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INVITED COMMENTARY

Genetics in Medicine Open to us all

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The completion of the Human Genome Project was the singularity of the genomic universe. Twenty years later with massively accumulated genomic knowledge and rapidly advancing genomic medicine, the American College of Medical Genetics and Genomics (ACMG) has launched *Genetics in Medicine Open (GIM Open)*, a gold open access journal for genetic and genomic science that reflects equitable, diverse, and inclusive approaches in research and clinical practice.

Why Launch This New Journal Now?

We have witnessed the big bang of genomics and genomic medicine, driven by Moore's law–beating breakthroughs in technology. It took the Human Genome Project 13 years and 3 billion dollars to sequence and analyze 3 billion base pairs of a human genome using Sanger sequencing, whereas in comparison, the most prevalent sequencing technology nowadays can accomplish the same task within a single day and under $1000. The drastically reduced cost and increased capacity, efficiency, and accuracy in production and analysis of DNA sequences have empowered large-scale family-based genomic sequencing programs. These are exemplified by the Center for Mendelian Genomics (CMG), the Undiagnosed Diseases Network (UDN), and the Genomics Research to Elucidate the Genetics of Rare diseases Consortium (GREGoR), deciphering genetic etiology of challenging genetic conditions as well as discovering new gene–disease relationships underlying human Mendelian disorders.[1-3] Multidisciplinary data have been generated during these projects, including terabytes of DNA sequence data from tens of thousands of families along with clinical phenotypes, RNA sequencing, functional characterization, animal models, metabolomics, and bioinformatic tools.

National genome sequencing projects in several countries that target the general population have also proliferated as a direct result of the advancement in genomic science and technologies. These are pioneered by the Icelandic deCode Project, the first major effort on linking genetic variation to human health conditions and care at a population level[4,5] followed by 2 other stellar examples, the UK Biobank project (UKBB) and the *All of Us* Research Program (AoURP). These latter projects, targeting generation of genome sequences of between half and 1 million national adult participants with links to health records, are implemented with the hope to comprehensively elucidate the interaction of genetic predisposition, environmental exposure, lifestyle, medication, socioeconomics, and phenotypic traits with greater power and therefore to advance personalized diagnosis, prognosis, and treatment.[6,7] Diversity is key to profiling and understanding human genomic variation as a whole, and it is one of the primary objectives of these national and international projects. Diversity has been strongly manifested in the AoURP, in which 80% of the

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participants are from groups that have been historically underrepresented in biomedical research.[7] Internationally, the Human Heredity and Health in Africa project (H3Africa) undertakes an unprecedented effort on sequencing and characterizing personal genomes from the African continent.[8] Undoubtedly, these projects will enrich our understanding of genomic variation and its role in evolution and health for all humans.

Evolution of the genomic science and technologies as well as accumulation of large genomic data sets have cultivated massive development of analytical tools, databases, guidelines, policies, and infrastructure to support and augment data generation, analysis, interpretation, storage, and sharing. *GIM Open* aims to be the leading journal in the field to publish gap-filling and cutting-edge science. In addition, *GIM Open* emphasizes equity, diversity, and inclusion in human genomic research by promoting studies that mitigate knowledge gaps for understudied populations. We are envisioning more diverse developments and innovations to advance the practice of genomic medicine surrounding the continued rapid growth of genomic data in the upcoming years. These principles should be evident in each of the following 6 areas of focus where possible.

Rapid Expansion of Computational, Populational, Functional, and Clinical Resources

Data provided by these resources are critical for evidence-based interpretation of human genomic variations. Computational tools, including those that support comprehensive detection and annotation of variants of all types, *in silico* predictors of variant pathogenicity, and literature search engine, will continue to be developed, validated, and added to the toolkits for both research and clinical efforts. For example, the Impact of Genomic Variation on Function (IGVF) Consortium consolidates both experimental and computational approaches and expertise to understand the effect of genomic variants on genome function and phenotypes. Existing large population databases, such as the Genome Aggregation Database (gnomAD), will be perhaps compared, supplemented, or integrated with other ongoing large populational sequencing efforts, such as UKBB, AoURP, H3Africa, to faithfully represent human diversity. Functional annotations of genes and genomic variations will continue to grow rapidly thanks to the expanding model organism catalog and high-throughput in vitro or in vivo assays to characterize functional consequences.[9] Clinical databases cataloging evidence-based and expert-curated human gene–variant–disease relationships and human genomic variations with interpreted clinical significance, such as the OMIM, ClinGen, and ClinVar, will continue to refresh with new gene–diseases relationships and in turn guide evidence-based clinical interpretation. These rapidly expanding resources also incentivize collaborations to drive discoveries of new mechanisms of human genetic diseases and improve analysis and interpretation of human genomic variations. Studies that expand the clinical and functional annotations of the human genome will always be a priority for *GIM Open*.

Innovative Genomic Technologies: Game Changers to Transform Genetic Diagnosis

Flash back to the late 2000s when next-generation sequencing (NGS) technology was introduced to the genomic community, there was little understanding of its data quality, variant interpretation, and utility in clinical care. Subsequently, computational tools and pipelines have been developed, benchmarked, and optimized, and standards and guidelines have been established and improved for data quality control, bioinformatic workflow, data analysis, and variant interpretation purposes to achieve high efficiency, reproducibility, accuracy, and precision. The third generation of genomic technologies, such as long-read sequencing and optical genomic mapping, have started to emerge as promising supplements or potential alternatives to the existing technologies by being specialized in sensitive interrogation of challenging complex genomic regions with highly homologous and repetitive sequences. The corroboration of variable genomic technologies, long and short, have led to the newest complete human genome reference T2T-CHM13.[10] Moreover, DNA methylation analysis has been recently developed as a clinical test to identify "episignatures" as biomarkers for a subgroup of Mendelian disorders.[11] Development and refinement of supporting tools and guidelines for these new technologies will follow a similar trajectory as the NGS development. Case examples will continue to emerge in the medical literature to showcase the clinical utility of these new technologies, which will be eventually recognized and implemented in both research and clinical set-ups. *GIM Open* will prioritize studies that investigate, use, or implement these new technologies to improve diagnosis or uncover novel mechanisms of diseases.

Clinical Practice of Genomic Medicine Shaped by Evidence-based Guidelines

Challenges have come along with the rapid development of genomic medicine. For example, owing to the extraordinary complexity and amount of genomic variants that are generated from routine clinical or research genomic sequencing, the ACMG and the Association for Molecular Pathology jointly published standards and guidelines for the

interpretation of sequence variants.[12] This guideline has become one of the most highly cited references of its kind as well as the foundation for other gene/condition-specific guidelines developed by ClinGen working groups. Technical standards for interpretation and reporting of constitutional copy-number variants have also been developed using a quantitative scoring framework, which will likely be used in future guideline development.[13] Practice standards and guidelines will continue to be developed to shape clinical practices that involve all aspects of genomic medicine, such as laboratory standards and workflow, data interpretation and reporting, diagnosis and therapies, genetic counseling, and ethical, legal, and social implications. *GIM Open* collaborates with the flagship journal *GIM* on publishing guideline articles from the ACMG. *GIM Open* is also interested in technical specifications that standardize laboratory processes of genomic data production, analysis, and interpretation. Specifications for variant interpretation that are developed based on gene- or disease-specific criteria, and studies that identify and mitigate socioeconomic and ethnical gaps of genomic medicine are also encouraged.

Artificial Intelligence as a Facilitator for Diagnosis and Research of Human Diseases

Artificial intelligence (AI) has already shown great promise in image-based diagnosis, for example using facial features to infer clinical diagnosis.[14] It has also started to flex its muscles in various aspects of clinical genomics, including variant calling, variant annotation and classification, and phenotype–genotype correlation. The decision-making process of a clinical molecular geneticist to determine the diagnostic variant from genomic data uses sophisticated algorithms involving identification, aggregation, weighing, and calculation of information that are relevant to the variant and subject's characteristics (ie, clinical phenotypes). Computers, if properly trained, can learn such human decision-making logic and execute the AI algorithm in real clinical genomic practice. AI technologies in clinical genomics, although still in their infancy, have been adopted by a few clinical genomic laboratories to accelerate genomic data interpretation. More challenges, limitations, and bias await to be identified and addressed during the evolution of AI's maturation and implementation. Studies that develop and investigate the efficacy of AI tools in genomic medicine and genomic research will be prioritized by *GIM Open*.

Implementation of Genomic Medicine in Clinical Care

Implementation science uses standardized and rigorous approaches and frameworks to evaluate and facilitate the uptake of evidence-based methods and research into practice. It also conducts outcome measurements so that the implemented approach can be iteratively evaluated, improved, and optimized by accounting for factors that are underrecognized during planning. The implementation of genomic medicine covers a variety of expertise involved in patient care workflow. Those may include, but are not limited to, laboratory procedures and methodology, bioinformatic pipelines, data analysis and interpretation framework, clinical informatics and infrastructure, data storage and management, return of genomic results, clinical management workflow, patient and provider education, integration of genomic data and electronic health record, clinical decision making, and therapeutic intervention. The early implementation projects focusing on pharmacogenomics, diagnostic testing, somatic cancer testing, and population screening have shown improved efficiency and effectiveness of patient care and in the meantime identified barriers and facilitators to the use of genomic medicine in the clinic, exposing opportunities for future research and development.[15] With more personal genomic data being generated, the focus may shift toward developing, understanding, and implementing mechanisms of delivering genomic results and subsequently advancing the effect of genomic medicine in clinical care. Studies that implement tools, procedures, and resources to facilitate integration of genomic medicine in clinical care will be a strongly emphasized topic in *GIM Open*.

Increased Desire and Demand in Data Open Sharing

The Bermuda Principles of 1996 (http://www.ornl.gov/hgmis) is a landmark of open science. It is also a precedent for later data-sharing policies and initiatives that cover much more diverse aspects of genomic medicine represented by stakeholders from both research and clinical territories. These data include genomic data of all kinds and at all levels (from microarray to NGS, from raw sequence reads to interpreted genomic variation), functional data and computational tools to support genomic data analysis and interpretation, and health-related data (phenotype, medication, environmental exposure, etc). Sharing clinical, functional, and variant data on platforms such as GeneMatcher and MatchMaker Exchange has fostered productive international collaborations to accelerate discovery and characterization of new disease mechanisms. Open access to large population data, such as sequence and trait data in UKBB, AoURP, and the database of Genotypes and Phenotypes (dbGaP), offers tremendous opportunity for all researchers to use the "big data" of high diversity and advance the cutting-edge of science. The ACMG also recognizes the importance of open data sharing and identifies the

knowledge and practice gaps.[16] These have been approached by large efforts such as the Global Alliance for Genomics and Health (GA4GH). We will expect more initiatives, either local or global, to address the need of policy frameworks and technical standards to reduce concerns and risks regarding legal/ethical issues and data privacy/security, execute effective data aggregation and harmonization, and ensure data interoperability and compatibility. *GIM Open* as a gold open access journal strongly encourages data deposition in public databases and mandates sharing of data and protocols. It welcomes research, review, commentaries, and perspectives that demonstrate the advantages, limitations, current status, and challenges of open data sharing.

Final Remarks

GIM Open is now calling for papers that respond to these challenges. In addition, *GIM Open* will consider exploratory research that innovates or implements new science and technologies in genomic medicine, including studies that are at preliminary stage but show strong scientific rigor, validity, reproducibility, and/or clinical potential.

We are in a golden era of genomic medicine. The technology advancements continue to generate massive and diverse genomic data, accompanied by increased availability of clinical and functional annotations and a plethora of effective and user-friendly tools and databases to help researchers to navigate the data lake. These ingredients of genomic research are truly stimulating. Importantly, guidelines and policies regarding bioethics need to be constantly developed, implemented, updated, and improved to direct investigators to ethically and productively harness the power of genomics. The future of genomic medicine will be steered toward developing and implementing innovative concepts and technologies for all health care stakeholders including patients, providers, and researchers—an open and equitable genomic medicine for all! This is where we introduce *GIM Open*, aiming to become a responsive and proactive journal that promotes the visibility of a broad range of topics related to genomic medicine and leads the field in publishing high-quality studies that are shepherded by our highly reputed editors. As an official journal of the ACMG, and closely collaborating with the flagship journal *GIM, GIM Open* will become a forum for sharing trailblazing science and education, an incubator for emerging new technologies and ideas, and a partner for the entire genomic medicine community.

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Conflict of Interest

B.Y. currently serves as the Editor-in-Chief of *Genetics in Medicine Open*.

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