Genomic medicine in Africa: a need for molecular genetics and pharmacogenomics experts

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ABSTRACT

The large-scale implementation of genomic medicine in Africa has not been actualized. This overview describes how routine molecular genetics and advanced protein engineering/structural biotechnology could accelerate the implementation of genomic medicine. By using data-mining and analysis approaches, we analyzed relevant information obtained from public genomic databases on pharmacogenomics biomarkers and reviewed published studies to discuss the ideas. The results showed that only 68 very important pharmacogenes currently exist, while 867 drug label annotations, 201 curated functional pathways, and 746 annotated drugs have been catalogued on the largest pharmacogenomics database (PharmGKB). Only about 5009 variants of the reported ~25,000 have been clinically annotated. Predominantly, the genetic variants were derived from 43 genes that contribute to 2318 clinically relevant variations in 57 diseases. Majority (~60%) of the clinically relevant genetic variations in the pharmacogenes are missense variants (1390). The enrichment analysis showed that 15 pharmacogenes are connected biologically and are involved in the metabolism of cardiovascular and cancer drugs. The review of studies showed that cardiovascular diseases are the most frequent non-communicable diseases responsible for approximately 13% of all deaths in Africa. Also, warfarin pharmacogenomics is the most studied drug on the continent, while CYP2D6, CYP2C9, DPD, and TPMT are the most investigated pharmacogenes with allele activities indicated in African and considered to be intermediate metaboliser for DPD and TPMT (8.4% and 11%). In summary, we highlighted a framework for implementing genomic medicine starting from the available resources on ground.

Introduction

Genomic medicine is a multidisciplinary field that involves the use of genomic information to identify biomarkers that can reflect the expression, function, or regulation of a gene for medicinal purposes. It has become one of the fastest-growing areas in health sciences. Since the discovery of the DNA double helix, several studies have detailed information on the molecular mechanisms and cellular processes of genetic inheritance, the stability of the genome, and identified mutation(s) that lead to a particular phenotype. Many techniques have been invented to identify, isolate, and manipulate molecular components in cells including DNA, RNA, and proteins. Improvements in the methods ensure that scientists can fully understand the DNA replication, repair, recombination, and transcription processes. The understanding of cell regulations and signaling pathways in complex biological processes and diseases is advantageous in drug discovery. Millions of genetic variations have been identified in humans. It is believed that some of these variations play active roles in drug treatments. Different levels of biological associations are to be studied before a drug can be designed based on genomic information. Genetically designed drugs may produce better efficacy than conventional drugs.

However, the large-scale implementation of genomic medicine in Africa is far from realization, despite that Africans are highly genetically diverse. Recently, the African Academy of Sciences experts published a framework for implementing genomic medicine in Africa. The discussions rest on two-pronged approach to address: (1) Filling the gaps in the locally relevant genomic research and (2) implementing clinical research for relevant diseases. They identified that clinical facilities for patient counseling, screening, treatment, and monitoring are essential parts of genomic medicine. Also, sample collection, processing and data generation facilities, data storage, curation, analysis,
interpretation, and sharing infrastructure are considered very important.

They also identified the need to make available genomic medicine training programmes for healthcare professionals as parts of the needs. Most importantly, they reflected on the need to advance knowledge bases with up-to-date information on genotype-phenotype link and actionability. Nonetheless, the framework was generalized. Perhaps, breaking the topics into different sections of genomic medicine will simplify the area to identify some of the specific challenges and solutions. Based on this, our study aligned the opinions of the experts and further reiterate that rare diseases contribute to increasing death and disabilities in Africa. Our study focused on pharmacogenomics and molecular genetics as the major link to implement genomic medicine in Africa. The study leveraged on the existing knowledge to provide information on the importance of pharmacogenetic data to genomic medicine in Africa.

Limited capacity is the forefront of the challenges facing the implementation of genomic medicine, because advanced genomic techniques are needed to implement genomic medicine. For example, it costs about $250 per sample for whole-exome sequencing of X50 coverage, and about $1800 for whole-genome sequencing. The issue regarding the storage systems and securing licenses for cloud computing also limit robust data analyses in genomic medicine. Beside, due to numerous identification of variants of unknown significance, more advanced knowledge and analyses are necessary to determine the relevance of these genetic variants to genomic medicine. The study aims to identify the gaps in knowledge and highlight the current state of genomic medicine in Africa to improve research interests in this area.

Results

There are currently 68 very important pharmacogenes and 168 pharmacogenomics testing panels publicly available. The panels were annotated majorly in the United States, Europe, and Asia. African genomic data currently represent only ~2\% of the available genomic data. There are 867 drug label annotations, 201 curated functional pathways, and 746 annotated drugs (Supplementary File 1) currently catalogued on the PharmGKB database for pharmacogenomics research. Only about 5009 variants of the reported ~25,000 have been clinically annotated. Predominantly, the genetic variants were derived from 43 genes that contribute to 2318 clinically relevant variations in 57 diseases. The overall variations include missense variants of 1390 (~60\%) and others (Figure 1).

Further analyses of the 43 genes revealed that 15 genes have a very strong biological co-expression and physical interactions involved in drug metabolism in cardiovascular and cancer drugs (Figure 2). The Cytochrome P450 2D6 (CYP2D6) is a critical pharmacogene that used ensemble classifier to analyze DPYD and TPMT genetic variability based on sequencing data from 138,842 individuals across eight populations and found the variant frequencies from 138,842 individuals across eight different populations (12,487 Africans, 17,720 Latinos, 5185 Ashkenazi Jews, 9977 East Asians, 64,603 Non-Finnish Europeans, 12,562 Finnish, 15,308 South Asians and 1000 Swedes). The majority of reduced function alleles in Africans are allotted to the population-specific variants Y186C, A450V, and V732G.

Materials and methods

We assembled pharmacogenetic information on the National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/), Ensembl (https://www.ensembl.org/), ClinVar, Online Mendelian Inheritance in Man (OMIM), and Geo Dataset. Specifically, we retrieved the .tsv files containing the Variant, Gene and Drug Relationship Data, Variant and Clinical Annotations Data, Drug Label Annotations and Clinical Variant Data on the PharmGKB (www.pharmgkb.org) as the leading resource for clinical and functional annotations of drugs used in genomics medicine for analyses. We extracted information on phenotypes, important pharmacogenes, and available drug markers. We filtered the pharmacogenes based on the functional annotation which has been done by various curators using the criteria for selecting variant which have been associated with certain phenotypes as well as variants with actionable PgX or informative PgX. Then, we performed enrichment analyses for the selected genes to determine their functional pathways in health and diseases by using the GeneMania tool (https://genemania.org) a tool that predicts the function of favorite genes and gene sets.
with minor allele frequencies (MAFs) of 2.2%, 0.3%, and 0.2%, respectively and constitute adverse drug reactions. Also, the ethnogeographic differences of clinically important DPD and TPMT allele activity indicated that African were mostly considered intermediate metabolizer for DPD and TPMT (8.4% and 11%) respectively. This is rare in the European populations which were considered poor metabolizers and in South Asian which were considered normal metabolizers. Nineteen studies have been reported on the genetics of warfarin treatment specifically among Africans where genes like CYP2C9, VKORC1, CYP4F2, APOE, CALU, GGCX, and EPHX1 were identified. The literature also point to some major challenges that are confronting genomic medicine in Africa which are data collection (diagnostics and screening), data analysis and unavailability of genomic panels for Africans, lack of awareness, and limited resources to justify the application of genomic medicine.

**Discussions**

Our study focused on identifying knowledge gaps in the pharmacogenomics studies in Africa, which is an important arm of genomic medicine. The data-mining approach uncovered disparities in metadata toward African genomic dataset. The absence of robust African dataset in global genomic databases is no longer a news. In perspective the genomic labeled drugs currently available are annotated based on non-African genomic datasets suggesting that the drugs might not be suitable for African populations.

Genetics is driving clinical research and modern medicine globally. Genetic discoveries make it easy to evaluate individual variability to genes, environment, and lifestyle. The ability to prioritize numerous disease-causing mutations has important ramifications for genomic medicine. To date, more than 4000 diseases have been linked to mutations in genes. Having genomic information about people is advantageous for diagnosis, prediction, and pharmacogenomics. New genetic variants and loci with important biological functions like DNA repair, metabolism and viral immunity are being uncovered from the African datasets that need to be considered in pharmacogenomic research. Sometimes, the function of one gene may affect other genes. The reason we performed the gene enrichment network analyses, was to identify closely related genes that may co-interact in the annotated drugs. Indeed, we identified that the DPYD gene has the highest clinically relevant variants with pharmacogenomics implications. The DPYD gene provides instructions for making an enzyme called dihydropyrimidine dehydrogenase, which is involved in the breakdown of molecules called uracil and thymine. The gene is described to influence cancer drug treatments and often co-interact with other functional genes.

There are many benefits in implementing translational pharmacogenomics research in Africa. For examples, warfarin remains the most widely prescribed and an anticoagulant of choice in Africa. Studying the variability in the pharmacokinetics and narrow therapeutic index of warfarin has yield significant information for understanding the metabolism, molecular targets and host-environment interactions. Based on 19 studies on the genetics of warfarin treatment specifically among Africans, genes like CYP2C9, VKORC1, CYP4F2, APOE, CALU, GGCX, and EPHX1 have been investigated. With the CYP2C9*2 and *3 alleles highly frequent among Egyptians, while rare in other African populations. CYP2C9*5, *8, *9, and *11, and VKORC1 Asp36Tyr genetic variants explained warfarin variability in Africans better, compared to CYP2C9*2 and *3.

Furthermore, the CYP2D6 gene which is a critical pharmacogene involved in the metabolism of ~20% of commonly used drugs across a broad spectrum of medical disciplines including psychiatry, pain management, oncology and cardiology have not been thoroughly investigated in the African populations. Earlier studies on the relationship between predicted and measured CYP2D6 phenotypes in the African populations (especially, South Africans, Zimbabwean, Kenyans, and Ugandans described this gene to be polymorphic and showed phenotypic frequencies variability of 1.3% for poor metabolizers (PM), 7.6% for intermediate metabolizers (IM) and 87.3% for extensive metabolizers (EM)). However, there is limited pharmacogenomics data in Africa that can be translated into clinical settings. There is an average of only 1 to 3 studies available on each of the known pharmacogenes in the whole continent comprising 54 countries. Nonetheless, more information about pharmacogenetics in African populations will continue to emerge from various initiatives like the African Pharmacogenomics Consortium (APC) of SAMRC/UCT Platform for Pharmacogenomics Research and Translation Research Unit, South Africa (https://www.samrc.ac.za/extramural-research-units/platform-pharmacogenomics-research-and-translation).

So, what can be done to overcome some of these challenges? We identified, molecular genetics has a huge role to play in genomic medicine. Since the completion of the human genome variation project, about 96% of the genome can be studied with high confidence. More than 80 million variant sites in the genome have been found so far and have infused enormous benefits to biomedical and medical research to date (https://www.genome.gov). The project leverages major techniques in molecular genetics. Thus, by using similar approaches, high-powered molecular genetics studies should be adequately implemented focusing on two key areas (discovery and translational). The targeted DNA sequencing panels for diagnosing diseases in patients will be integral in genomic medicine practice. Studies have shown that genetic testing can improve disease diagnosis and treatment. There is a need to prioritize techniques that can rapidly discover unique genetic variants and produce well-annotated genotype-phenotype data. Moreover, in translational studies, genetic profiling will be an integral part of drug discovery in the future. The genetic profiling of genes and protein functions should be a major priority. Presently, the protein data bank (PDB) contains more than 126,000 3D structures of various biological macromolecules (https://www.rcsb.org/) that can be used for establishing the putative effects of mutations clinically and therapeutically. Nonetheless, the functions of proteins of highly polymorphic genes in drug metabolism still warrant
expansive functional investigations. It means that Africa needs experts in genetic and protein engineering that can extensively annotate genomic pathways to reveal important findings. If a novel pathway requires an enzyme to act on novel substrates, expertise in protein and metabolic engineering would be needed, like the massive production of therapeutic agents in pharmaceutical, research, and healthcare services to treat immune disorders which involve models of ribosome binding sites that demand expertise. The implementations of discovery and translational research in molecular genetics have the potential to attract pharmaceutical companies that will invest in pharmacogenomics research so that Africa will be able to produce population-specific treatments in the future. We highlighted in some techniques in molecular genetics that are used for nucleic acids studies, editing of genes, and analysis of metabolic pathways. The introduction of next-generation sequencing is revolutionizing the field of molecular genetics and genomic medicine. Also, advances in CRISPR Cas9, fluorescence nanoscopy, microfluidics, induced pluripotent stem cells (iPSCs), and optogenetic are proven to establish new prospects in genomic medicine. In addition, protein docking, and enzymes analyses contribute to the understanding of biological pathways and establish diseases and drug discoveries. It is imperative to consider developing capacity for high computing power as well to maximize molecular genetics studies.

Effective collaboration is important for achieving large-scale genomic medicine in Africa. The vision of Human Heredity and Health in Africa (H3Africa) consortium (https://h3africa.org/) is providing some answers already. H3Africa currently has up to 51 ongoing projects addressing the need of African genomic research to understand the genetic causes of common diseases in Africa like malaria, tuberculosis, sickle cell disease, diabetes. However, there is gap in knowledge of how the findings from these project will translate to human health. Our study adds a piece to the knowledge required to implement genomic medicine as described in Figure 3, this pattern describe a synergy of basic, clinical genetics, and translational studies (Figure 3) which can be achieved through investments in innovation and training. The good news is that the H3Africa project and the African Society of Human Genetics (https://www.afshg.org/) have been stabilized in over 30 locations in Africa majorly in South Africa, Nigeria, Egypt, Tunisia, Uganda, Democratic Republic of Congo, Tanzania, Mali, Ghana, Cameroon,
Morocco, and Kenya. The proposed framework will benefit by leveraging on H3Africa collaborations for the training and applications of molecular genetics, clinical genetics, biotechnology, and pharmacogenomics to drive genomic medicine forward in Africa. It is important to promote the awareness among the populace and negotiate research funding from the governments. One of the major reasons scientists in Africa do not get adequate support from the government is that government needs data, evidence, and conviction that people will appreciate the initiative before they can come to terms. However, foreign support still supersedes research support in Africa. The only way that African scientists can get adequate support from the populace is to continue to create awareness and education about genomic medicine. The future of modern medicine is translational. The stakeholders should harmonize the existing molecular genetics laboratories in urban and rural areas. This will necessitate molecular genetics training programs among interested healthcare providers. The demand for molecular geneticists in the future will increase drastically and Africa will benefit immensely from these programs.

For example, in 2019, the African Pharmacogenomics Consortium (APC) planned to develop a website/database for the genetics of drug effectiveness in African datasets, however, to date, the server is not currently running or accessible. The limitations maybe due to the facts that the initiative plan to consolidate pharmacogenomics research and its implementation in Africa through strategic collaborations of Africans based in Africa leveraging expertise from international partners. This initiative would benefit immensely on the successes of African Genome Variation Project (https://www.sanger.ac.uk/science/collaboration/afri-can-genome-variation-project). However, we believe that even if millions of African variations are obtained through AGVP or the Three Million African Genomes (3MAG), which would build capacity on the continent in genomics research and its applications, and governance, nonetheless, we should be reminded that even on the PharmKGB that currently has over 25,000 annotated variants, only a few ~800 are actionable pharmacogenomic biomarkers. The reason is that it usually takes a lot of effort and clinical trials to produce a drug, of which the numerous drugs available in the markets have not been studied genetically. Hence, in the future, it would be great to have an initiative that we proposed to do in future study which would profile daily administered drugs pharmacologically and genetically in terms of active biomarkers derived from the African populations.

### Conclusions

The hallmarks of molecular genetics to drive genomic medicine programs in Africa in the discovery stage should focus mainly on genetic profiling, haplotype analysis, single nucleotide polymorphism analysis, drug responses, target identification, and gene expression analysis. While the translation stage should focus on expansive functional studies, pharmacogenomics annotated drug production, drug repurposing, and clinical trials. It is important to draw motivations from the successes of genetics research in Africa so far and to leverage the existing collaborations to attain greater success for genomic medicine in Africa. Since genomic medicine

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**Table 1.** Brief information on selected pharmacogenes with plausible effects in African datasets.

| Gene       | Disease-associated alleles | Implicated diseases                                                                 |
|------------|----------------------------|-------------------------------------------------------------------------------------|
| CACNA1S    | Calcium voltage-gated channel | 3                                                                                   |
| CFTR       | Cystic fibrosis transmembrane conductance regulator | 40                                                                    |
| CYP2D2     | Cytochrome P450 2D6         | 310                                                                                 |
| CYP2B6     | Cytochrome P450 family 2 subfamily b member 6 | 35                                                                                 |
| CYP2C19    | Cytochrome P450 family 2 subfamily C member 19 | 34                                                                                 |
| CYP2C9     | Cytochrome P450 family 2 subfamily C member 9 | 71                                                                                 |
| CYP3A5     | Cytochrome P450 family 3 subfamily a member 5 | 9                                                                                   |
| CYP4F2     | Cytochrome P450 family 4 subfamily f member 2 | 3                                                                                   |
| DPDYD      | Dihydropyrimidine dehydrogenase | 83                                                                                   |
| IFNL3      | Interferon lambda 3         | 2                                                                                   |
| NUDT15     | Nudix hydrolase 15          | 20                                                                                  |
| RYR1       | Ryanodine receptor 1        | 49                                                                                  |
| SLCO1B1    | Solute carrier organic anion transporter family member 1B1 | 37                                                                                 |
| TPM1       | Thiopurine S-methyltransferase | 46                                                                                  |
| UGT1A1     | UDP glucuronosyltransferase family 1 member A1 | 9                                                                                   |
| VKORC1     | Vitamin K epoxide reductase complex subunit 1 | 2                                                                                   |
relied evidence for a link between a genetic feature and a clinical action. There is no doubt that genomic medicine is on the right path in Africa. The knowledge of genetic sequencing for disease diagnoses have increased tremendously through various initiatives like the H3Africa. Also, therapeutic intervention broaden on genomic sciences knowledge will continue to advance if the current policies for implementing genomic medicine in Africa are sustained.

Transparency

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Declaration of financial/other relationships

The authors declared that there is no conflict of interest. A reviewer on this manuscript has disclosed that they are a non-executive director and shareholder of Gknowmix (Pty) Ltd. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Author contributions

OGO conceptualized the idea, performed literature and resources search, annotated data, and drafted the manuscripts. MH assisted with the literature search and validated data.

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Data availability statement

Data used in the study can be requested from the corresponding author.

References

[1] Roth SC. What is genomic medicine? J Med Libr Assoc. 2019;107(3):442–448.
[2] Travers A, Muskhelishvili G. DNA structure and function. Febs J. 2015;282(12):2279–2295.
[3] Khan S, Ullah MW, Siddique R, et al. Role of recombinant DNA technology to improve life. Int J Genomics. 2016;2016:e2405954.
[4] Jongeneel CV, Kotze MJ, Bhat-Luximon A, et al. A view on genomic medicine activities in Africa: implications for policy. Front Genet. 2022; [cited 2022 Aug 3]. Available from: doi: 10.3389/fgene.2022.769919
[5] Grosse SD, Gudgeon JM. Cost or price of sequencing? Implications for economic evaluations in genomic medicine. Genet Med. 2021;23(10):1833–1835.
[6] Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–4424.
[7] Zhou Y, Dagli Hernandez C, Lauschke VM. Population-scale predictions of DPD and TPMT phenotypes using a quantitative pharmacogene-specific ensemble classifier. Br J Cancer. 2020;123(12):1782–1789.
[8] Ashley EA. Towards precision medicine. Nat Rev Genet. 2016;17(9):507–522.
[9] Mattick JS, Dziadek MA, Terrill BN, et al. The impact of genomics on the future of medicine and health. Med J Aust. 2014;201(1). [cited 2021 Oct 12]. Available from: https://www.mja.com.au/journal/2014/201/1/impact-genomics-future-medicine-and-health.
[10] Marian AJ. Clinical interpretation and management of genetic variants. JACC Basic Transl Sci. 2020;5(10):1029–1042.
[11] Jackson M, Marks L, May GH, et al. The genetic basis of disease. Essays Biochem. 2018;62(5):643–723.
[12] Vozikis A, Cooper DN, Mitropoulou C, et al. Test pricing and reimbursement in genomic medicine: towards a general strategy. Public Health Genomics. 2016;19(6):352–363.
[13] Choudhury A, Ramsay M, Hazehurst S, et al. Whole-genome sequencing for an enhanced understanding of genetic variation among South Africans. Nat Commun. 2017;8(1):2062.
[14] Ndazza A, Muyambo S, Mntla P, et al. Profiling of warfarin pharmacokinetics-associated genetic variants: Black Africans portray unique genetic markers important for an African specific warfarin pharmacogenetics-dosing algorithm. J Thromb Haemost. 2021;19(12):2957–2973.
Oluka MN, Matimba A, Okalebo FA, et al. Characterization of inter-ethnic genetic variability of CYP2D6, CYP2C19, CYP2B6, NAT2 and GSTs in the bantu and nilotic populations of Kenya and implications for the chemotherapy of infectious diseases. Afr J Pharmacol Ther. 2014;3(2). [cited 2022 Aug 3]. Available from:

Dodgen TM, Labuschagne CDJ, van Schalkwyk A, et al. Pharmacogenetic comparison of CYP2D6 predictive and measured phenotypes in a South African cohort. Pharmacogenomics J. 2016;16(6):566–572.

Miura J, Obua C, Abbo C, et al. CYP2D6 genetic variation in Ugandans. Eur J Clin Pharmacol. 2022;78(1):697–708.

Esplin ED, Oei L, Snyder MP. Personalized sequencing and the future of medicine: discovery, diagnosis and defeat of disease. Pharmacogenomics. 2014;15(14):1771–1790.

Rehm HL. Disease-targeted sequencing: a cornerstone in the clinic. Nat Rev Genet. 2013;14(4):295–300.

Horton RH, Lucassen AM. Recent developments in genetic/genomic medicine. Clin Sci. 2019;133(5):697–708.

Zeggini E, Gloyn AL, Barton AC, et al. Translational genomics and precision medicine: moving from the lab to the clinic. Science. 2019;365(6460):1409–1413.

Carestia A, Kim SJ, Horling F, et al. Modulation of the liver immune microenvironment by the adeno-associated virus serotype 8 gene therapy vector. Mol Ther Methods Clin Dev. 2021;20:95–108.

Brar GA, Weissman JS. Ribosome profiling reveals the what, when, where and how of protein synthesis. Nat Rev Mol Cell Biol. 2015;16(11):651–664.

Breker M, Schuldiner M. The emergence of proteome-wide technologies: systematic analysis of proteins comes of age. Nat Rev Mol Cell Biol. 2014;15(7):453–464.

Mohr SE, Smith JA, Shamu CE, et al. RNAi screening comes of age: improved techniques and complementary approaches. Nat Rev Mol Cell Biol. 2014;15(9):591–600.

Roth-Walter F, Adcock IM, Benito-Villalvilla C, et al. Immune modulation via T regulatory cell enhancement: disease-modifying therapies for autoimmunity and their potential for chronic allergic and inflammatory diseases—an EAACI position paper of the task force on immunopharmacology (TIPCO). Allergy. 2021;76(1):90–113.

Saliba AE, Vonkova I, Gavin AC. The systematic analysis of protein-lipid interactions comes of age. Nat Rev Mol Cell Biol. 2015;16(12):753–761.

Rinschen MM, Ivanisevic J, Giera M, et al. Identification of bioactive metabolites using activity metabolomics. Nat Rev Mol Cell Biol. 2019;20(6):353–367.

Goodwin S, McPherson JD, McCombie WR. Coming of age: ten years of next-generation sequencing technologies. Nat Rev Genet. 2016;17(6):333–351.

Duncombe TA, Tentori AM, Herr AE. Microfluidics: reframing biological enquiry. Nat Rev Mol Cell Biol. 2015;16(9):554–567.

Jerkovic I, Cavalli G. Understanding 3D genome organization by multidisciplinary methods. Nat Rev Mol Cell Biol. 2021;22(8):511–528.

Larance M, Lamond AI. Multidimensional proteomics for cell biology. Nat Rev Mol Cell Biol. 2015;16(5):269–280.

Lopes R, Korkmaz G, Agami R. Applying CRISPR–Cas9 tools to identify and characterize transcriptional enhancers. Nat Rev Mol Cell Biol. 2016;17(9):597–604.

Pickar-Olive A, Gersbach CA. The next generation of CRISPR–cas technologies and applications. Nat Rev Mol Cell Biol. 2019;20(8):490–507.

Sahl SJ, Hell SW, Jakobs S. Fluorescence nanoscopy in cell biology. Nat Rev Mol Cell Biol. 2017;18(11):685–701.

Shamir ER, Ewald AJ. Three-dimensional organotypic culture: experimental models of mammalian biology and disease. Nat Rev Mol Cell Biol. 2014;15(10):647–664.

Tischer D, Weiner OD. Illuminating cell signalling with optogenetic tools. Nat Rev Mol Cell Biol. 2014;15(8):551–558.

Bhattacharya R, Rose PW, Burley SK, et al. Impact of genetic variation on three dimensional structure and function of proteins. PLoS One. 2017;12(3):e0171355.

Glusman G, Rose PW, Prlic A, et al. Mapping genetic variations to three-dimensional protein structures to enhance variant interpretation: a proposed framework. Genome Med. 2017;9(1):113.

Meng XY, Zhang HX, Mezei M, et al. Molecular docking: a powerful approach for structure-based drug discovery. Curr Comput Aided Drug Des. 2011;7(2):146–157.

Tanjo T, Kawai Y, Tokunaga K, et al. Practical guide for managing large-scale human genome data in research. J Hum Genet. 2021;66(1):39–52.

Wonkam A. Sequence three million genomes across Africa. Nature. 2021;590(7845):209–211.