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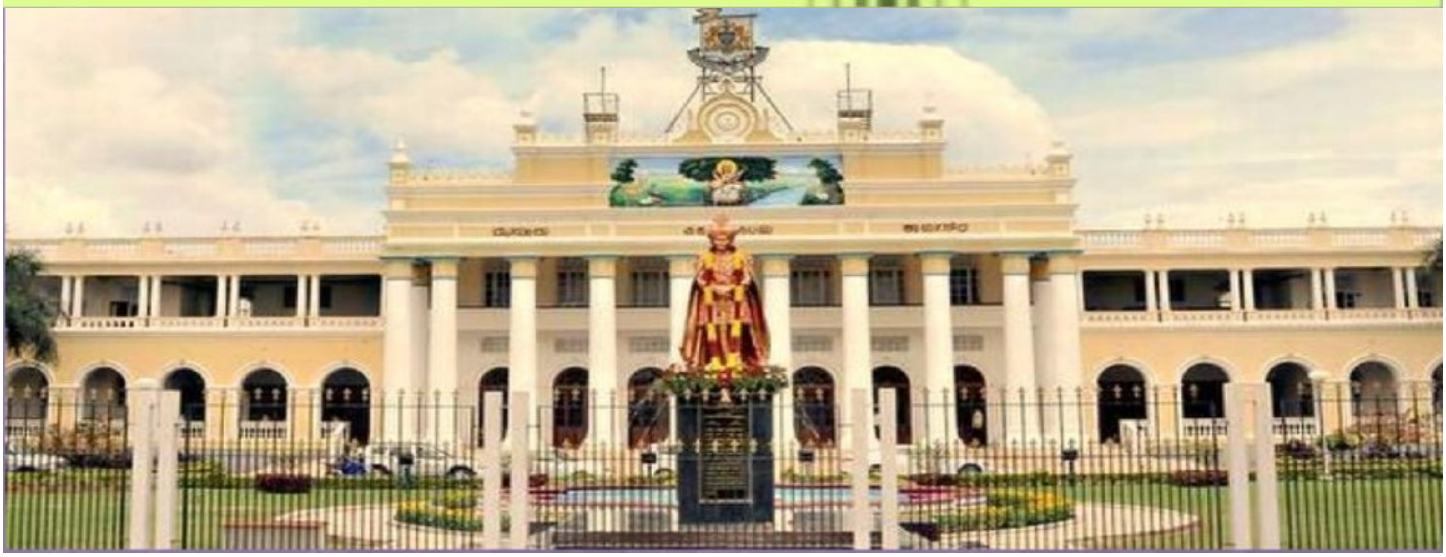
University of Mysore

(Estd.1916)

POSTGRADUATE DIPLOMA IN PERSONALISED GENOMIC MEDICINE



UNIVERSITY OF MYSORE

Title of the Program

"Post-graduate Diploma Program in Personalized Genomic Medicine"

For Skill Development

PREAMBLE:

The Information and potential use of genomic discoveries are no longer issues left for scientists and medical professionals to handle, but have become ones for the public at large. Rarely a day passes without genomics related story reported in the media. The proposed diploma program is designed to provide advanced knowledge dissemination in the field of genome sciences, applications and laboratory skills needed for molecular diagnostics and precision medicine procedures conducted in a clinical or research environment. The program is intended for those individuals who wish to enhance their laboratory expertise and knowledge in molecular-based methods.

Precision medicine has the potential to fundamentally change how health care is practiced, but requires a trained health care workforce that understands the complexities of this field. One important component of precision medicine is the use of an individual's genomic information to offer targeted treatment, tailored to the individual. Our course aims to provide participants with advanced knowledge of genomics, an overview of the clinical applications of genomic medicine, the skills to evaluate the clinical validity and utility of new tests, and an appreciation of the associated ethical and social issues inherent in this field.

The course is geared towards individuals with a background in the biological sciences and a basic understanding of genetics. It is designed to be succinct and clinically focused, offering both conceptual and practical information about real-world applications of genomics. The syllabus offers a basic knowledge

on genomics relevant to the individual patient as well as to patient populations. Further, the lessons also focus on applications of genomics and present the material as case studies, highlighting the strengths, limitations, and issues that arise in the use of each test.

Next-generation sequencing (NGS) has the potential to make genome sequencing an integral aspect of personalized medicine in the near future. The sensitivity and specificity of genetically characterizing mutations in patients has profound implications for treatment choices and predicting potential responses. NGS is arguably one of the most significant technological advances in biological sciences of the last 30 years; we therefore should provide scientific workforce capable of exploiting various NGS platforms to help in advancing the quality of health care.

1. Name of the University/ Institution: **University of Mysore**
2. Title of proposed course: **Post-graduate Diploma Program in Personalized Genomic Medicine (PGDPGM)** (under Computational Biology category)
3. Duration of the Course: **12 months (1 Year/2 semesters)**
4. Duration of the Program: **3 Years**
5. Objectives of the course:
    a. **To impart extensive theoretical and practical knowledge required for genomic personalized precision medicine**

    b. **To create and train scientific workforce to meet the growing pace of Next-generation sequencing (NGS) in clinical genomics**

    c. **To train and conduct research on valid clinical subjects**

6. Number of seats per year: **12**
7. Mode of selection of students: **National level through written entrance test**
8. Eligibility for admission
    - Post-Graduate in Medical Science (MD/MD-Ayurveda/MDS)

- Post-Graduate in Basic Sciences in Biotechnology/Genetics/ Applied Genetics/Genomics/Molecular Biology/Biochemistry/ Zoology/Life Sciences or in equivalent areas
- Post-Graduate in Engineering Sciences (e.g. M.Tech in Biotechnology)
- Post-Graduate in Pharmaceutical Sciences (MPS)

UNIVERSITY OF MYSORE
Department of Studies in Genetics and Genomics

CREDIT MATRIX FOR

Post-graduate Diploma Program in Personalized Genomic Medicine

(PGDPGM) 2017-18

Semester I					
Paper code	Title of the Course	L	T	P	Credit
1.1	**Human Genetics and Diseases**	3	1	0	**4**
1.2	**Human Genomics**	3	1	0	**4**
1.3	**Molecular Genomics**	3	1	0	**4**
1.4	**Precision Genomic Medicine**	3	1	0	**4**
1.5	**Genetics and Genomics - Practical - I**	0	0	4	**4**
1.6	**Personalized genomic medicine- Practical - II**	0	0	4	**4**
	Total Credits				**24**
Semester II					
Paper code	Title of the Course	L	T	P	Credit
2.1	**Interactive Session**	0	2	0	**2**
2.2	**Seminar presentation**	0	2	0	**2**
2.3	**Project/Dissertation**	0	2	10	**12**
	Total				**16**
	Grand Total Credits				**40**

CHAIRMAN
BOS in Genetics

Detailed syllabus

Paper 1.1: Human Genetics and Diseases 48 Hrs

Unit I **16Hrs**

Human Genetics: Introduction to human genetics, human chromosomes, karyotyping, chromosome structure and function, Pedigree analysis, Patterns of Inheritance, Mendelian inheritance, Sex linked Inheritance, Linkage and Interaction of genes, Types of human genetic Diseases.

Unit II **16 Hrs**

Genetic basis of Diseases and disorders: a) Monogenic diseases, b) Inborn errors of metabolism, c) Neurogenetic disorders, d) Genetic disorders of Haemopoetic systems, e) Genetic disorders of eye, f) Muscle genetic disorders, g) Genetic disorders in skeleton and skin, h)) Congenital heart diseases,i) Learning disorders, j) Genetics of Infertility, k) Cognitive disorders, l) Complex syndromes, m) Mitochondrial syndromes.

UNIT III **16 Hrs**

Diagnosis, Counseling, Therapy and Ethics: a) Prenatal diagnosis: Noninvasive methods and Invasive methods, b)Technology in reproductive assistance, c) Genetic counseling in Mendelian and multifactorial syndromes, d) Gene therapy - Viral and Non-viral methods, Stem cell therapy, RNAi in treatment, miRNAs in cancer: tumor suppressors and oncogenes, e) Ethics -Legal, social and ethical considerations. Protection against Discrimination based on Genetic Information: The Genetic Information and Nondiscrimination Act (GINA).

Paper 1.2: Human Genomics 48Hrs

Unit I **16 Hrs**

i) Human genome: Genome organization, gene organization, gene expression and regulation- at chromatin level, transcription and translational levels, epigenetics and epigenomics.

ii) Genome projects: The Human genome project, HapMap Project, The 1000 genome project, and The ENCODE Project.

iii) **Epidemiology:** Diseases in Populations, population specific diseases and protection, Minor allele frequency, genome architecture between populations, adaptive evolution of human genome.

Unit II **16 Hrs**

i) Genomic variations: Single Base Variations (Synonymous, Nonsynonymous, Stop gain, read through, splice site, promoter and TFBs mutations/polymorphisms), Multi Base Variations (Insertions, Deletions, Frame shift), Copy Number Variations (Duplications, Deletions), Structural Variations (Translocations, Inversions).

ii) Human genome mapping methods: Genetic mapping: Linkage analysis (RFLP/MS/SNP), Gene identification using positional and functional cloning approach, Physical mapping: Fluorescence in situ hybridization, comparative genome hybridization, High resolution mapping - STS/EST/MS/SNP/sequencing, Genome-wide association studies: SNP Genotyping- Massarray-Snapshot technique, Axiom genotyping, Sequenom MassARRAY iPLEX Platform.

Unit III **16 Hrs**

i) Structural genomics: (a) Assembly of a contiguous DNA sequence, whole –genome shotgun sequencing. (b) Understanding a genome sequence: locating the genes in a genome sequence, determining the functions of individual genes.

ii) Functional genomics: Study of transcriptome (By RNAseq, and Microarray analysis) and Proteome (Interacting proteins by phage display and Yeast two hybrid system, In vitro translation).

iii) Human-Microbial Genomics: Introduction to Metagenomics, Comparative Microbial Genomics: From Sequence to Significance, Infectious Diseases, Emerging Infectious Diseases, Microbial gut flora, Gut-Brain axis, Molecular Phylogenetic Techniques.

Paper 1.3: Molecular Genomics 48 Hrs

Unit I **16 Hrs**

i) Genome Structure and Sequence: Whole Genome Sequencing (WGS) (Illumina, Ion, PacBio, MinION), Whole Exome Sequencing (WES) (Agilent capture kits, Illumina-Truseq, Nextera), Targeted Sequencing, Disease specific panels (Cardiac, Brain, Lung diseases), Cancer panels (all onco panels), and Nutri-genomics panel to identify mutations.

ii) Transcriptome: Real-Time RT-PCR, Microarray, and RNAseq of Disease Cells Vs Normal Cells and Tumor cells Vs Normal Cells.

iii) **Proteome**: Protein characterization by Mass spectrometry – fundamentals, mass spectrometry ionization techniques, mass analyzers – MALDI-TOF, MS-MS, LC-MS-MS; In-gel digestion, peptide mass fragmentation. Mass-spectrometry data: basics, spectra; Sequence data: databases, tools and resources; Mass-spectrometry search engines, Mass spectra analysis – identification, molecular weight, determination of peptide sequence, determination of post-translational modifications, Human Protein Atlas, Human Proteome Map, Protein Networks: String and GeneMANIA Proteome: Co-expression, Co-localization, Physical Interactions, Genetic Interactions, Pathways and Shared Protein Domains of proteins.

Unit II **16 Hrs**

i) Biological pathways: Ingenuity Pathway Analysis, Elsevier Pathway Studio, Biocyc, KEGG, WikiPathways, Pathway Commons, and networks based pathway builder.

ii) Regulatory regions: Identifying transcription factors for a coding gene using Transcription Factor Databases like PAZAR and others. Identifying enhancers in the human genome and annotating them to identify mutations in genome. Identifying promoters and transcription factor binding sites for genes.

iii) Role of mutations in Translational Regulatory regions: 5'-cap, secondary structures, multiple uAUGs (up-stream AUGs), IRESs (internal ribosome entry sites), positioning of AUG sequence in Kozak's context, polyadenylation signals and motifs, such as IREs (iron-responsive elements), and Ribosome Binding Sites using MIRVAS and other tools.

Unit III **16 Hrs**

i) Cancer Genome: Identifying driver and passenger gene mutations using CRAVAT and other tools, Identifying translocations (balanced and unbalanced) and inversions, Identifying enhancer elements near translocations and inversions.

ii) miRNA genome: Identifying gene targets for miRNAs (miRdb and others), identifying regulatory miRNA's for coding genes, identifying miRNA-mRNA binding sites, Understanding the role of 3'UTR mutations and miRNA gene mutations in altered miRNA-mRNA pairing using BiBiServ-RNA Hybrid.

Paper 1.4: Precision Genomic Medicine 48 Hrs

Unit I **16 Hrs**

i) Using WGS/WES: NGS Raw data FASTA Sequence alignment, Genome assemblies of NCBI and UCSC, Variants calling, .VCF files, .VCF annotations, Pipelines for disease specific and traits specific mutation identification, mutation annotation (wANNOVAR, SG-ADVISER and others), gene enrichment analysis, disease gene and candidate gene identification strategies, gene-protein and protein-protein network construction, gene-based drug selection (PharmGKB, DrugBank, DGIdb, Druggable Human Proteome), Building pathways using genes bearing mutations, strategies for identifying both known and novel genes for diseases, strategies for identifying both known and novel mutations/polymorphisms in genes, disease risk and protection assessment.

ii) Nutrigenomics: Identifying good and poor metabolizers, Interpretation, Statistics and Data Quality Assurance in Genome Analysis

Unit II **16 Hrs**

i) Genotype based: drug toxicity estimation, drug response efficacy, and drug dosing recommendations. Personalized Genomic Medicine map creation, clinical development of drugs and biologics, drug repositioning, personalized report preparation, strategies for deciding treatment options, counseling patient and family members, ethics and conversing with clinicians and healthcare personnel.

ii) Microarray Transcriptome: Clinical & molecular diagnostics using microarray, microarray based gene expression in cancer cells for personalized treatment, identifying molecular targets for cancer, tumor profiling for targeting cancer treatment and the use of blood-based gene expression profiles in cancer prognosis.

Unit III **16 Hrs**

i) Next Generation Sequencing: Handling Big Data, The use of next-generation sequencing for solving diagnostic dilemmas, Methods used in patient populations to uncover associations between genome variation and common diseases, Predictive tests for common, complex diseases.

ii) Drug Development: Pharmacogenomic testing for drug selection, dosing and predicting adverse effects of commonly prescribed drugs, drug-drug interactions. In silico protein modelling, drug target prediction, 3D drug molecule structure and drug-protein docking

iii) **Minding The Business of Genomics**: The Commercialization of Genetic Testing, Obstacles in Establishing Genetic Testing as Consumer Product,Connecting Consumer Needs with Genetic Testing through Marketing,Challenges to Marketing Genetic Testing ,Stimulating Market Growth for Genetic Testing,Integrating Genetic Testing with Clinical Practice. Opportunities and Challenges in the Genomic Era.

Paper 1.5: Practical -1 Genetics and Genomics - 4x2x16=128 Hrs

1. Visit to Institution of Excellence, Vijnana Bhavan, University of Mysore for whole Genome/Exome Sequencing demonstration using NGS.
2. Leukocyte culture and Karyotyping
3. Isolation of DNA from Human Blood by phenol-chloroform extraction method and/ or spin column based.
4. Primer design and DNA amplification by PCR method.
5. Cloning by TA method (Ligation)
6. Competent cell preparation
7. Performing transformation using cloned DNA.
8. Isolation of recombinant DNA
9. Performing restriction digestion, and electrophoresis.
10. Isolation of mRNA from blood sample.
11. cDNA conversion and quantification of expression with real-time PCR of any gene of interest.
12. CNV duplication mapping and Deletion Mapping techniques
13. Whole genome expression analysis using microarray.
14. Integrating expression data with variant annotations, enrichment analysis.
15. Identifying eQTLs to understand the regulatory protein relationships.
16. Whole genome expression analysis using RNASeq.
17. Visit to genetics and genomics Diagnostics Company.

Paper 1.6 Practical -2: Personalized genomic Medicine

4x2x16=128 Hrs

1. Processing .fastq/.bam/.vcf files in several genome aligning programs to perform genome alignment using NGS PROGRAMS: StrandNGS, SVS Golden Helix, Genome Browser, CLC Genomics Workbench, and NCBI Workbench.
2. Performing genome alignment, Whole genome/exome sequence analysis, variant annotations of SNP, InDels and CNVs (VeP, wANNOVAR, SG-ADVISER, IVA etc.), pathway and network establishment.
3. Whole genome/exome sequence analysis.

4. Variant annotations of SNP, InDels and CNVs using Variant Analysis Programs: customized pipelines, Ingenuity Variant Analysis, wANNOVAR, Ensembl-VeP (Variant effector Predictor), and regulomeDB.
5. Gene sequencing with sanger method, gene panel sequencing with NGS.
6. Whole Genome Scans using Microarray based Genome-Wide SNP 6.0 chip.
7. SNP Data Analysis using Golden Helix program and Affymetrix Genotyping Console and CNV Association Software, Genome-wide Association study, CNV studies and CNV annotation.
8. Integrating NGS and expression data in Ingenuity Pathways Analysis and Ingenuity Variant Analysis to identify upstream and downstream targets.
9. Whole Genome sequence analysis to identify structural variations (Gene, Mutations, and Polymorphisms) and their enrichment analysis.
10. Genome-wide Hot-spot detection using HD-CNV and Circos plot generation.
11. Expression and Enrichment analysis: GenespringGX, Affymetrix Transcriptome Analysis Console, WebGestalt, EnrichR, Gorrila, and DAVID.
12. Protein Interaction Network Programs: Cytoscape-GeneMANIA, Ingenuity Pathway Analysis (IPA), Pathway Studio, KEGG and Wikipathways, and Pathway Commons.

Semester II — 16 Credits

Paper 2.1: Interactive Session — **2x2x16=64 Hrs**

Counseling skills and Discussion of utility of NGS in clinical diagnostics and personalized medicine

Paper 2.2: Seminar presentation — **2x2x16=64 Hrs**

1) Published paper in the personalized Genomic Medicine presentation

2) Major Project presentation

Paper 2.3: Project/Dissertation — **12x2x16= 384 Hrs**

Case Studies - Addressing a scientific issue using experimental tools and submission of the report.

Reference:

1. Maxam, A. M., and W. Gilbert. "A New Method for Sequencing DNA." *Proceedings of the National Academy of Sciences of the United States of America* 74, no. 2 (1977): 560–4.
2. Sanger, F., S. Nicklen, et al. "DNA Sequencing with Chain-Terminating Inhibitors." *Proceedings of the National Academy of Sciences of the United States of America* 74, no. 12 (1977): 5463–7.
3. Li, R., A. Montpetit, et al. "Somatic Point Mutations Occurring Early in Development: A Onozygotic Twin Study." *Journal of Medical Genetics* 51, no. 1 (2014): 28–34.

4. Quail, M. A., M. Smith, et al. "A Tale of Three Next Generation Sequencing Platforms: Comparison of Ion Torrent, Pacific Biosciences and Illumina MiSeq sequencers." *BMC Genomics* 13 (2012): 341.
5. Vance, C., A. Al-Chalabi, et al. "Familial Amyotrophic Lateral Sclerosis with Frontotemporal Dementia is Linked to a Locus on Chromosome 9p13.2–21.3." *Brain* 129, no. 4 (2006): 868–76.
6. DeJesus-Hernandez, M., I. R. Mackenzie, et al. "Expanded GGGGCC Hexanucleotide Repeat in Non-Coding Region of C9ORF72 Causes Chromosome 9p-Linked Frontotemporal Dementia and Amyotrophic Lateral Sclerosis." *Neuron* 72, no. 2 (2011): 245–56.
7. Blauw, H. M., C. P. Barnes, et al. "SMN1 Gene Duplications are Associated with Sporadic ALS." *Neurology* 78, no. 11 (2012): 776–80.
8. Nishiguchi, K. M., R. G. Tearle, et al. "Whole Genome Sequencing in Patients with Retinitis Pigmentosa Reveals Pathogenic DNA Structural Changes and NEK2 as a New Disease Gene." *Proceedings of the National Academy of Sciences of the United States of America* 110, no. 40 (2013): 16139–44.
9. Zhang, J., P. Meltzer, et al. "Application of Chromosome Microdissection Probes for Elucidation of BCR-ABL Fusion and Variant Philadelphia Chromosome Translocations in Chronic Myelogenous Leukemia." *Blood* 81, no. 12 (1993): 3365–71.
10. Shah, N. P., J. M. Nicoll, et al. "Multiple BCR-ABL Kinase Domain Mutations Confer Polyclonal Resistance to the Tyrosine Kinase Inhibitor Imatinib (STI571) in Chronic Phase and Blast Crisis Chronic Myeloid Leukemia." *Cancer Cell* 2, no. 2 (2002): 117–25.
11. Kotowski, I. K., A. Pertsemlidis, et al. "A Spectrum of PCSK9 Alleles Contributes to Plasma Levels of Low-Density Lipoprotein Cholesterol." *American Journal of Human Genetics* 78, no. 3 (2006): 410–22.
12. Stein, E. A., S. Mellis, et al. "Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol." *New England Journal of Medicine* 366, no. 12 (2012): 1108–18.
13. O'Huallachain, M., K. J. Karczewski, et al. "Extensive Genetic Variation in Somatic Human Tissues." *Proceedings of the National Academy of Sciences of the United States of America* 109, no. 44 (2012): 18018–23.
14. Ng, B. G., K. J. Buckingham, et al. "Mosaicism of the UDP-Galactose Transporter SLC35A2 Causes a Congenital Disorder of Glycosylation." *American Journal of Human Genetics* 92, no. 4 (2013): 632–6.
15. Do, C. B., J. Y. Tung, et al. "Web-Based Genome-Wide Association Study Identifies Two Novel Loci and A Substantial Genetic Component for Parkinson's Disease." *PLoS Genetics* 7 no. 6 (2011): e1002141.
16. Kwak, D., A. Kam, et al. "Open-Phylo: A Customizable Crowd-Computing Platform for Multi Sequence Alignment." *Genome Biology* 14, no. 10 (2013): R116.
17. Chen, Z., J. L. Wang, et al. "Using next-Generation Sequencing as a Genetic Diagnostic Tool in Rare Autosomal Recessive Neurologic Mendelian Disorders." *Neurobiology of Aging* 34, no. 10 (2013): 2442.e11–7.
18. Bainbridge, M. N., W. Wiszniewski, et al. "Whole-Genome Sequencing for Optimized Patient Management." *Science Translational Medicine* 3, no. 87 (2011): 87re3.

Course Format

1. This is a Professional diploma course with 40 credits spanning 12 months including examination.
2. The program consists of lecture-based sessions, hands-on laboratory sessions and research dissertation. Classroom lectures and laboratory sessions are offered based on realistic scenarios. For the diploma, students must complete all credit hours (40) with a 5.5 grade point average.
3. Course is aimed at generating genome analysis specialists in the field of clinical genetic diagnosis.
4. This diploma course will be equivalent to M.Phil degree.

Plan and strategy for placement of students graduating with post - graduate diploma in personalized genomic medicine

A). The following 5 companies have expressed interest through the Letter of Intent to receive the trained students for internship and potential employment. These companies have extended their co-operation and copy of their letters are enclosed.

a) Interpretomics
b) Genotpyic Technology Pvt. Ltd.
c) Eurofins Clinical Genetics India Pvt. Ltd
d) PathCare Labs, Hyderabad
e) Strand Life Sciences, Bengaluru

B). The Centre for Proficiency Development and Placement Services (CPDPS) of the University of Mysore will assist in placement of the diploma students.

The objectives of CPDPS are as follows:

i) identifies students' innate capabilities and interests, besides and beyond their subject fundamentals, and helps them fine tune their preparedness for employability;

ii) designs and organizes tailor-made training programmes in collaboration with the Industry Sector and Trainer agencies to enhance the capacity of students for varied competencies;

iii) has periodic interaction with the corporate sector and other agencies providing prospects for placements so as to understand the nitty-gritty of employability.

iv) keeps liaison with different institutions, industries, government departments and such other organizations and collects information about job opportunities, knowledge and skills required for different jobs, disseminates this information among prospective candidates looking for placements, and facilitates graduates to have face to face interactions with prospective employers in view of placements.

v) provides support services to enable graduates to develop their entrepreneurship-capacity so as to venture into self-employed initiatives vis-à-vis their areas of interest, competence and viability.

C). The CPDPS will direct the trained batch of students for internship and potential employment in these companies.

5. Proposed fee structure: **Rs.50,000 for the course**
6. Recognition of program: **PG Diploma in Personalized Genomic Medicine from University**