prof. Mammen Chandy, a pioneer in hematology and bone marrow transplantation in India.

Industry participation played an important role in the conference, with several leading global and national organizations supporting the event, reflecting the strong interface between academia and industry. Beyond scientific deliberations, the conference also provided ample opportunities for networking and informal interactions among delegates.

In conclusion, the 50th Annual Meeting of the Indian Society of Human Genetics was a resounding success, both scientifically and organizationally. The conference not only celebrated five decades of progress in human genetics but also highlighted the dynamic transition towards translational genomics and precision medicine. Under the dedicated stewardship of its organizers and the unwavering support of the ISHG leadership, ISHG 2026 set a high benchmark for future conferences and reaffirmed the Society's commitment to advancing human genetics for the benefit of patients and populations.

Genesis and Evolution of Population Genetic Studies in India

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Genetic studies in Indian populations had an early start. Since its inception, the Indian Society of Human Genetics (ISHG) played a leading role in catalysing population genetic studies. The proceedings of the first ISHG conference, edited by L. D. Sanghvi and published by Orient Longman, New Delhi, in 1974, was titled Human Population Genetics in India. The paper I presented at the first ISHG conference – as an undergraduate student of the Indian Statistical Institute (ISI) – on the prevalence of hypertrichosis of the ear (hairy pinnae) and its mode of inheritance was published in these proceedings (pages 269–276).

I have been attending the annual ISHG conferences for a long time. My memory of the journey of human genetics through ISHG has faded considerably. Nevertheless, I shall try to recall as much as I can, and as honestly as I can. It is not unlikely that I will miss describing some landmarks and naming some leaders. I beg to be excused for my failing memory.

Population genetics studies in India have mainly focused on genetic affinities and differences among populations. The measurement of population affinities using genetic data was preceded by the use of anthropometric data. Among landmark studies, B. S. Guha, as part of the 1931 Census of India, collected body measurements from numerous tribal and caste populations and published his findings in a report titled Racial Affinities of the People of India. He later extended these analyses and published the 1944 book Racial Elements in the Population (H. Milford, London).

Mendel's laws were rediscovered in 1900. Soon thereafter, intensive efforts were made to understand the inheritance of human traits such as height. Karl Pearson led these studies in England. Because methods for analysing such data did not exist, Pearson invented various methods, including correlation and regression, to quantify relationships between trait values – for example, the heights of parents and their children.

In 1915, Prasanta Chandra Mahalanobis – who founded the Indian Statistical Institute in 1931 – returned to Calcutta (now Kolkata) from King's College, London, for a vacation after completing his Tripos. He had intended to return to England to do his Ph.D. The war intervened. He could not return to England. Brojendranath Seal, Professor of Philosophy of Calcutta University, told him "Prasanta, you have to do in India similar to what Karl Pearson has done in England." Mahalanobis took this advice seriously. In the mid-1930s, he met D.N. Majumdar, an eminent anthropologist, and the two together designed and conducted a study among 22 population groups of the United Provinces (comprising primarily parts of Uttar Pradesh and Uttarakhand) at various levels of social hierarchy and acculturation. C.R. Rao – an associate of Mahalanobis who later rose to great heights as a statistician – joined them and analysed the anthropometric measurements collected. Two main conclusions of this study were: (i) "Among the groups ... there is close correspondence between social status and resemblance to the Brahmins," and (ii) "There are a number of cases in which physical evidence definitely indicates possible origins contrary to accepted opinion." This anthropometric survey of populations resulted in the invention of the most widely used statistical measure of group affinity using quantitative data – Mahalanobis' D2. Shortly thereafter, a similar survey was undertaken in undivided Bengal (now, West Bengal and Bangladesh). The Bengal anthropometric survey report published in 1945 provided some interesting insights: (i) "One of the important contributions ... is the demonstration of regional differences within a social group, that is, between individuals adopting the same caste, tribal or religious name (label), but living in different areas (districts). ... This shows that a term like 'Brahmins of Bengal' has to be used with some caution" (ii) "Another interesting feature ... is that sometimes there is closer resemblance between caste groups within a district than between individuals of the same caste group belonging to different districts." Such inferences led Mahalanobis to conclude that "Anthropometry alone cannot tell the tale (rephrased as 'about population affinities in relation to social affinities' by the author); we have to supplement by other physical, genetic and serological data ...". ABO blood group data were then collected from several of the population groups included in the Bengal study. But these data also did not provide useful inferences. D.N. Majumdar then stated "Until we have reinforced our findings by data on other systems, MNS and Rh, we do not think the picture of blood

groups based on the ABO system, can give any clue to ethnic origin of the castes in Bengal, or for that matter, of any other part of the country." What a scientifically prophetic statement!

Even after the U.P. and Bengal anthropometric surveys, similar surveys were undertaken in other regions of India; for example, by Irawati Karve and V.M. Dandekar published as "Anthropometric Measurements of Maharashtra," 1951. In 1961, S.S. Sarkar published his "Racial classification of India" in the Bulletin of the Anthropological Survey of India.

In 1953, L. D. Sanghvi published a seminal paper titled "Comparison of genetical and morphological methods for a study of biological differences," in the American Journal of Physical Anthropology, based on his Ph. D thesis at Columbia University, USA, proposing the first measure of genetic distance between populations. Sanghvi, who later founded ISHG and was its first President, helped shift population studies toward genetic data, in conformity with Mahalanobis's recommendation. A landmark 1962 study was published in the American Journal of Physical Anthropology titled "Study of blood groups, abnormal hemoglobins and other genetical characters in some tribes of Gujarat" by G. N. Vyas, H. M. Bhatia, P. K. Sukumaran, V. Balakrishnan, and L.D. Sanghvi. Bhatia, Sukumaran, and Balakrishnan were founding or early ISHG members; Balakrishnan served for many years as Treasurer.

Kailash Chandra ("KC") Malhotra is a founding member of ISHG who did his Ph. D with Irawati Karve and has been an enthusiastic organizer and supporter of many activities of ISHG. Karve and Malhotra published "A biological comparison of eight endogamous groups of the same rank" in 1968 in Current Anthropology. Among many powerful inferences, they wrote "Although the data from a biological survey cannot positively confirm a sociological hypothesis (rephrased as 'such as the one that they sought out to test' by the author); it is significant that there is nothing in the data to contradict it."

The Anthropological Survey of India (AnSI) then carried out a large number of genetical studies among populations in many local regions of India. The results of these studies were regularly presented in the annual conferences of the ISHG. Thus, ISHG provided not only a platform for presentation of the results of these studies, but the post-presentation discussions promoted empirical studies on population genetics in India.

In 2021, the AnSI compiled a book that embodied the independent and collaborative work of 49 scientists and was the output of AnSI's national project "DNA polymorphism of contemporary Indian population." The book was published under the title *"Genomic Diversity in the People of India."*

As I stated earlier, KC played a key role in promoting the ISHG and population genetics in India. He was the Indian P.I. of a collaborative project between India and the USSR Academy of Sciences. During the decade of the 1970s, a large number of papers were published from the work done in this collaborative project, primarily pertaining to population groups of western and northern India. I was then doing my Ph.D at the ISI. I was asked to carry out statistical analyses of these data; I did so and co-authored many of the papers published from this project. This project provided a fillip to the biochemical genetics laboratory of the ISI, under the supervision of Biswa Nath Mukherjee jointly with Swapan Kumar Das. Subsequently this laboratory became a "go to" laboratory for many human geneticists in India. S.L. Kate and J.V. Undevia, senior members of ISHG, who carried out genetic studies among the Parsees and other populations of Maharashtra were closely associated.

The report of the "All India bio-anthropological survey" carried out by the AnSI was published in 1988. The first volume of the People of India project spearheaded by the Director-General of AnSI, Kumar Suresh Singh, was published by Oxford under the same title in 1985. Bio-ethnographic descriptions of many other Indian States were subsequently published.

The ISHG and the Indian Anthropological Society jointly published, in 1981, the results of a major population biology project under the title "Biology of the People of Tamil Nadu," with L.D. Sanghvi, V. Balakrishnan and Irawati Karve as "contributors."

Genetic studies of Indian populations expanded rapidly in the 1980s and 1990s, aided by new technologies for detecting genomic variation, including restriction fragment length polymorphisms (RFLPs). The Department of Biotechnology funded the collaborative GENDIPP (Genetic Differentiation in Indian Populations Project), which I proposed and which was carried out by ISI (P.I.s: Bidyut Roy and myself), Indian Institute of Chemical Biology (P.I.: Susanta Roychoudhury), and Saha Institute of Nuclear Physics (P.I.: Nitai P. Bhattacharyya). This pioneering pan-India, multi-institutional effort provided a reasonable view of genetic differentiation and structure among ethnic populations across India, although it was based on only about 40 genetic markers.

There was recognition that a larger number of genetic markers was required for reliable estimates of population genetic differentiation. Around 2000, Samir K. Brahmachari – then Director-General of the Government of India's Council for Scientific and Industrial Research (CSIR) – initiated what was then India's largest population-genetic study. The Indian Genome Variation Consortium, led by Institute of Genomics and Integrative Biology and including several CSIR institutes and the ISI, analysed 1,870 individuals from 55 population groups using 405 genomic markers. Published in 2008 in the Journal of Genetics as "Genetic landscape of the people of India: a canvas for disease gene exploration," the study yielded important insights pertaining to both population genetics and medical genetics.

It was then of obvious interest to understand the evolutionary relationships of Indian populations in relation to the rest of Asia. Under the leadership of the President of the Human Genome Consortium (HUGO), Edison Liu, a Pan-Asia SNP Consortium was formed, in which several of us from India participated. Genotypes at 54794 autosomal SNP loci on 1928 individuals representing 73 Asian and two non-Asian populations (for calibration) were generated and analysed. The results published in Science in 2009, showed among other important conclusions, that Indian populations evolved earlier compared to most other Asian populations.

Another landmark study carried out by Lalji Singh and K. Thangaraj – both former Presidents of ISHG – jointly with David Reich and his colleagues at the Broad Institute, USA, was published in the same year (2009). Their paper in Nature titled "Reconstructing Indian population history," concluded that contemporary populations of mainland India resulted from admixture between two ancient ancestral populations which they termed as ASI (ancestral south Indian) and ANI (ancestral north Indian).

Later, by more extensive population sampling, we estimated that the number of ancestral populations was four, not two. Our paper was published in the Proceedings of the National Academy of Sciences, USA, in 2016.

Spencer Wells launched The Genographic Project in 2005 and collaborated with Indian scientists led by RM Pitchappan. This project resulted in the creation of a mitochondrial DNA database and some interesting population-level inferences from mtDNA data of Indians.

With the advent of whole-genome sequencing, a project was undertaken to sequence genomes of individuals from different Asian populations to draw evolutionary, and also medical (e.g., prediction of responses to drugs) inferences. About 600 individuals from about 40 populations of India were sequenced. The results were published in Nature in 2019.

DBT has coalesced a great leap forward by funding a whole-genome sequencing study of 10000 Indians. A commentary "Mapping genetic diversity with the GenomeIndia project" has been published in April 2025 in Nature Genetics. We are anxiously awaiting the publication of the results.

The ISHG and members of the Society have played prominent roles in initiating and expanding genetic – later genomic – studies on population groups of India.

The Golden Decade of Human Genetics in India (1990–2000): Molecular Transition and Institutional Growth

Jai Rup Singh[1] and Anjana Munshi[2]

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The decade from 1990 to 2000 marked a defining phase in the growth of human genetics in India. It was during these years that the discipline moved from a focused academic specialty of population genetics (detailed by Prof. Partha Majumdar, in the preceding chapter) into a rapidly expanding scientific and clinical field. The discipline underwent a major transformation from a largely descriptive science based on classical genetics, cytogenetics, anthropology and biochemical markers into a clinically relevant, and molecularly driven multidisciplinary field. The period witnessed the introduction of molecular diagnostics, establishment of specialized centres and departments, rapid expansion of trained manpower, strengthening of national and international collaborations, and recognition of India's unique genetic diversity. The foundations laid during this decade ultimately prepared the country for the genomic era.

Prior to this period, several pioneers played a crucial role in laying the foundations of human genetics in India. As an off-shoot of an active Anthropology Department, headed by Prof. M.R. Chakravartti, the Department of Human Genetics in Andhra University was the first to be established in 1972 in the country. The focus was on large scale population studies of tribal and non-tribal groups, of human variations at multiple levels, and phenotype-to-genotype (not contemporary genotype-to-phenotype) correlations initiated by eminent leaders including Profs. P. Veerraju, Venkateshwara Rao and others. Late Prof. Archana Sharma, at the University of Calcutta contributed extensively to human cytogenetics and environmental mutagenesis (in addition to her primary affiliation with the Botany Department, Calcutta University and her pioneering work in plant cytogenetics). Late Prof. I.P. Singh initiated human cytogenetics in the Anthropology Department at the University of Delhi and, along with Prof. M.K. Bhasin, strengthened anthropological genetics and studies on population diversity. Their work provided valuable baseline information for later molecular studies on Indian populations.

In the early 1990s, cytogenetics in India was still largely dependent on light microscopy and G-banding techniques for the identification of chromosomal abnormalities. While these methods were useful for detecting major chromosomal alterations, they were inadequate for identifying submicroscopic changes. The adoption of molecular approaches in cytogenetics significantly changed the landscape. The introduction of molecular cytogenetic techniques like fluorescence in situ hybridization (FISH) led to the improved evaluation of chromosomal anomalies in interphase nuclei as well as at metaphase stage. This technique improved the diagnostic accuracy of congenital disorders, different cancers, etc. and served as an important bridge between molecular genetics and classical cytogenetics. The transition from descriptive cytogenetics to molecular-based diagnostics became one of the defining developments of this decade. The laboratories across various parts of the country gradually adopted these technologies and thereby created a very strong bedrock for genetic diagnostics and research in the subsequent years.

The entry of genetics into mainstream clinical medicine was led by a group of visionary physicians and scientists. Late Prof. I.C. Verma at AIIMS, New Delhi played a pioneering role in integrating molecular genetics into prenatal diagnosis, dysmorphology and genetic counselling. His work highlighted the burden of inherited disorders in India and the urgent need for community-based genetic services. To name a few others, late Prof. I.M. Thomas, affiliated with St John's Medical College, Bengaluru contributed significantly towards strengthening medical and human genetics in southern India. Prof. P.P. Reddy at the Institute of Genetics, Osmania University, Hyderabad contributed extensively to cytogenetics and genetic diagnostics. Late Prof. Y.R. Ahuja, Department of Genetics, at Osmania University worked on mutagenesis, chromosome instability and fragile X. At AIIMS, New Delhi, Prof. Kiran Kucheria introduced molecular cytogenetics and regularised interphase FISH diagnostics while Prof. N.K. Mehra pioneered immunogenetics and studies on HLA-associated

disease susceptibility. Prof. Madhulika Kabra associated with Late Prof. I.C. Verma primarily worked on cytogenetics, inborn errors of metabolism and some early PCR based testing of common genetic diseases. At SGPGIMS, Lucknow, Late Prof. S.S. Agarwal established one of India's first independent departments of medical genetics within a teaching medical institution. The department became an important centre for biochemical screening, molecular diagnostics, prenatal diagnosis and specialised training in medical genetics. It also helped produce a generation of clinicians and researchers who have subsequently established medical genetics programmes in different parts of the country.

During this time, Guru Nanak Dev University (GNDU), Amritsar, emerged as an important centre for human genetics under the leadership of Prof. Jai Rup Singh (the lead author of this article). The university established the Centre for Genetic Disorders and developed teaching programmes including M.Sc., M.Phil., and Ph. D courses in Human Genetics. Automated karyotyping, molecular cytogenetics, and population genetics studies were introduced during this period. GNDU also organised several national and international workshops and symposia that helped train young researchers across the country. The university developed collaborations with numerous national and international institutions and emerged as one of the active centres for human genetics training and research during the decade. Prof. Thelma B.K., of the Department of Genetics, University of Delhi south campus, was the first to provide molecular diagnosis for pre-mutation and full mutation of Fragile-X syndrome to probands and extended family members, referred by clinicians across India. Several other scientists contributed significantly during this period. Prof. H.K. Goswami, Barkatullah University, Bhopal, and late Prof. P.M. Gopinath at Madras University strengthened cytogenetics research. Dr. Frenny Sheth and Dr. Jayesh Sheth at FRIGE in Ahmedabad expanded prenatal diagnostic services in the private sector. Major contributions came from Prof R.N.K. Bamezai and Prof. B.K. Thelma in northern India; Prof. Geeta Talukder and Dr. A.R. Banerjee in eastern India, Dr. Usha Dave, Dr. Hema Purandare and Dr. Prochi Madon in private genetic services, and Prof. B.N. Apte in newborn screening and metabolic disorders, in Mumbai. Prof. Shubha R. Phadke at SGPGIMS, Lucknow made major contributions in dysmorphology and clinical delineation of syndromes linked to molecular defects.

Ocular genetics emerged as one of GNDU's strengths. A group of scientists, led by Prof. Jai Rup Singh and Dr. Daljit Singh, conducted numerous research projects on congenital cataract, glaucoma, and retinopathies. It resulted in the discovery of about 150 phenotypes of congenital cataract and helped in locating some of the genetic defects, besides building up an important biobank. This research work helped in gaining a good understanding of hereditary ophthalmic problems in Indian families, as well as establishing links with other researchers internationally. At Shankara Nethralaya, Chennai, under the leadership of Dr. G. Kumaramanickavel, molecular genetics was applied to eye problems, and many retinal disease markers were identified.

A few other specialised areas in human genetics emerged in response to clinical needs and the country's highly endogamous population. The public health threat of haemoglobinopathies prompted the establishment of the ICMR-NIIH (Mumbai), directed by Dr. Dipika Mohanty. In-depth molecular studies on thalassemia, sickle cell disease, and other haemoglobin variants provided detailed mapping of mutations in different ethnic and tribal groups of India. At Christian Medical College (CMC), Vellore, Prof. Mammen Chandy integrated molecular diagnostics with clinical haematology and bone marrow transplantation, demonstrating lifesaving benefits of genetics research. In the north, PGIMER, Chandigarh established itself as a hub for biochemical and haematological genetics, with Prof. G. Garewal and Prof. Reena Das making significant strides in studying inherited blood disorders in North Indian populations.

The field of neurogenetics emerged as a hot new field at the National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru. A few clinicians including Prof. M. Gowrie Devi, and Prof. Uday Muthane focused on understanding the genetic basis of neurodegenerative disorders

There was another major change that occurred during the same period in human population genetics. The rich ethnic composition and diversity, along with India's history of endogamy, made it a very important area for continued research in population genetics. Previous studies relied mostly on serological and biochemical markers like blood group and haptoglobin markers. Early efforts at ISI, Kolkata by Prof. K.C. Malhotra, Prof. Partha P. Majumder and a few others (covered in the preceding article by the latter) were continued by using mtDNA, autosomal, and Y-Chromosome markers, with focus on migration, endogamy, and genetic

drift among Indian populations. Another major institute that brought about the change was the Centre for Cellular and Molecular Biology, Hyderabad, where late Dr. Lalji Singh subsequently with his younger colleague Dr. K. Thangaraj, and several international collaborators, made significant contributions to molecular phylogenetic and human population studies. In fact, late Dr. Lalji Singh also developed an indigenous method for DNA fingerprinting using Bkm probes that were derived from the banded krait. Using this methodology, he made notable contributions to solving early paternity cases, parentage disputes, and forensic cases in the country. Importantly, this breakthrough led to genesis of the Centre for DNA Fingerprinting and Diagnostics (CDFD) at Hyderabad. At the same time, the contributions of Prof. S.K. Brahmachari of the Centre for Biochemical Technology, later IGIB in New Delhi, strengthened computational and functional genomics.

There were several university-based research groups that made valuable contributions to the field. Professors from the University of Delhi (Prof. M.K. Bhasin), Osmania University (late Prof. J.S. Murthy and Prof. P.P. Reddy), University of Madras (Late Prof. P.M. Gopinath and late Prof. A. Ramesh), GNDU (Prof. A.J.S. Bhanwer), Punjabi University (Prof. S.M.S. Chahal), Panjab University (Prof. R.C. Sobti), Madurai Kamaraj University (Prof. R.M. Pitchappan), and Jawaharlal Nehru University (Prof. R.N.K. Bamezai) provided valuable information regarding HLA polymorphism, molecular markers, and Indian population diversity. Institutions such as Kurukshetra University, Andhra University, and IISc., Bengaluru also contributed in various specialised fields.

It was heartening that National funding agencies, including the DBT, DST, CSIR, and ICMR strongly supported the rapid expansion of human genetics in India during this period. Their support also facilitated hospitals and universities to procure advanced instruments, develop specialised manpower, and strengthen laboratory infrastructure. Programs including DST-FIST and DST-SAIF helped the universities to establish these facilities. The financial assistance also facilitated the growth of institutions, like AIIMS, New Delhi, SGPGIMS, Lucknow and PGIMER, Chandigarh, which became important centres for clinical genetics in northern India.

More Indian scientists became part of global initiatives during this period. Their participation in the Human Genome Diversity Project brought many Indian scientists into contact with international collaborators. Collaborations were established with centres in the USA, UK & Europe dealing with various aspects of genetics, like cardiovascular genetics, neurodegenerative disorders, ophthalmological disorders, and genetic studies of population diversity. A major success during this period was the gradual shift towards the development of indigenous genomic research in Indian laboratories. This helped in performing sophisticated molecular genetic analysis within India itself rather than exporting the biological samples abroad.

Commercialisation became a very important feature of this growth. An increase in the number of private laboratories, IVF Clinics, prenatal diagnostic centres, and other assisted reproductive technologies made genetic services available to more people. However, at the same time it created ethical and regulatory concerns. Misuse of prenatal sex determination and investigations driven commercially led to the passing of the PCPNDT Act in 1994. The institutional ethics committees and guidelines for genetic research also became mandatory. The growing awareness regarding privacy of genetic data, informed consent, exploitation of tribal populations, reproductive choice, biopiracy, and ownership of biological material was also witnessed during this decade. These debates culminated in serious engagement with the ethical, legal and social implications of genetic research in India.

However, the development of molecular and clinical genetics resulted in internal conflicts in the field as well. Classical genetics, anthropology, and university-based cytogenetics were steadily losing visibility compared to the newly developed molecular genetics approaches. Clinicians, molecular biologists, anthropologists, cytogeneticists and population geneticists also differed considerably in their opinions regarding the future directions of human genetics. Despite all these differences, an impressive scientific basis for further genomic research was laid in India. It proved that India has the capability to adopt the newest molecular technologies and apply these to its own healthcare services.

The legacy of this “Golden Decade” left a strong imprint on India's visibility in global human genomics research. The development of scientific infrastructure, international co-operation, and scientific culture enabled our country to participate in large-scale genomic initiatives along with disease-mapping programmes. Although challenges including equitable access to genetic healthcare as well as ethical implementation still remain, the strong foundations laid during this remarkable decade continue to drive the advancements of human genetics in India.

A Pilgrimage of Unique Kind: Fifty Years of Indian Society of Human Genetics (ISHG)

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Introduction

It was an honor to be able to speak about our august society on the golden jubilee meet at PGIMER, Chandigarh. I would like to thank Prof. Thelma and her team along with the organizing committee members to think of such a programme where the past members are asked to reminisce the highs and lows of the society over the last 50 years.

Fifty years is not a long time in the life of an organization; however, the mortals who look after the organization are not so fortunate hence, I can see five members of the organization i.e. Prof. K.C. Malhotra, Prof. Partha Majumder, and Prof. Jai Rup Singh, Prof. R.N.K. Bamezai and myself have been given this task to cover the growth and development during this period. Genetics over recent years has flourished into a fully formed banyan tree with many branches and subbranches like classical Mendelian genetics, Clinical genetics, Cytogenetics, Population genetics, Molecular genetics, Microbial genetics, Molecular biology, and its ramification into various 'Omics' disciplines following human genome mapping and understanding the rules of the game, and transcriptome, gene-environment interactions etc.

The Beginning

This was not so fifty years back and more so that was the case for India. So, in 1971 a few likeminded scientists and doctors met under the leadership of the famous statistician Dr. L.D. Sanghvi of Cancer Research Institute (CRI), Mumbai that was known as Human Variation Unit which in later years split into two ICMR centers, i.e. My Institute that time known as Blood Group reference Centre (BGRC), and Institute for human reproduction (IRR). The third centre was under BARC and was called Cancer Research Institute (CRI). Dr. Sanghvi was joined by Dr. H.N. Bhatia and Dr. A. L. Baxi of BGRC, Dr. G. S. Mutalik and Dr. S.L. Kate of BJ medical College and Pune University, Dr. K.C. Malhotra of Anthropological Society of India, Prof. K.C. Das (Haematologist and my Mentor) in PGIMER, Chandigarh, Dr. P.K. Sukumaran and Dr. J. V. Undevia of CRI, Prof. S.R. Das of Kolkata, Dr. D. P. Mukherjee of Tirupati, who all became the founder members of the society, today known as Indian Society of Human Genetics (ISHG).

The key role played by Dr. G.S. Mutalik in forming the society has often been highlighted. The major role of nurturing the society by statisticians, anthropologists and few basic scientists carried the society during early years mainly through studying the Indian population with their simple biological traits like a few enzyme polymorphisms, and distribution of haemoglobinopathy and various blood groups and other antigens. However, there were a very few clinical haematologists or clinical geneticists way back in India then. Searching through the depth of my memory, I can only recollect the name of Prof. I.C. Verma and Prof. Manorama Thomas running such clinics. I am sure many pediatricians did see cases of various eponymous syndromes with genetic origin but widespread availability of cytogenetic studies and specially Giemsa banded cytogenetics were nonexistent. However, a marker chromosome i.e. Philadelphia Chromosome and various monosomies and trisomies were described in Indian literature. As a result of these restrictions, the number of clinical geneticists working in the laboratory were limited. During these early days, membership of the society was mainly amongst population geneticists, statisticians, anthropologists and blood group serologists or a few of them who were looking for other biochemical markers like haemoglobin or other simply demonstrable polymorphic biochemical markers to study populations.

In the thick and thin of time (1990-2015)

This is the period I became most familiar with the society. I joined as the Assistant Director of Institute of Immunohaematology in Mumbai, an ICMR Institute previously called Blood Group reference Centre headed at that time by Dr. H. N. Bhatia, an internationally acclaimed blood group serologist. Dr Dipika Mohanty became the Director of the Institute and tried to revive the activities of ISHG. Dr. G. S. Murthy from Hyderabad was trying to publish a

journal of the Society, which till that date only had occasional bulletin and irregular annual meets to run the society. Finance was a big challenge to run such a society. Though the big institutes like Indian Statistical Institute, BARC, Anthropological Society of India, Department of Anatomy of few medical colleges and AIIMS, New Delhi were nominally associated with the society, the activity of the society was something more we desired to have. Meanwhile there were tremendous advances in cytogenetics, molecular genetics and molecular biology internationally. The enthusiasm of completing human genome project was going on at break neck speed at the international level (but India by choice was not a part). Industries offering machines and chemicals for all such tests were getting available. No other branches of medicine required the help of such techniques in stratifying patients than the field of haematology and oncology. As a result of this, membership of the society kept on increasing. Many medical colleges in the country with haematology and oncology and pediatrics department became interested, their faculty and residents as well as students took membership of the society. Members from Institutes like Centre for Cellular and Molecular Biology (CCMB), Hyderabad, Rajiv Gandhi Centre for Biotechnology (RGCB), Thiruvananthapuram, NIMHANS, Bangalore, JNU, New Delhi, Punjabi University, Delhi University, BARC biology division, and Madurai Kamraj University joined the society.

The journal of the society had a setback when the main force behind the journal, Prof. Murthy from Hyderabad passed away prematurely. After some hesitation, Dr Dipika Mohanty, the then Director of IIH (subsequently called NIIH and now called National Institute for Research on Blood and Immune Disorders (NIRBID), ICMR Mumbai took over the publication of the Journal in 2000. After Dr. Mohanty's retirement, I became the editor of the journal and could get it indexed. Indian Journal of Human Genetics slowly picked up the momentum, represented by publication from many well-known national and international authors but the representation from the members of the society were meagre which also continues today. This habit and tendency not to quote Indian authors or work of our own colleagues when after appropriate substantially reduces the international visibility of the articles published in National Journals and affect their impact factor. The journal was eventually indexed in NCBI data base and its impact factor rose to almost 0.7 and then the journal stopped publishing because of financial reasons from its 29th volume in 2014. Presently the society publishes a newsletter, I hope it will be soon upgraded into a full-fledged journal.

Current progress (2016-present)

I gather the society is now making steady progress under able leaderships and with more than 1500 members of the society and in various conferences their ever-increasing presence fills me with a sense of achievement and joy.

Conclusion

Individual's working lifespan is limited but for an institution 50 years is still very young. On this 50th anniversary of the society standing with stalwarts like Prof. K.C. Malhotra, Prof. Partha Majumdar, Prof. Jai Rup Singh, and Prof. R.N.K. Bamezai under the able leadership of Prof. Thelma and countless other younger colleagues and students fills me with joy. PGIMER, Chandigarh is the institution where I started learning karyotyping under my mentor, Prof. K.C. Das, a founding member of the society. This gives me a sense of home coming, as well as a sort of pilgrimage of a unique kind. I fondly remember Dr. Dipika Mohanty, Dr. S.L. Kate, Late Dr. S. Nayak, Late Dr. L.D. Sanghvi, Dr. Chauhan, Dr. Kiran Kucheria, Late Dr. Manorama Thomas, Late Dr. J.S. Murthy, Late Dr. J.V. Undevia, Late Prof. I.C. Verma and countless others for nurturing ISHG from its beginning.

Jai Hind!

Reminiscing The Journey of Human Genetics Research in the Framework of the ISHG-An Opinion

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Reminiscing the journey of the Indian Society of Human Genetics (ISHG) for the past 53 years is definitely a mixed bag of 'delight of achievements and pain of challenges.'

It has been an interesting journey of growth and learning, since some of us have grown along with the society which had an informal, personal touch, assumably because of small numbers or the prevalent disposition of the leadership at that time. Yet the scientific exchanges were intense between Anthropologists, those who worked on Blood types and disorders, and a small band of Cytogeneticists. With time, though, a strong emphasis on the 'field-work and epidemiology' took a back seat.

Back then in the year 1975, after two years of formal registration of ISHG and the 1st conference in 1974, I attended the 2nd Annual conference at ISI (Indian Statistical Institute), Kolkata. Finding the affection and support, which continued in my future years, from Prof. KC Malhotra and Professor L D Sanghvi, was a key take away from that conference apart from meeting other members who were very kind and encouraging in years to come.

Presenting my work on, 'Prenatal diagnosis of genetic disorders and management of high-risk pregnancies' on the ISHG platform in 1975 was contemporary to the research abroad, as an upcoming area of human genetics and cytogenetics for prospective genetic counseling and prevention. Paradoxically, such a service despite getting initiated more than half a century back remained confined and not easily accessible all over the country. Probably the involvement of the ISHG as a professional society with a participatory and knowledgeable decision-making role while framing policies at the national level, could have prevented the neglect and the delay. I suppose we all have to learn from the past experiences.

Another related highlight is about an opportunity I had two decades back to hold the XXXI Annual Conference of the ISHG in the Year 2006 at JNU, New Delhi, where along with the annual conference an 'International Symposium on Genomics and Public Health' was held. This I felt was important facet of human genetics vis-à-vis a commitment towards the masses. The emphasis on the public health in human genetics in India since then has had a long lag phase. A representation of ISHG experts possibly could have brought this aspect to the notice of the decision-makers within ministries and funding agencies to quell a two-decade delay.

Learning from the history and past experiences as a member of ISHG I also feel, we missed an opportunity at National level to be the part of the global effort to map and sequence human genome in 90s, when inclusion of China happened much later during the period giving them the visibility and the dividends. Some of our cytogeneticists who were good at in-situ hybridization and FISH could have contributed in mid 1990s to the positioning of unassigned genes on specific chromosome-band locations and thereby contributed to the visibility of the Nation on the global scene with the available strengths at hand. Same could have been true for bioinformaticians and molecular biologists working together towards this goal of putative mapping exercise. A suggestion in this regard was made to the DBT in an open forum and the then Task Force on the subject. The participatory role of the ISHG experts and as a society in the future for posterity is suggested to carve out a path of influencing decision making through the structured expert groups within the Society.

ISHG today has around 1500 members belonging to the academia, clinical practice, research institutes and industry. We have a requisite critical mass in diverse areas of the subject of human genetics, who at individual and group level have contributed to the precision in diagnosis and intervention in genetic diseases. Added to this has been an effort by individuals, groups and the institutions through IndiGen (CSIR) and Genome India (DBT) projects, opening opportunities for further research to understand diverse population groups in India and the diseases they suffer from.

ISHG along with these individuals and groups could take a leadership role in suggesting to the government the nuanced understanding of the limitations and future requirements of

the scale required, choice of sampling, appropriate representation of the 4000 odd ethnic groups and thousands of endogamous entities within the country with different socio-psychological and cultural backgrounds and languages to qualify as a 'reference' which we can call Indian, and the observations validated across different platforms and multiple groups blindly.

The scientific dimensions to account for are many, keeping in view the knowledge base and the technology upgradation from time to time in epigenomics, epi-transcriptomics, 3D understanding of the chromatin and its influence on gene expressions, to understand both rare, simple and complex diseases and their genomic and clinical heterogeneity to draw a precise genotype-phenotype relationship.

Understanding the etiology to precisely diagnose, and prevent or intervene for cure or management has adopted such dimensions elsewhere (1), which the community of ISHG needs to ponder over as to how could we attain the same standards with similar approaches tweaked to our benefit or researching on alternative approaches with a mass-appeal. The expert groups of the knowledgeable members within the ISHG have to lay down guidelines and SOPs for uniformity across the laboratories and institutions, and complement the efforts of the funding agencies and the government.

We are very far from the path of in-vivo deliveries for gene therapy (1) in rare or simple disorders, as was recently demonstrated for Urea cycle disorder abroad. The development of such-tools and platforms in genetic diseases has just been initiated in India. Interwoven with the fundamental knowledge of pleiotropy, epistasis, in the evolutionary background, to mechanistically understand endo- or intermediate phenotypes to unravel the key etiological genotype-phenotype correlates for targeting, is anybody's guess. The deep understanding (2) of this in younger generation remains half-baked. ISHG has made efforts to bridge this gap through virtual seminars, training workshops, but the direction has to be defined and strategized appropriately, looking at the strengths we have within the ISHG.

Formulation of priorities and laying down the path to guide the government and funding agencies, if adopted as one of the roles in future by the ISHG, the possibility of the public health dimensions to figure predominantly would be high. In Indian context, pursuing epidemiology and molecular epidemiology with simple, cost-effective, efficient technology which is accessible to the last man in a remote village or a slum in an urban area is a challenge in the future (3,4). This has to be under serious discussion within the expert groups of the ISHG, and recommendations made accordingly to the funding agencies and the relevant ministries. Thus, brain storming at frequent intervals with defined goals, and asking for representation of ISHG in government bodies and funding agencies for a purpose, is essential.

We have to adopt a twin path, of doing high end science and efficient delivery to the public, simultaneously (2,3,4). Apart from meeting and greeting each other and exchange scientific knowledge at the ISHG conferences, the analysis, intervention and prevention strategies have to translate the benefits to the masses without ambiguity and indecision, since assurance a-priori of disease-free well-being is the favoured choice in precision-centric decision making. There are high expectations in the society outside. ISHG as a body of human geneticists has to ponder over these to remain relevant and globally visible.

It feels wonderful to be here amongst the august gathering of experts. As a member of ISHG with a history behind me, and as a concerned member of the community outside of the ISHG who cares for the resources used and the outcomes harnessed, there is always a lot to share. Towards the end, I thank the ISHG, its leadership and the organizers for this opportunity, and wish the Society well.

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Six stubborn problems of non-coding RNA biology

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At the 50th anniversary of the Indian Society of Human Genetics annual meeting, research talks covered a wide range of topics, showing the impact of human genetics on many fields. Instead of strictly defining human genetics, the organizers included RNA biology, cancer diagnostics, and related areas. Non-coding RNAs were notably absent at the selfie point featuring a photo frame with important gene names placed around the edges. Despite their frequent occurrence in the genome and involvement in physiological and pathological processes, they did not get enough attention from clinicians and gene hunters. Many genome-wide studies like GWAS and RNA-sequencing often identify non-coding RNAs among the top hits, but they are usually excluded from genes prioritized for detailed study. Reflecting on this gap, we believe one major reason is that the current techniques and tools for non-coding RNA research have limitations that require new ideas and solutions. Here we review (Figure 1) the most challenging and exciting tools to develop for RNA biology, serving as a guide for budding researchers who may find novel ways to close these gaps.

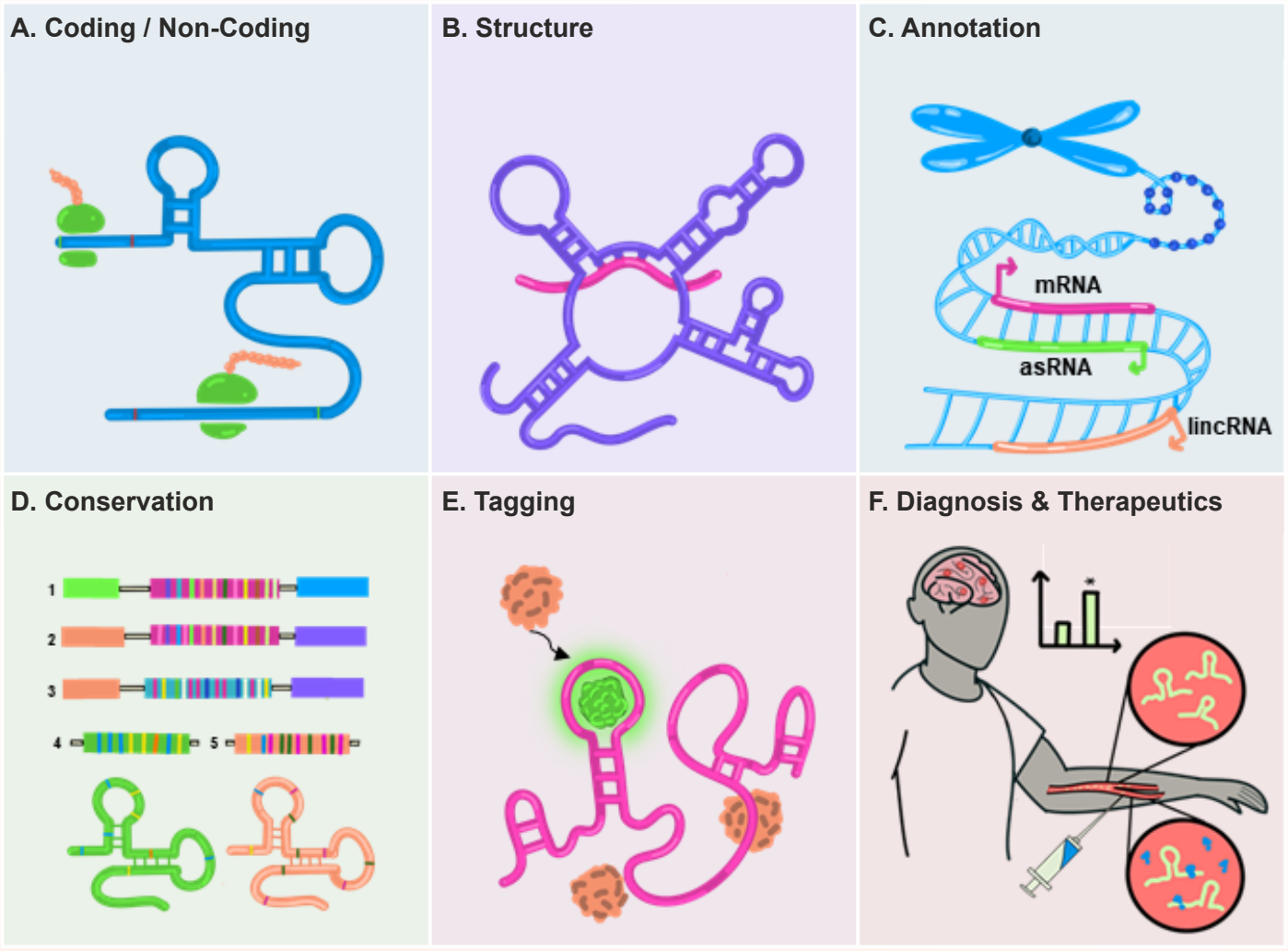

Figure 1: Overview of key challenges in non-coding RNA (ncRNA) biology.

A) Characterization of ncRNAs containing short open reading frames. B) Elucidation of ncRNA structural features. C) Generation of accurate, comprehensive, and complete annotations of ncRNA genes within the genome. mRNA- messenger RNA, asRNA- Antisense RNA, lincRNA- long intergenic ncRNA. D) Investigation of all aspects of ncRNA conservation, including sequence (D.1 and D.2), syntenic (D.2 and D.3), and structural (D.4 and D.5) conservation. E) Development of RNA tags for efficient visualization in live cells, tissues, or animals. F) Identification and application of ncRNA targets for innovative diagnostic and therapeutic strategies in disease contexts.

Coding and non-coding RNAs: shifting boundaries

A defining attribute of long non-coding RNAs (lncRNAs) - the lack of an Open Reading Frame (ORF) longer than 100 codons - is currently being challenged. The ORF threshold is arbitrary and was historically reinforced by limitations in detecting small peptides and active translation. Thus, longer ORFs (sORFs) fell between the boundaries set for protein-coding genes and non-coding RNAs. With the advent of ribosome profiling, it was found that genomes are pervasively transcribed and translated outside conventional protein-coding regions to give rise to microproteins (1). Over the last 10 years, microproteins have been functionally characterised as gene regulators (2) and cell-signalling molecules. They have also been reported to contain conserved protein domains. Interestingly, like lncRNAs, microproteins also exhibit the highest diversity and tissue-specificity in the brain, suggesting regulatory roles in complex tissues.

The concept of "non-coding" lncRNAs is being revisited similar to how "junk" lncRNAs were years ago. Since sORFs lie between coding and non-coding, studies suggest they serve as a means of evolution for protein-coding genes. LncRNAs function through structure and sequence features, which may influence their evolution and conservation - this idea has long existed. However, sORFs have recently gained attention, so their role in influencing lncRNA features and evolution has not been systematically studied.

We propose that since translation of sORFs is a strictly sequence-dependent feature, they have the potential of driving a more sequence-directed conservation of sORF-containing lncRNAs. Testing such hypotheses will require cross-species and cross-tissue micropeptide and lncRNA data at scale. Databases and browsers, including OpenProt, sORF repository, GWIPS-viz, and Trips-viz, are presently state-of-the-art for sORFs. As databases like these become richer, with more profiling across organisms and tissues, scientists will be better equipped to probe micropeptide functions and their contributions to lncRNA-mediated regulation.

RNA structure: the elusive shape

Crick famously said, "to understand function, one must study structure". RNA biology is far from this because functional studies have advanced while RNA structure remains a black box. About 90% of PDB structures are proteins, with only a few thousand RNA structures, even though RNA transcripts outnumber proteins in the cell. Small-molecule probes that bind specific bases or the backbone have been used to create basic maps of RNA folds. However, methods to prepare large amounts of RNA for structural studies while preserving in vivo structure remain a major bottleneck. Crosslinking RNA molecules near each other with chemical agents, followed by recovery and sequencing, allows visualization of RNA in the context of its neighbors. Since most RNAs work closely with RNA-binding proteins, ribonucleoprotein complexes may be more informative than RNA alone. Immunoprecipitation of RNA-protein complexes using proximity crosslinking and antibodies against proteins can quickly provide information about these complexes. Massively parallel sequencing of RNA fragments associated with RNA-binding proteins is much needed. Another use of this information is that Fab antibody fragments against these proteins enable mapping of 3D RNA structure using X-ray crystallography and Nuclear magnetic resonance (3).

RNA annotation: fixing the genomic context

The annotation of protein-coding transcripts is much more accurate than that of lncRNAs across organisms. Low expression levels, limited understanding of their sequence features, weak conservation, and high spatiotemporal specificity hinder lncRNA sequencing and annotation, creating a major bottleneck for understanding the genome function and regulation. LncRNAs are essential in gene regulation at various levels; however, we still lack a complete understanding of their mechanisms. Incorrect genomic feature representation changes the interpretation of other regulatory elements; for example, interpreting mutations and SNPs depends on whether a disease-causing variant lies in an intergenic or lncRNA-overlapping region.

The rapid increase in Next Generation Sequencing capacity has led to high-depth transcriptomic sequencing and the discovery of thousands of lncRNAs. Although short-read sequencing provides greater depth, enabling lncRNA detection, most experiments target polyA-tailed RNAs, leaving out many non-polyA-tailed lncRNAs, including circRNAs and eRNAs. Another disadvantage of short-read sequencing is lower accuracy in de novo transcript assembly, essential for discovering transcript isoforms. Long-read sequencing overcomes these limits but sacrifices sequencing depth. Advances in capture long-read sequencing enable probe-mediated enrichment of known and predicted lncRNAs via probe-tiling along the gene, increasing recovery of low-abundance lncRNAs and improving isoform-level characterization. The highly restricted expression of lncRNAs requires experiments targeting developmental stages and niche cell populations using single-cell and spatial transcriptomics to capture even rare isoforms. Recently, the Schier lab developed weMERFISH for zebrafish, a probe-based spatial transcriptomic technique visualizing target RNA expression at subcellular resolution in whole embryos (4). This technique can potentially extend to lncRNAs using sequence-specific probes.

The continuing use of misannotated genomic features has far-reaching implications in experimental and computational biology, potentially leading to erroneous mechanistic interpretations of gene regulation and limiting the successful translation of discoveries.

Conservation: sequence and beyond

Dobzhansky said, "Nothing in biology makes sense except in the light of evolution". Non-coding RNAs are generally thought to be less conserved than protein-coding ones. However, this may be reflective of the broad scope of conservation itself: syntenic, structural, and sequence conservation, and the dSyn/dNS formula. We must accept that a single conservation model may not capture the functional diversity of ncRNAs. Sequence-dependent lncRNA functions, like miRNA sponging and R-loop formation, may appear more conserved. Conversely, lncRNAs without functional sORFs, miRNA binding sites, or direct DNA-binding features may have structural roles and be conserved via structural features during evolution (5). Syntenic conservation helps identify non-coding RNAs that are evolutionarily related and functionally similar but lack high sequence conservation. Shared promoters, enhancers, and other regulatory regions can also indicate conservation in lncRNAs. Patches of conservation within a non-coding RNA should be treated specially and inform 3D structure prediction. We propose a comprehensive study of features within non-coding RNAs (e.g., conserved patches) and their genomic context (e.g., proximity to regulatory elements, synteny) to build conservation models relevant to lncRNAs. Using a small set of well-characterized non-coding RNAs, separate models may be built for (i) RNA components of ribonucleoproteins like telomerase and rRNA, (ii) chromatin-associated ncRNAs like MALAT1 and XIST, and (iii) lncRNAs with binding sites for other ncRNAs such as sponges like CDR1as and TUG1. Basing these models on a small set of well-characterized lncRNAs allows in silico modeling and long evolutionary experiments in the lab. Natural polymorphisms and phenotypic consequences can also be interpreted using large human population genotype-phenotype studies.

RNA visualization: Nothing like GFP

The RNA biology field currently lacks an equivalent of fluorescent markers similar to Green Fluorescent Protein (GFP) - a versatile, engineerable tag for live tracking in cells and organisms. The low abundance and complexity of RNAs and limited structural information make designing specific nucleic acid probes for lncRNA detection difficult (6). Different groups have tried indirect methods, tagging RNA with motifs that bind dCAS9-GFP or Maltose Binding Protein (MBP)-GFP. Tandem repeats of a 19-nucleotide stem-loop in RNA bind the viral MS2 coat protein, which is fluorescently tagged. The dCAS9-GFP system uses an inactive Cas9 protein that does not edit the genome but localizes to a site via a specific sgRNA. Sensitivity can be adjusted by changing the number of binding sites. A more direct approach uses RNA aptamers that bind fluorescent dyes. First-generation aptamers identified by SELEX were the Spinach and Broccoli systems. Later, the Mango series, from a 39-nucleotide stem-loop, was used with dyes like TO1-Biotin. Improved versions present mutated aptamers as linear arrays of dye-binding sites. Once transcribed, these tags bind fluorescent dye and enhance fluorescence several-fold (7). The latest versions, named Pepper, do not use the G-quadruplex scaffold but form a complex 3D structure working with dye HBC530. A clever innovation merges this system with the toehold system as a miRNA sensor: an RNA aptamer fused with a region complementary to an miRNA. When the miRNA binds and opens the Pepper RNA, the dye binds and fluoresces. Without the miRNA, the folded structure blocks the dye-binding domain. m6A-methylation of Pepper enhances fluorescence, opening up new applications. However, all these studies are in cell lines

with reporter genes like mCherry. Detecting low-abundance lncRNAs in vivo, in a live animal, like GFP illuminates proteins, remains a daunting challenge.

Diagnosis and therapeutics- often overlooked

"What we observe is not nature itself, but nature exposed to our method of questioning"- Werner Heisenberg. A largely protein-centric framework overshadowed the importance of lncRNAs in disease pathophysiology, shaping which discoveries were made and what biology was visible. For instance, we have only begun to unravel the role of non-coding RNAs in the mammalian brain.

lncRNAs are attractive as blood-borne biomarkers, especially for neurological and neuropsychiatric conditions (8) for the following reasons. 1) They obviate invasive methods of sample collection via cerebrospinal fluid and brain biopsy for diagnosis. 2) Diagnosis of some conditions, such as Autism Spectrum Disorder, Schizophrenia, and Major Depressive Disorder, is based on psychometric tests, which require a specialist and are also prone to misdiagnosis and delayed diagnosis. Quantification or detection of dysregulated blood markers alleviates this issue. 3) Most of these conditions present with comorbidities, causing them to partially share symptoms; for example, Schizophrenia Susceptibility Disorder and ASD. Thus, disease-specific biomarkers, derived from multiomics studies in large patient cohorts are required. 4) Circulating biomarkers are potential early diagnostic targets that can be tested before the onset or severe progression of the disease. 5) Similarly, they can potentially serve as objective markers of disease prognosis with treatment.

Another emerging application is therapeutic targeting of lncRNAs. The field is in its infancy and utilises antisense oligonucleotides, siRNA-mediated knockdown, and CRISPR-Cas9 mediated knock-out of target lncRNAs. In contrast, upregulation uses CRISPR-activation (CRISPRa) and exogenous transgene delivery to overexpress targets. The methodologies still suffer from off-targeting and inefficiency. Studies have demonstrated a reduction in Alzheimer's disease-related symptoms in animal models via BACE1-AS lncRNA knockdown (9) and the rescue of phenotypes related to neurodevelopmental disorders observed in SCN2A haploinsufficient mice using CRISPRa (10). The complex and heterogeneous manifestations of neurological and neuropsychiatric conditions make them a formidable yet primary target for novel therapeutic and biomarker discovery, and lncRNAs remain an underexploited reservoir.

Conclusion

These six challenges are well recognized within the RNA biology community, yet they persist and require innovative ideas, advanced tools, and interdisciplinary research. Progress in any of these areas is likely to have a cascading impact, as the challenges are inherently interconnected. For example, improved annotation would facilitate the development of more reliable criteria for distinguishing coding from non-coding RNAs, while enhanced structural understanding would enable more precise targeting. Additionally, models for evolutionary constraints would complement insights gained from structural constraints.

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Wordsmithing RNA: The Expanding Role of Antisense Oligonucleotides in Monogenic Disorders

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Introduction

Rare diseases collectively affect more than 300 million people worldwide, with approximately 70–80% having a genetic basis (1). Although definitions vary geographically, a rare disease is generally defined as one affecting fewer than 5–10 per 10,000 individuals. In the United States, it is defined as affecting fewer than 200,000 individuals, whereas the European Union defines it as affecting fewer than 5 per 10,000 people. In India, the National Policy for Rare Diseases (2021) recognizes rare diseases as conditions requiring specialized diagnosis and multidisciplinary management because of their low prevalence, high disease burden, and substantial socioeconomic impact. Nearly 80% of rare diseases are monogenic, with more than 4,000 disorders described in the Online Mendelian Inheritance in Man (OMIM) database. These disorders arise from pathogenic variants in a single gene and exhibit diverse molecular mechanisms, including loss-of-function, toxic gain-of-function, dominant-negative effects, aberrant RNA splicing, and altered gene dosage. They frequently present during infancy or childhood and are associated with progressive disability, significant morbidity, and premature mortality.

Advances in molecular genetics and next-generation sequencing have revolutionized the diagnosis of rare genetic disorders and provided unprecedented insights into disease mechanisms, enabling the development of therapies that target the underlying molecular defect rather than merely alleviating symptoms. However, disease-modifying treatments remain available for only approximately 5% of rare diseases, highlighting a substantial unmet clinical need (2). The first mechanism-based therapies emerged in the 1990s with enzyme replacement therapy (ERT) for lysosomal storage disorders, beginning with Gaucher disease. Subsequently, substrate reduction therapy, pharmacological chaperones, and hematopoietic stem cell transplantation (HSCT) expanded therapeutic options for selected inherited metabolic and immunological disorders. More recent advances in molecular medicine have led to the development of gene replacement, genome editing, RNA interference (RNAi), and antisense oligonucleotide (ASO) therapies. While gene therapy and genome-editing technologies such as CRISPR–Cas9 hold tremendous promise, challenges related to their development, delivery, durability, safety, and variant-specific applicability continue to limit their widespread use. Among RNA-targeted therapies, ASOs have emerged as one of the most versatile precision medicine platforms. By binding complementary RNA sequences, ASOs can selectively degrade transcripts or modulate pre-mRNA splicing. Their programmable design allows rapid customization for individual genes and pathogenic variants, making them particularly suited for rare and ultra-rare monogenic disorders. The clinical success of therapies for spinal muscular atrophy, Duchenne muscular dystrophy, hereditary transthyretin amyloidosis, and SOD1-associated amyotrophic lateral sclerosis has firmly established ASOs as a transformative approach for precision treatment of genetic diseases.

Mechanisms of ASO Action

The therapeutic activity of ASOs is determined by their chemical composition and mechanism of interaction with target RNA. Although all ASOs recognize their targets through complementary Watson–Crick base pairing, their biological effects differ depending on whether they promote RNA degradation or alter RNA processing. Based on their mechanism of action, ASOs can be broadly classified into **RNase H1-dependent ASOs**, which induce degradation of target transcripts, and steric-blocking ASOs, which modulate RNA processing without degrading the transcript. In parallel, **small interfering RNAs (siRNAs)** represent a complementary RNA-targeting strategy that suppresses gene expression through the endogenous RNA interference (RNAi) pathway. Selection of the appropriate therapeutic approach depends on the underlying molecular pathology of the disease and the desired therapeutic outcome **(Table 1).**

RNase H1-Dependent Transcript Knockdown ASOs (Gapmer ASOs)

Gapmer ASOs are designed to selectively reduce the abundance of disease-causing transcripts. They consist of a central stretch of DNA nucleotides ("gap") flanked by

chemically modified ribonucleotides that enhance nuclease resistance, target affinity, and pharmacokinetic properties. Following cellular uptake, the ASO hybridizes with its complementary target RNA to form a DNA-RNA heteroduplex, which is recognized by the endogenous enzyme RNase H1. RNase H1 specifically cleaves the RNA strand of the duplex while leaving the ASO intact, allowing it to participate in multiple rounds of target degradation. The resulting reduction in mRNA levels leads to decreased synthesis of the corresponding protein (2). Gapmer ASOs are particularly effective for disorders caused by **toxic gain-of-function or dominant-negative** mutations, where reducing the expression of the mutant transcript can alleviate disease pathology. They may also be designed to selectively target mutant alleles when sufficient sequence differences exist between the pathogenic and wild-type transcripts. Approved and investigational examples include suppression of **SOD1** transcripts in amyotrophic lateral sclerosis, **HTT** transcripts in Huntington disease, and **TTR** transcripts in hereditary transthyretin amyloidosis.

Steric-Blocking or Splice-Switching ASOs (ssASOs)

Unlike gapmer ASOs, splice-switching ASOs (ssASOs) do not activate RNase H1 or degrade their target RNA. Instead, they bind specific sequences within pre-mRNA and sterically block the interaction of spliceosomal components or RNA-binding proteins with splice sites and regulatory elements. By modulating exon recognition during pre-mRNA processing, ssASOs can restore normal splicing or intentionally alter splicing patterns to produce a therapeutically beneficial transcript. Depending on the disease mechanism, ssASOs may promote exon inclusion, induce exon skipping, suppress pseudoexon incorporation, block cryptic splice sites, or modulate the activity of splicing enhancers and silencers (3,4). These strategies enable correction of diverse splicing abnormalities caused by pathogenic variants. Clinical success has been demonstrated in spinal muscular atrophy, where nusinersen promotes inclusion of exon 7 in SMN2, thereby increasing production of functional SMN protein. Similarly, exon-skipping ASOs used in Duchenne muscular dystrophy restore the translational reading frame of the DMD transcript, allowing synthesis of a shortened but functional dystrophin protein (5).

RNA Interference (RNAi)-Mediated Transcript Silencing

Although siRNAs are structurally distinct from ASOs, they constitute an important class of RNA-targeted therapeutics and are often considered alongside antisense technologies. siRNAs are short double-stranded RNA molecules, typically 21–23 nucleotides in length, that exploit the endogenous RNA interference (RNAi) pathway. After entering the cytoplasm, the guide strand is incorporated into the RNA-induced silencing complex (RISC), which recognizes complementary mRNA molecules and catalyzes their cleavage. Unlike gapmer ASOs, which rely on RNase H1 and can function in both the nucleus and cytoplasm, siRNAs primarily act in the cytoplasm through RISC-mediated degradation of mature mRNA (6). RNAi therapeutics have shown particular success in liver-directed diseases owing to efficient hepatocyte delivery using N-acetylgalactosamine (GalNAc) conjugation. Clinically approved siRNA therapies have demonstrated efficacy in hereditary transthyretin amyloidosis, primary hyperoxaluria type 1, and acute hepatic porphyria (7).

Disease Mechanisms Amenable to ASO Therapy

The therapeutic application of ASOs is guided by the underlying molecular mechanism rather than the clinical phenotype. Depending on the pathogenic defect, ASOs can suppress toxic transcripts, correct aberrant RNA splicing, selectively silence mutant alleles, or modulate modifier genes and disease-associated pathway (8).

Toxic Gain-of-Function Disorders

In toxic gain-of-function disorders, mutant RNA or proteins acquire pathogenic properties that damage cells. Transcript knockdown using gapmer ASOs or siRNAs reduces production of the toxic gene product. Representative examples include Huntington disease, SOD1-associated amyotrophic lateral sclerosis, where the approved ASO tofersen suppresses mutant SOD1, and hereditary transthyretin amyloidosis, in which lowering TTR expression reduces amyloid deposition.

Loss-of-Function Disorders

Loss-of-function disorders require restoration of functional protein expression, most commonly through splice correction or exon skipping. The best-established example is spinal muscular atrophy (SMA), where nusinersen promotes exon 7 inclusion in SMN2, compensating for loss of SMN1. In Duchenne muscular dystrophy, exon-skipping ASOs restore the DMD reading frame to produce a partially functional dystrophin protein. Similar splice-switching approaches are being explored for ataxia-telangiectasia, inherited retinal diseases, and cystic fibrosis caused by splice-altering variants.

Dominant-Negative Disorders

Dominant-negative mutations produce abnormal proteins that interfere with normal protein function. In these disorders, allele-specific ASOs selectively suppress the mutant transcript while preserving the wild-type allele. This strategy is under investigation for disorders such as osteogenesis imperfecta and epidermolysis bullosa.

Targeting Modifier Genes and Disease Pathways

ASOs can also target modifier genes or downstream pathways rather than the primary disease-causing gene. The best example is SMA, where nusinersen targets SMN2 instead of the defective SMN1. Similar approaches aimed at modulating inflammatory or fibrotic pathways may further expand the therapeutic potential of ASOs for disorders in which direct gene correction is not feasible.

Together, these examples demonstrate that ASO therapies can be tailored to diverse pathogenic mechanisms, making them a highly adaptable platform for precision medicine in rare monogenic disorders.

Considerations for Developing ASO Therapies

Successful development of ASO therapies requires a clear understanding of disease biology, target RNA, and clinical phenotype. Defining the underlying disease mechanism is essential for selecting the appropriate ASO strategy, with transcript knockdown generally suited for toxic gain-of-function and dominant-negative disorders, and splice-switching ASOs for splice defects and selected loss-of-function variants. Equally important is determining variant amenability, as not all pathogenic variants can be effectively targeted.

The target tissue is another key consideration because efficient delivery varies among organs. Although the liver and central nervous system are readily accessible, delivery to skeletal muscle, heart, and other tissues remains challenging. Disease severity, progression, biomarkers, and timing of intervention also influence therapeutic success, with early treatment often providing the greatest clinical benefit (Figure 1).

Finally, translation into clinical practice requires optimization of ASO chemistry, dosing, pharmacokinetics, and long-term safety, together with well-defined clinical outcome measures. Manufacturing feasibility, regulatory approval, and cost-effectiveness remain important considerations, particularly for individualized N-of-1 and N-of-few therapies.

N-of-1 and N-of-Few ASO Therapies

The success of ASO therapeutics has extended precision medicine beyond conventional drug development to includeindividualized treatments, commonly referred to as N-of-1 and N-of-few therapies (https://www.n1collaborative.org/). Unlike traditional drug development, which targets large patient populations, these approaches are designed for a single patient or a small group of patients sharing the same or functionally similar pathogenic variants. They are particularly relevant for ultra-rare genetic disorders, where conventional drug development is often impractical because of the extremely limited number of affected individuals and the consequent exorbitant costs.

The landmark example of an N-of-1 ASO therapy is milasen, developed for a child with CLN7 neuronal ceroid lipofuscinosis caused by a unique deep intronic variant in the MFSD8. The patient-specific splice-switching ASO restored normal splicing and reduced seizure frequency, providing the first proof of concept that individualized RNA therapies can be developed within clinically meaningful timelines (9).

Building on this success, the concept has evolved toward N-of-few therapies, in which a single ASO is designed for a small cohort of patients carrying identical or mechanistically similar variants. By allowing shared preclinical validation, manufacturing, and regulatory evaluation, this approach offers a more practical and scalable framework for personalized RNA therapeutics while reducing development time and cost.

Despite their promise, N-of-1 and N-of-few therapies face scientific and regulatory challenges, including demonstrating variant amenability, functional validation, clinically meaningful outcome measures, individualized manufacturing, and long-term safety. However, advances in genomic diagnostics, ASO design, and evolving regulatory frameworks are expected to accelerate personalized RNA therapeutics for patients with ultra-rare monogenic disorders (10).

Technical Possibilities and Limitations

Advances in oligonucleotide chemistry have transformed ASOs into a powerful platform for precision medicine. Chemical modifications, including phosphorothioate (PS) backbones, 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), locked nucleic acids (LNAs), and phosphorodiamidate morpholino oligomers (PMOs), have improved stability, target affinity, pharmacokinetics, and safety. Advances in computational design, artificial intelligence, and high-throughput functional assays have accelerated target identification and preclinical validation,while emerging

delivery strategies such as GalNAc conjugation and lipid nanoparticles are expanding tissue-specific applications.

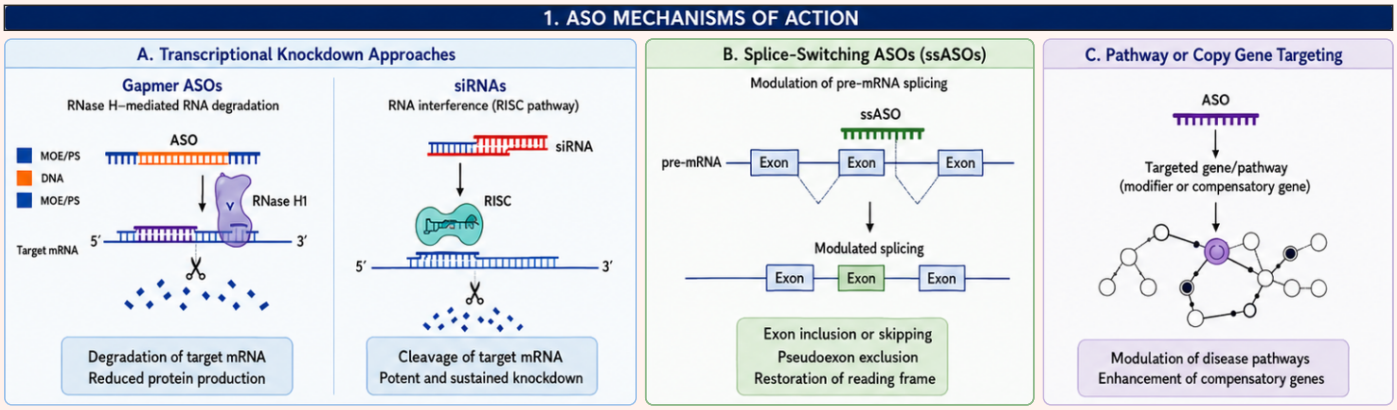
Despite these advances, several challenges remain. Efficient delivery to tissues such as skeletal muscle, heart, and the central nervous system is still limited, and repeated dosing is required because ASOs do not permanently modify the genome. Safety concerns, including off-target effects, immune activation, and organ toxicity, necessitate careful optimization of ASO chemistry and dosing. In addition, the genetic heterogeneity of rare diseases complicates mutation-specific therapy development, regulatory approval, and cost-effectiveness. Continued improvements in delivery technologies, regulatory frameworks, and long-term safety evaluation will be essential for broader clinical implementation of ASO therapeutics.

Conclusion

ASOs have emerged as a versatile platform for precision medicine in rare monogenic disorders by enabling targeted modulation of RNA through transcript knockdown, splice correction, or regulation of modifier genes. Clinical successes such as nusinersen and tofersen have validated the therapeutic potential of RNA-based interventions. Although challenges related to delivery, safety, regulatory approval, and individualized treatment remain, continued advances in oligonucleotide chemistry, delivery technologies, and functional genomics are expected to broaden the clinical application of ASO therapeutics and accelerate the development of personalized treatments for rare genetic diseases.

Table 1. Comparison of Major RNA-Targeting Therapeutic Strategies

Feature	Gapmer ASOs	Splice-Switching ASOs	siRNAs
Primary Mechanism	RNase H1-mediated RNA degradation	Steric blockade of pre-mRNA splicing	RNA interference (RISC-mediated mRNA degradation)
Target	Pre-mRNA and mRNA	Primarily pre-mRNA	Cytoplasmic mRNA
RNA Degradation	Yes	No	Yes
Cellular compartment	Nucleus and cytoplasm	Predominantly nucleus	Cytoplasm
Therapeutic objective	Reduce transcript abundance	Correct or modify RNA splicing	Reduce transcript abundance
Best suited for	Toxic gain-of-function	Loss-of-function due to aberrant splicing, exon skipping, pseudoexons	Toxic gain-of-function and gene silencing, especially liver diseases
Representative diseases	SOD1-associated ALS, Huntington disease, hereditary transthyretin amyloidosis	Spinal muscular atrophy, Duchenne muscular dystrophy, splice-related inherited retinal diseases	Hereditary transthyretin amyloidosis, primary hyperoxaluria, acute hepatic porphyria



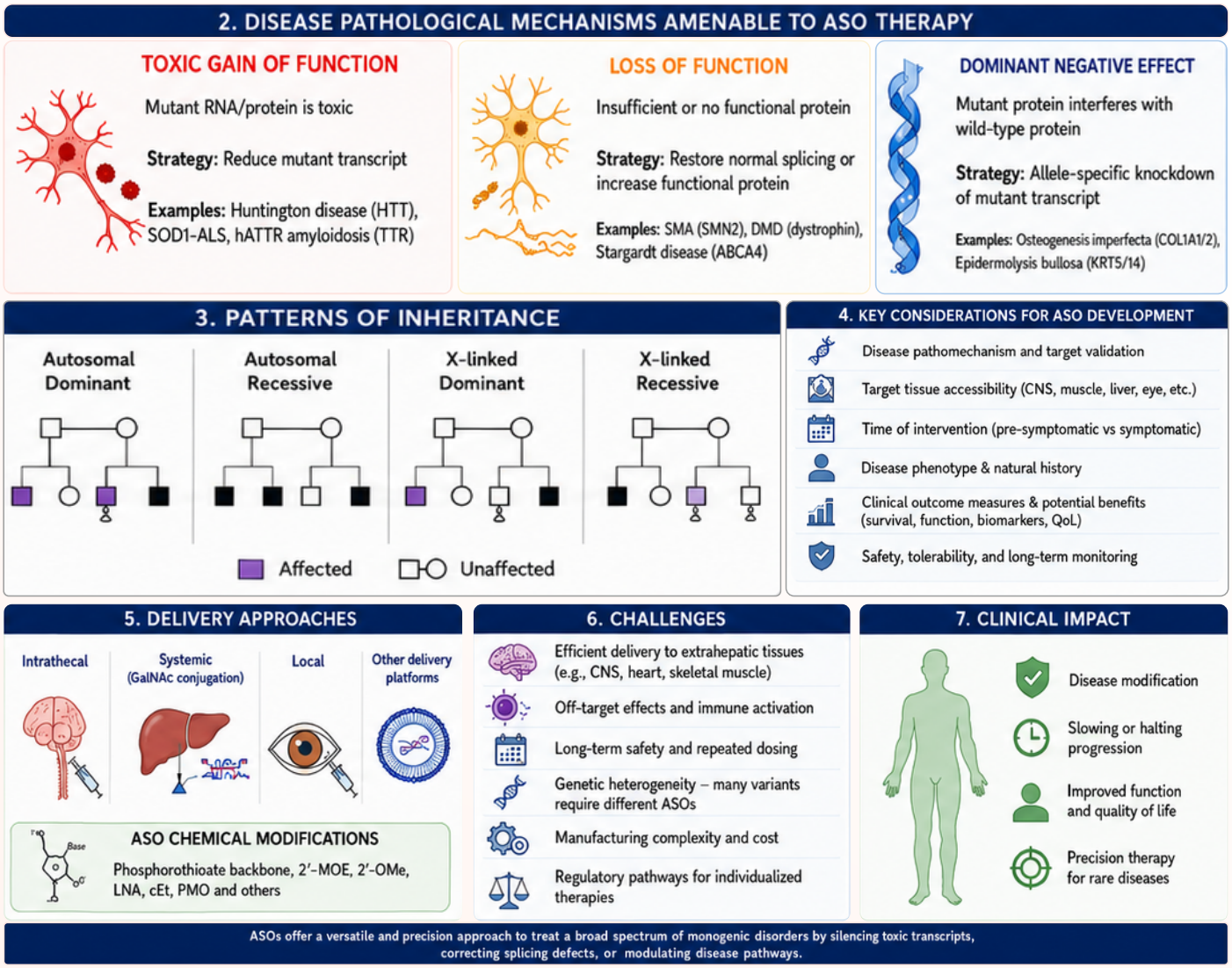


Figure 1. Antisense oligonucleotide therapeutic strategies for monogenic disorders

[Image generated using ChatGPT (GPT-5.6 Luna, OpenAI) and subsequently reviewed, edited, and verified by the author].

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When One Is Enough: The Power and Limits of N-of-1 Molecular Medicine

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Genetic Disorders: A Global Burden

Genetic disorders are one of the most serious but underappreciated health crises of our time. Nearly 7000 distinct rare diseases affect roughly 4% of the global population. About 80% have a genetic etiology, with 70% manifesting during childhood and 30% of those children dying before age five. Yet despite decades of progress, approximately 95% of these have no approved treatment, and the average diagnostic odyssey stretches to nearly five years (1).

Ultra-rare single-gene disorders including neurodevelopmental disorders (NDDs) which comprise intellectual disability, autism spectrum disorder, and developmental encephalopathies are right at the epicenter of this crisis. Over 1500 genes have been implicated in NDDs. Many pathogenic variants arise de novo, some of them unique to a single individual (2). For these patients, traditional drug development pipelines offer little hope: the commercial market is too small, the biology too heterogeneous, and no clinical trial can be powered for a cohort of one. This is precisely the gap that N-of-1 therapy seeks to fill, placing the individual rather than the population at the center of therapeutic design.

The Urgency of Early Identification: Lessons from IEMs

The importance of early diagnosis in genetic disease is best illustrated by inborn errors of metabolism (IEMs). Conditions such as phenylketonuria, maple syrup urine disease, and urea cycle disorders (UCD) cause irreversible neurocognitive damage within weeks of birth if untreated, yet respond dramatically to dietary or enzyme-based interventions when identified through newborn screening. The lesson is clear: the developing brain is extremely vulnerable and the window for meaningful intervention is narrow and irreversible (3).

This lesson carries profound relevance for NDDs more broadly. Synaptic plasticity, neural circuit formation, and myelination are all time-sensitive processes. NDDs are not static; neurological damage accumulates progressively during critical developmental windows. Identifying a pathogenic variant, ideally through whole-genome sequencing (WGS) at or near birth, is therefore not merely a diagnostic exercise but a therapeutic imperative. Every month of delay turns these disorders from treatable degeneration to irreversible condition.

Advances in genomic technology have transformed the diagnostic landscape. Trio-based WGS now achieves diagnostic yields of 30-50% in previously unsolved paediatric neurological cases. The bottleneck has shifted from diagnosis to treatment, and it is here that N-of-1 therapy enters the picture.

From Population Medicine to the Individual therapy: What is N-of-1 Therapy?

For most of modern medical history, drug development has operated on a simple premise: identify a disease shared by adequate number of people, find a molecule that modifies its course, and scale it into a marketable treatment. Although this model has delivered remarkable medicines, it is built on the assumption of commonality. A drug is viable when it can recover its development costs across a sufficiently large patient population. For the child whose epilepsy is caused by a de novo variant in a gene no pharmaceutical company has a programme for, this model offers nothing. The disease is real, the suffering is real, but their numbers, often fewer than a handful of patients worldwide, make them commercially unviable.

As mentioned earlier, the availability of NGS has made this gap impossible to ignore. WGS has revealed that a substantial number of patients with severe early-onset disease carry private variants; pathogenic changes so rare that they exist in only one known individual or a family line. N-of-1 therapy is the direct response: the design, manufacture, and administration of a therapeutic molecule built for a single patient, targeting their specific variant. Antisense oligonucleotides (ASOs) offer the most adaptable framework for this sequence-specific targeting. Depending on the pathogenic mechanism, these tools can be tailored to

to achieve precise splice correction, transcript knockdown, or translational modulation at the pre-mRNA level (4). Because a new ASO differs from a previously approved one only in its sequence, some regulatory and toxicological groundwork can be shared, and a bespoke molecule can in principle be designed in weeks once the causative variant is known.

For conditions where gene replacement rather than transcript modulation is required, adeno-associated viral (AAV) vectors offer a complementary approach - engineered for tissue-specific tropism and capable of sustained transgene expression in post-mitotic cells including neurons and photoreceptors. More recently, base-editing-based CRISPR has entered the N-of-1 space, enabling precise nucleotide conversion at a target locus without inducing double strand breaks, and delivered to solid organs including the liver via lipid nanoparticle formulations. Together, these modalities mean that for almost any category of pathogenic variant, there is now a conceivable therapeutic strategy. What N-of-1 medicine asks is whether that strategy can be executed fast enough, safely enough, and at a cost that does not render it accessible only to the privileged few. Table 1 outlines the typical pipeline.

Table 1: The N-of-1 Therapy Pipeline for Neurodevelopmental Disorders and IEMs.

Step	Stage	Key Actions
01	Clinical Suspicion	Family history, Phenotyping, Biochemical workup
02	Genomic Diagnosis	Trio-WGS/WES, Variant classification
03	Variant Assessment	Pathogenicity scoring, ASO/AAV amenability, iPSC/organoid modelling
04	Bespoke Therapy Design	ASO design, Vector construction, GMP manufacturing, Preclinical safety
05	Regulatory Pathway	FDA Expanded Access/EMA Compassionate Use, IND submission, Ethics approval
06	N-of-1 Trial & Monitoring	Personalized endpoints, Biomarker tracking, Long-term follow-up, Registry entry

WGS: whole-genome sequencing; WES: whole-exome sequencing; ASO: antisense oligonucleotide; AAV: adeno-associated virus; iPSC: induced pluripotent stem cell; GMP: Good Manufacturing Practice; IND: Investigational New Drug application

Landmark N-of-1 Cases: From Proof-of-Concept to Clinical Precedent

1) Milasen - The Watershed Moment: In 2018, six-year-old Mila Makovec was diagnosed with a fatal form of late-infantile Batten disease caused by a private intronic Alu-element insertion in CLN7. Neurogeneticist Timothy Yu at Boston Children's Hospital designed milasen - an ASO targeting the aberrant splice site - within one year and administered it intrathecally under FDA emergency access authorization (5). Seizure frequency decreased and disease progression stabilized, establishing that a bespoke ASO could be designed, manufactured, and delivered within a clinically meaningful timeframe.

2) Ataxia-Telangiectasia. The same The same ASO framework was subsequently applied to a two-year-old with ataxia-telangiectasia. The resulting molecule, atipeksen, restored the ATM expression (6). The child had been receiving treatment for over three years at the time of publication, a demonstration of the feasibility of long-term N-of-1 management.

3) KIF1A-Associated Neurological Disorder and the n-Lorem Model: The non-profit n-Lorem Foundation was founded to transition N-of-1 ASO therapeutics from independent academic investigators to a scalable pipeline. Its first patient, Susannah, carried a KIF1A p.Pro305Leu variant causing refractory seizures and severe neurodevelopmental regression. An allele-specific ASO was administered intrathecally. At the time of publication, with 9 months of treatment, her seizure frequency fell from 100–290 episodes per day to fewer than 30 per week, daily falls dropped from over 26 to a maximum of seven, speech and attention improved (7).

4) KJ Muldoon - Base Editing an IEM: Perhaps the most striking recent case is that of KJ Muldoon, a baby boy born with severe OTC deficiency, a UCD causing lethal hyperammonaemia. Researchers at the Children's Hospital of Philadelphia and Penn Medicine designed a bespoke base-editing therapy delivered via lipid nanoparticles (LNP) to correct the pathogenic variant in the infant's liver. The therapy reduced ammonia levels sufficiently for KJ to

to survive and ultimately receive a liver transplant (8). The case is significant on multiple counts: it applied N-of-1 principles to an IEM rather than a neurological condition, used base-editing rather than ASOs or conventional vectors, and showed that in metabolic disease, the intervention window is measured in weeks.

5) Inherited Retinal Disorders: The eye has become a proving ground for N-of-1 gene therapy. Luxturna (voretigene neparvovec), the first approved in vivo AAV gene therapy, replaces defective RPE65 in Leber Congenital Amaurosis type 2, restoring functional vision before total blindness ensues (9). It established the regulatory, surgical, and immunological framework upon which truly personalized retinal gene therapies are now being built.

6) ALS and the Tofersen Precedent: The FDA approval of Tofersen (Qalsody), an ASO targeting SOD1 mRNA in familial ALS, validates genotype directed ASO therapy at the regulatory level and may ease the path for N-of-1 variants in related neurodegenerative contexts (10).

Challenges:

Though treating rare genetic disorders seems like a possibility due to the advancement in gene editing tools and reality of N-of-1 therapy, it does come with its own set of challenges.

Cost and Accessibility: A single N-of-1 ASO costs approximately USD 1-1.6 million to develop, excluding long-term monitoring and manufacturing (4). Fundraising of this magnitude requires extraordinary personal resources or philanthropic support, raising profound equity concerns. Families with greater socioeconomic resources or proximity to specialist academic centers are disproportionately positioned to access these therapies.

Regulatory Complexity: The N-of-1 trial sits at an uncomfortable intersection between clinical treatment and experimental research. In the US, FDA Expanded Access pathways exist but require IND filings and monitoring frameworks designed for population-level trials; harmonized international guidelines for N-of-1 ASO development remain a work in progress (4).

Preclinical Validation: Each N-of-1 patient is by definition the first human recipient of their specific drug, making preclinical safety testing mandatory but challenging. Patient-derived iPSC models and cerebral organoids are emerging as genetically matched preclinical surrogates, though regulatory acceptance of organoid-based pharmacology as a substitute for formal GLP toxicology studies remains jurisdiction-dependent.

Outcome Measurement and Knowledge Aggregation: Traditional trial endpoints like statistical significance, pre-specified outcomes, placebo controls are incompatible with a single patient. N-of-1 trials must rely on time-series designs, caregiver-reported outcomes, and surrogate molecular endpoints. There is also the risk that individualized cases generate knowledge that is never shared; proposals to mandate registry enrolment for all N-of-1 recipients remain to be implemented at scale (2).

Future Directions: The trajectory of N-of-1 therapy is one of cautious optimism. Machine learning-based ASO design tools are beginning to reduce the empirical burden of target identification. GMP-compatible synthesis platforms are becoming more modular and cost-efficient. The KJ Muldoon case opens a new frontier for base and prime editing via LNP delivery - potentially faster and less invasive than viral vectors for hepatic and other solid organ targets. Regulatory engagement is also deepening: the FDA's Project Facilitate and accelerated review mechanisms for ultra-rare conditions signal institutional commitment to enabling bespoke medicine.

Looking further ahead, the convergence of rapid WGS at birth, AI-assisted variant interpretation, and scalable oligonucleotide synthesis could compress the timeline from diagnosis to therapy from the current 18-24 months to weeks.

Concluding Remarks in the Indian Context

NDDs caused by private genetic variants represent the most extreme instance of the rare disease treatment gap. The cases described above demonstrate that N-of-1 therapy can reach even the most extreme frontier of precision medicine. The early clinical results are encouraging, and the ethical mandate is clear, but the harder task remains: building the regulatory, manufacturing, economic, and knowledge-sharing infrastructure to move this paradigm from exceptional cases to systematic practice.

Genetic disorders are often thought of as "rare," but in India, with a population of 1.4 billion, their combined impact is anything but small. An estimated 70 million people, roughly 1 in 20 Indians, are living with rare diseases, most of them genetic in origin, and every year close to half a million babies are born with congenital conditions requiring lifelong care. These numbers make clear that rare diseases are not a niche issue but a growing and pressing challenge for the healthcare system. Access to treatment remains a huge challenge, largely because of very high drug costs. A notable shift came in 2025, when the Supreme Court of India

allowed a generic version of risdiplam for spinal muscular atrophy to enter the market, resulting in about a 97% drop in price: a reflection of growing recognition that life-saving medicines must be made more affordable and accessible.

For the field of human genetics, the work of translating N-of-1 medicine from proof of concept to equitable practice begins now. By investing in GMP manufacturing capacity, regulatory harmonization, and patient registry infrastructure, India can ensure that the nation, despite its substantial rare disease burden, is not merely a recipient of this paradigm, but has every capacity to help shape it.

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The Indian Society of Human Genetics

(Registered under S.R. Act, 1860)

Announcements

The Indian Society for Human Genetics (ISHG) invites nominations for Dr. L.D. Sanghvi Oration Award for the year 2027. The award will be conferred during the ISHG-2027 Annual meeting at ICMR-National Institute for Research on Blood and Immune Disorders (ICMR-NIRBID), Mumbai, February 2-4, 2027.

Last date for submission of the nominations: 30.11.2026

The nominations (as a single PDF file) should be submitted to:

The Secretary, ISHG

(ishg.secretariat@gmail.com)

Guidelines:

The Society instituted the Dr. L.D. Sanghvi Oration to be awarded every two years.

1. Objective:

The oration is intended as a tribute to the pioneering role of Dr. L.D. Sanghvi in the development of Human Genetics research in India and to show the appreciation of the Society for sustained and significant contribution made by a fellow scientist to the field of Human Genetics very early on in India.

2. Eligibility:

When the call for the award is announced by ISHG once in two years, and at least three months prior to the respective annual meeting, any Indian scientist who has worked in India for at least 15 years and has made a significant contribution to Human Genetics and related fields is eligible to be nominated, by an annual or life member of ISHG. The nominee should not have been a recipient of the Prof. I. C. Verma Lifetime Achievement Award under the Indian Society of Human Genetics. A scientist can receive the award only once.

3. Procedure for selection

- At least six to eight weeks prior to the oration during the annual ISHG meeting, the President will constitute a committee of three eminent scientists for screening nominations and selection of the awardee.
- No member of the Executive council can serve as a member of the Selection Committee.
- The president shall also choose a chairperson from among the members of the Selection Committee and inform the members accordingly and about the criteria for eligibility.
- The Selection Committee may, if necessary, call for Bio-data from additional scientists whom they wish to consider.
- The Selection Committee shall choose only one person to give the oration in the respective year.
- The Chairperson of the Selection Committee shall communicate the name of the scientist selected to The Secretary, ISHG at least three to four weeks before the respective annual meeting.
- The Secretary shall then immediately inform and request the nominee to give the Oration at the following Annual meeting and obtain a detailed Bio-data of the nominee.

4. Privileges:

- The nominee shall be invited to give the oration at a Special Session of one hour duration at the Annual meeting.
- The nominee shall be presented with a citation and a silver plaque following the oration.
- The nominee would be entitled to an economy class round trip air fare to the venue of the Annual meeting, which would be borne by the Society; and to local hospitality which will be provided by the organizers of the respective Annual meeting.
- The Society may publish in some form the oration and/or citation; and the Bio-data of the nominee.

The Indian Society of Human Genetics

(Registered under S.R. Act, 1860)

Announcements

The Indian Society for Human Genetics (ISHG) invites applications for ISHG Young Scientist Award for the year 2027.

Last date for submission of applications: 30.11.2026

The applications should be submitted to:
The Secretary, ISHG (ishg.secretariat@gmail.com)

General guidelines of ISHG-Young Scientist Award

Scope:

Every year the ISHG gives three Young Scientist Awards (YSA) in the field of Human Genetics. ISHG invites applications for YSA at least three months prior to the annual meeting. Applications received are screened by a committee of 3-4 expert members duly identified by the President and Secretary. A maximum of nine applicants would be short-listed and invited for the work presentation during the following annual ISHG meeting. As a mark of recognition, the best three works in order of merit would be selected subject to presentation and defence of the work. The three selected candidates (first, second and third) would be awarded a medal, a certificate and cash prize as detailed below; and a round-trip travel by 3 Tier AC via shortest route, all of which will be borne by the society. The three winners for the YSA would also be given a waiver of registration fee by the organisers of the respective annual meeting. The decision of the selection committee regarding the awards would be final. Awards would be declared during the General Body Meeting held during annual ISHG meeting and presented to the winners during the Valedictory function.

Age Limit:

The candidate must not have completed 35 years of age by 31st December of the preceding year or 3 months prior to the conference whichever is later. An age proof certificate must accompany the full-length research paper being submitted for YSA screening.

Number of awards: Three

Award presentation: ISHG Young Scientist Award

Award carries a medal, certificate, and prize money of Rs. 3000 (1st prize), Rs. 2,000 (2nd prize) and Rs. 1,000 (3rd prize) together with travel cover and registration waiver.

Criteria for selection

The candidate should be a member of ISHG. If the candidate is not a member, he/she can apply for the annual or life membership along with the submission of the YSA application.

The applicant should submit the following documents namely (i) Completed application form; (ii) A structured abstract (1000 words); (iii) Proof of date of birth; (iv) Brief biodata (not exceeding 2 pages); (v) Reprints of all published papers; and (vi) A letter from the mentor stating that the paper submitted for the competition is the applicant's work only, through email to ishg.secretariat@gmail.com. The candidate should also send one printed copy of the above documents by post to The Secretary, ISHG at the Secretariat address provided.

The abstract submitted must be the outcome of sole/major work done by the candidate as authenticated by the

candidate's claim for being the first author of the paper. A letter from the mentor should support this claim. If the work is a part of Doctoral thesis a certificate from the guide that the candidate is mainly responsible for the findings and interpretation, attested and countersigned as above should be enclosed. The format for the application form is given below.

Guidelines for YSA session

The committee of experts for evaluation of the oral presentation of YSA during the annual meeting will be constituted by the President and Secretary from among the experts participating in the meeting and not by the local organizing committee. The experts should refrain from evaluating the submissions of his or her student or students from his or her institute contesting for the YSA and will remain a non-voting member under this special circumstance. An alternate expert may be nominated for such candidates.

A total of nine candidates, shortlisted for consideration for the awards, would be invited to present their papers at the Annual meeting of the Society. The presentation would generally be for 12 minutes followed by 3 minutes of discussion. The YSA session should be held during prime time (forenoon session preferably on the first day, if not on 2nd day of the meeting but before the general body meeting) and as a main session and not as a parallel session. The decision of the selection committee regarding the awards would be final.

Note: All candidates who are not among the nine shortlisted, may be allowed for presentation of the work as a poster.

Application Form for ISHG Young Scientist Award

Name and Address:	
Qualification:	
Date of Birth*:	
Institution where work was carried out:	
Email ID:	
Telephone (Work/ Home):	
Mobile No.:	
Years of research experience:	
Papers published (if any) excluding those communicated or under preparation**:	
Number of reprints enclosed in three sets:	

* Attested copy of one of the following should be submitted: Birth Certificate/ SSLC/HSC/CBSE marks card.

** Reprints of all the published papers should be submitted

Check List:

- Evidence of date of birth
- Application form
- Structured abstract (not exceeding 1000 words)
- Brief biodata not exceeding 2 pages
- Reprints of all published papers

All correspondence should be sent to:

The Secretary, ISHG (ishg.secretariat@gmail.com) before the deadline.

Address:

ISHG Secretariat,
Centre for DNA Fingerprinting and Diagnostics (CDFD),
Inner Ring Rd, Opposite Metro Rail Pillar No. NUP-9, Survey Colony,
Industrial Development Area, Uppal,
Hyderabad, Telangana-500039.

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