CYPRUS SOCIETY OF HUMAN GENETICS

10th International Conference

31st OCTOBER - 1st NOVEMBER 2025

Shacolas Educational Center for Clinical Medicine, Nicosia, Cyprus

cshg.org.cy

Dear Colleagues,

On behalf of the Board of the Cyprus Society of Human Genetics, it is my great pleasure to welcome you to the 10th International Conference of the Cyprus Society of Human Genetics, taking place in Nicosia at the Shacolas Educational Centre for Clinical Medicine, University of Cyprus.

This milestone conference brings together an exceptional group of scientists, clinicians, and researchers to explore the frontiers of human genetics and molecular medicine. The scientific program reflects the breadth and depth of our field, spanning federated genomic analyses, cancer mechanisms and therapies, advances in sequencing technologies, reproductive genetics, and the growing role of artificial intelligence in health and disease.

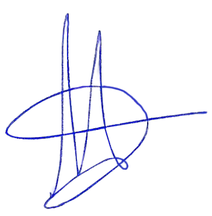
Over the next two days, we will hear from distinguished speakers and colleagues from Cyprus and abroad who are shaping the future of genetics — from translational research and bioinformatics to gene therapy and clinical innovation. Their contributions reaffirm our shared commitment to precision medicine and to improving health outcomes through scientific excellence.

Through this conference and our ongoing educational initiatives, the Cyprus Society of Human Genetics continues to promote collaboration, knowledge exchange, and the advancement of genetic medicine in Cyprus. Our mission is to unite all professionals working in this dynamic field and to support education, research, and clinical excellence for the benefit of our society.

I would also like to extend our sincere appreciation to our sponsors and partners, whose generous support makes this event possible. Their collaboration and continued investment in advancing genetic science are deeply valued.

I wish you all an inspiring and productive conference experience.

Kind regards,



Marios Ioannides, PhD

President, Cyprus Society of Human Genetics

GENERAL

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CONFERENCE PROGRAM

KEYNOTE LECTURES

INIVTED ABSTRACTS

SELECTED ABSTRACTS

POSTER ABSTRACTS

INVITED LECTURES - BIOGRAPHS

ACKNOWLEDGEMENTS & CONFERENCE HOSTS

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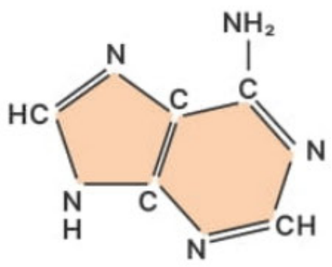
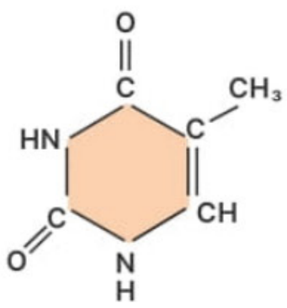
Genetic variation and methylation data in a single assay

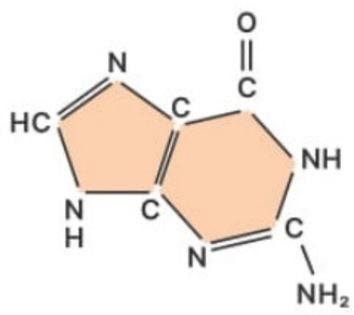
DNA is inherently multiomic, with modified bases that hold epigenetic information. The Illumina 5-base solution detects 5-methylcytosine (5mC) along with unmodified bases, A, T, G, and C, for multiomic insights.



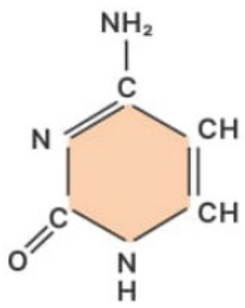
Adenine
A



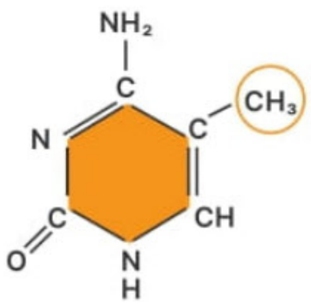
Thymine
T



Guanine
G



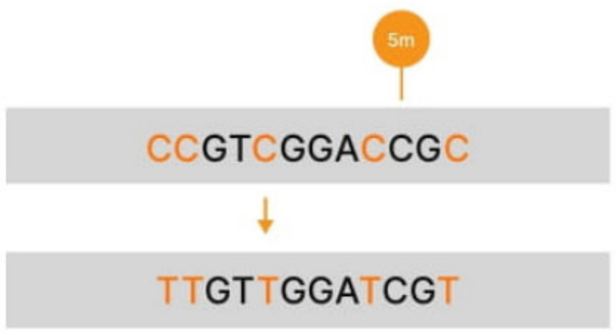
Cytosine
C



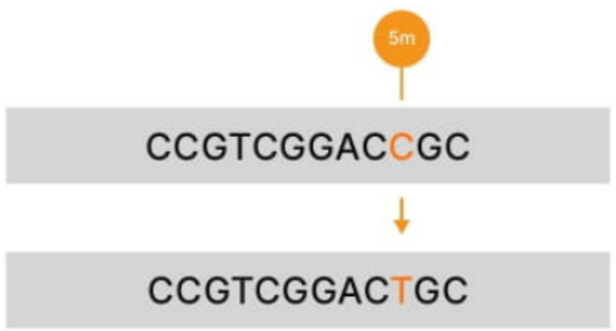
5-Methylcytosine
5mC

Novel chemistry allows direct conversion of 5mC to T

Common methods for detecting DNA methylation use bisulfite or enzymes to convert unmethylated C to T. This reduces nucleotide diversity, making reads harder to align. Bisulfite treatment can also damage DNA, leaving data gaps. Illumina 5-base chemistry directly converts only 5mC to T in a simple, single step, which is nondamaging to DNA and retains library complexity.



Bisulfite or on-market enzymatic conversion



Illumina 5-base conversion

Advantages of the Illumina 5-base solution over other methylation detection methods

Metric	Bisulfite	On-market enzymatic	Illumina 5-base
DNA damage	High **X**	Medium **X**	Low √
Nucleotide diversity	Low **X**	Low **X**	High √
Workflow complexity	High **X**	High **X**	Low √
Methylation detection accuracy	High √	High √	High √
Variant detection accuracy	Low **X**	Low **X**	High √

Better efficiency

√ Advantages **X** Disadvantages

Streamline multiomic workflows

- Simple, single-step 5mC to T base conversion
- Easy library preparation completed in less than a day*

* For whole-genome workflow.

Make every read count

- Combined methylome and genome insights with high coverage uniformity
- Maximum sequencing output with greater mapping efficiency

Simplify data interpretation

- High-accuracy dual genomic and epigenomic annotations powered by DRAGEN™ analysis
- Easy-to-use, clear visualizations and analysis with Illumina Connected Multiomics

Comprehensive insights, unprecedented simplicity

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Illumina Constellation mapped read technology

On-flow cell library prep and cluster proximity information unlock long-distance genomic information and novel insights.

- Elimate most traditional library prep steps
- Resolve challenging-to-map regions and large structural variations
- Generate phased sequencing data for deeper genomic insights

Prep for sequencing with unparalleled ease

DNA templates, extracted from samples using standard or high molecular weight methods, are introduced directly to the flow cell surface, where they are captured, tagmented into clusters, and sequenced.

Minimal prep for sequencing

Add diluted DNA and two reagents to the sequencing system cartridge

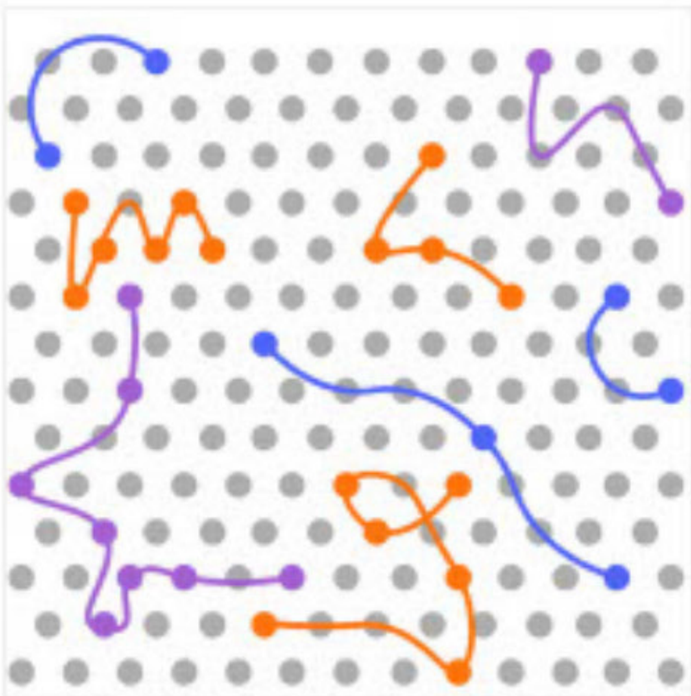
Prep library on flow cell and sequence

Analyze using novel DRAGEN™ algorithms

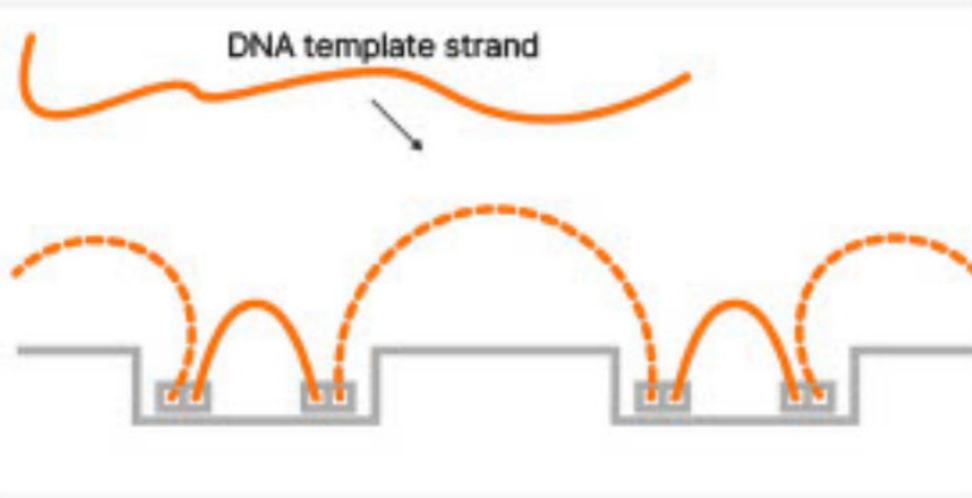
The power of proximity

The highly simplified workflow results in neighboring clusters having a high probability of mapping to the same DNA template strand, enabling the use of proximity information to determine genomic location with high accuracy.

DNA attaches to the flow cell in a constellation pattern



Top view of DNA strands across the flow cell surface. Image represents a small percentage of the tile.



Side view of the template DNA undergoing tagmentation on the flow cell.

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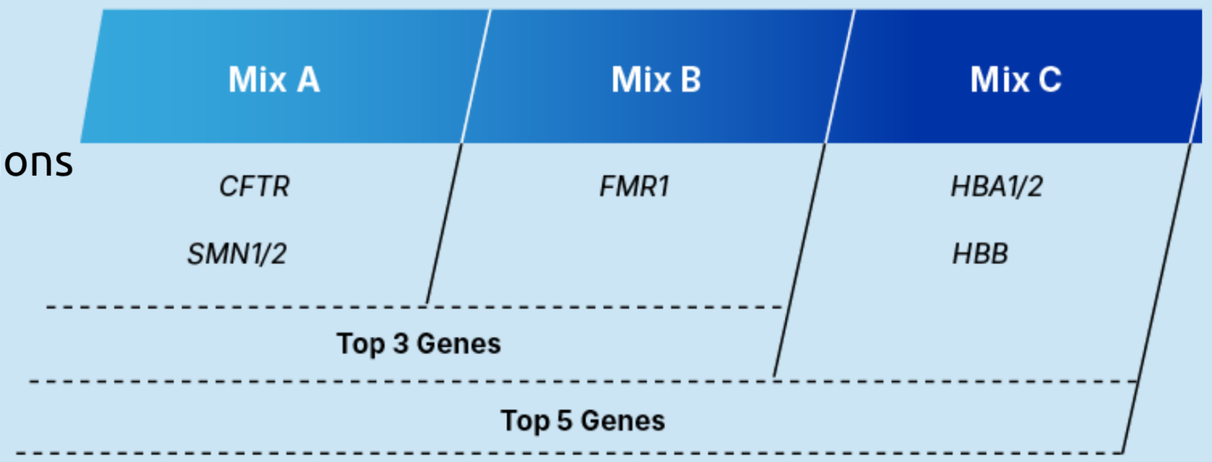

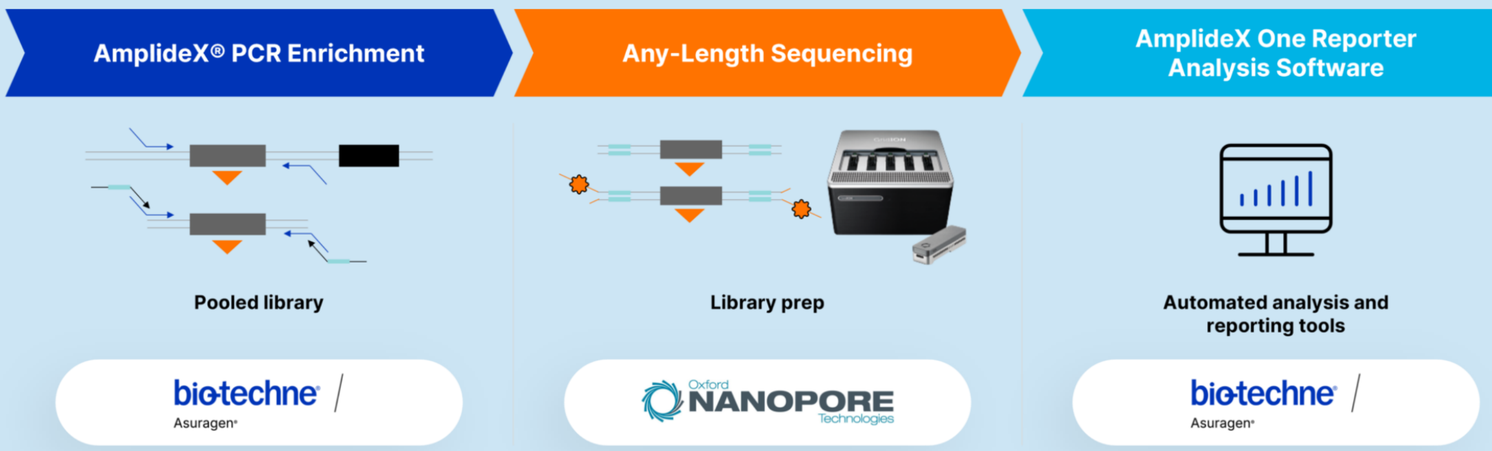

Workflow:

1. Long-range PCR
2. Pooling & purification
3. Library prep
4. Sequencing
5. Analysis & reporting

Performance:

- Up to 96 samples per MinION flow cell
- Sample types: blood, cheek swab, saliva
- Total time: ~5h hands-on, ~9h total

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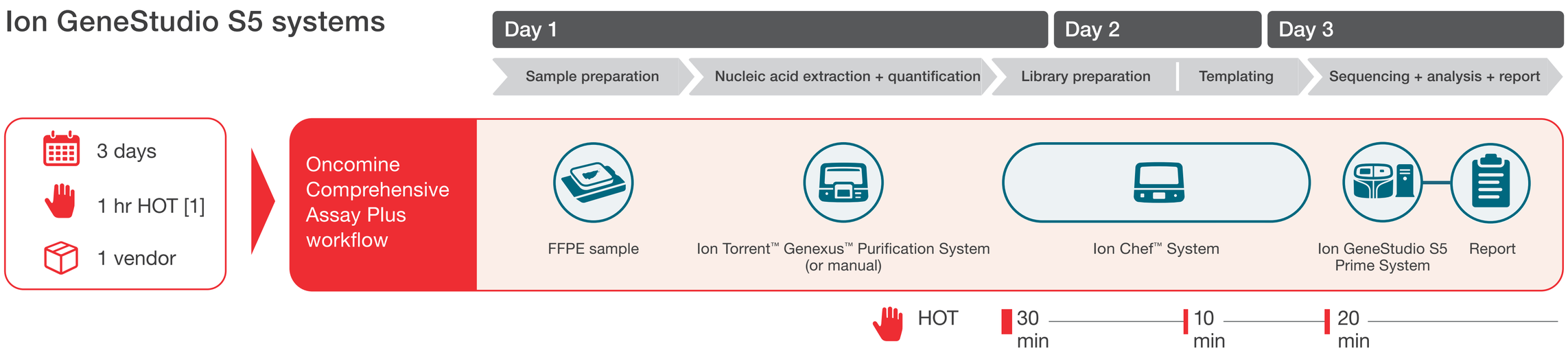
Ion GeneStudio S5 systems



Bring the power of in-house CGP to your lab with Ion Chef and Ion GeneStudio S5 systems

The Oncomine Comprehensive Assay Plus can be run on the Ion GeneStudio S5 Prime System or the Ion GeneStudio™ S5 Plus System with the Ion 550™ chip. Ion GeneStudio S5 systems are easy to use and leverage the speed of semiconductor sequencing for high-quality sequencing data. When paired with the Ion Chef System for automated library preparation and templating, the NGS workflow can be further streamlined with minimal HOT.

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Product	Quantity	Cat. No.
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Oncomine Comprehensive Assay Plus RNA, automated library preparation	32 samples	A49671
Oncomine Comprehensive Assay Plus, manual library preparation	24 samples	A48577
Oncomine Comprehensive Assay Plus RNA, manual library preparation	24 samples	A48578

References

1. One hr hands-on time for the Oncomine Comprehensive Assay Plus for library prep and sequencing compared to competitor literature stating 10.5 hr needed for manual workflow—current as of August 2024.
2. Jantus-Lewintre, E., et al. (2023). Multicentric evaluation of amplicon-based next-generation sequencing solution for local comprehensive molecular tumor profiling. ESMO Poster 219P.
3. Internal R&D data.
4. Normanno, N. (2023). Future Clinical Perspective of HRD Testing in Ovarian Cancer Samples Using NGS CGP. Genome Web Webinar May 2023.

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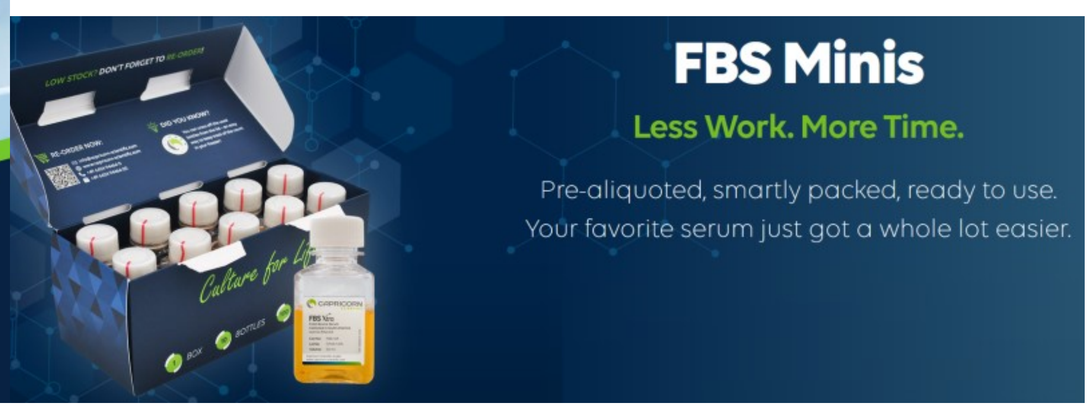

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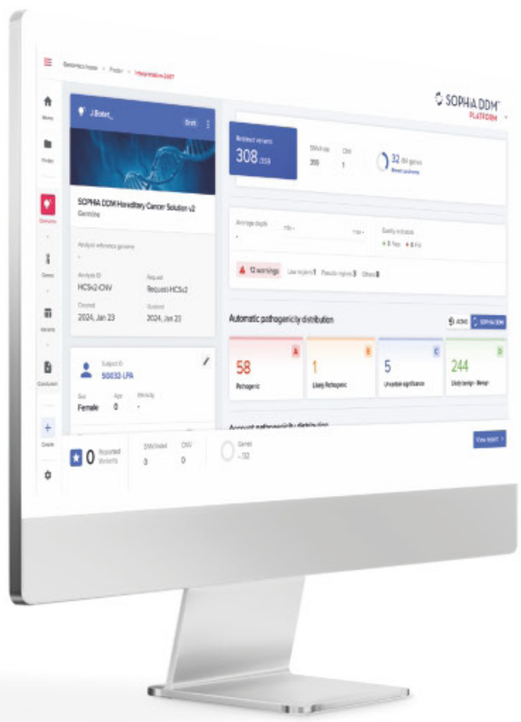
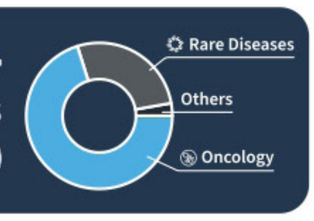


1.9 Million+ Genomic Profiles ANALYZED



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~30,000
genomic analyses per month

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- Reproductive biology
- Microbiology
- Infectious diseases
- Bioinformatics

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FRIDAY OCTOBER 31ST		
(14:00) REGISTRATION & COFFEE		
OPENING		
14:30		Welcome Address CSHG, *Marios Ioannides*, President of the Cyprus Society of Human Genetics
14:40		Welcome Address, *Ministry of Health*
14:50	Keynote Lecture	The Genome of Europe: Towards using Genetic Information in Health Care and Prevention *André Uitterlinden*, Erasmus University Medical Center
	Session 1	Federated analyses of genetic data Chair: *Gregory Papagregoriou*
15:30	Invited Lecture	The CYPROME Genomics Platform: A Framework for Precision Medicine in Cyprus, *Apostolos Malatras*, biobank.cy Center of Excellence, University of Cyprus
15:50	Invited Lecture	Bioinformatics Insights into Network Roadmaps Linking EBV to Multiple Sclerosis *George Spyrou*, The Cyprus Institute of Neurology and Genetics
16:10	Invited Lecture	Cancer and adaptation: What is the evidence? *Konstantinos Voskarides*, University of Nicosia
16:30	Invited Lecture	Breast cancer risk prediction *Kyriaki Michailidou*, The Cyprus Institute of Neurology and Genetics
(16:50) COFFEE BREAK		
	Session 2	Cancer Diagnosis, Mechanisms & Therapies Chairs: *Panos Papageorgis*, *Kostas Koufaris*
17:10	Invited Lecture	A synergistic approach for modulating the tumor microenvironment to improve therapeutic outcomes in cancer, *Fotios Mpekris*, The Cyprus Institute of Neurology and Genetics
17:30	Invited Lecture	Liquid Biopsy-Guided Therapy Selection; Insights into Clinical Application in Cancer *Chrysa Soteriou*, Medicover Genetics
17:50	Invited Lecture	Mapping the Breakome in BRCA1/2 Mutation Carriers Reveals Early DNA Damage Landscapes in Breast Oncogenesis, *Rami Aqeilan*, Cyprus Cancer Research Institute
18:10	Invited Lecture	Molecular Pathways Driving the Transition from Dormancy to Colonization in Metastatic Breast Cancer, *Christiana Neophytou*, European University Cyprus
SELECTED ABSTRACT SESSION I		
18:30	Selected Abstract	Improving Risk Prediction through Rare Variant Classification in Breast Cancer Genes *Damianos Michaelides*, The Cyprus Institute of Neurology and Genetics
18:40	Selected Abstract	Fine-mapping in East Asian-ancestry individuals to refine breast cancer risk loci *Maria Zanti*, The Cyprus Institute of Neurology and Genetics
18:50	Selected Abstract	An efficient strategy to resolve the structural complexity of the RCCX locus in Congenital Adrenal Hyperplasia, *Pavlos Fanis*, The Cyprus Institute of Neurology and Genetics
(19:00) COCKTAIL - POSTER VIEWING		

SATURDAY NOVEMBER 1ST		
(09:00-10:00) REGISTRATION & COFFEE		
10:00	Keynote Lecture	New genetic syndromes in Endocrine Oncology: from the clinic to the lab & back *Konstantinos Stratakis* (virtual), ASTREA Health
	Session 3	Therapies for Inherited Disorders Chairs: *Paschalis Nicolaou*, *Petros Patsalis*
10:40	Invited Lecture	Treatment with 4-phenylbutyrate improves the kidney phenotype in a mouse model of Alport syndrome with a pathogenic variant in Col4a3 *Christoforos Odiatis*, biobank.cy Center of Excellence, University of Cyprus
11:00	Invited Lecture	Advanced Therapies for Genetic Blood Disorders *Panayiota Papassava*, The Cyprus Institute of Neurology and Genetics
11:20	Invited Lecture	Emerging Therapeutic Approaches for Myotonic Dystrophy Type 1 *Andrie Koutsoulidou*, The Cyprus Institute of Neurology and Genetics
11:40	Invited Lecture	Gene therapies for rare neuromuscular disorders *Kleopas Kleopa*, The Cyprus Institute of Neurology and Genetics
SELECTED ABSTRACT SESSION II		
12:00	Selected Abstract	EDIT-4-IRON: Genome Editing Strategies for Iron Regulation in Hereditary and Acquired Hematological Disorders, *Mohamed Azzam*, The Cyprus Institute of Neurology and Genetics
12:10	Selected Abstract	Widespread tissue delivery of antagomiRs via intramuscular administration *Christodoulos Messios*, The Cyprus Institute of Neurology and Genetics
12:20	Selected Abstract	From basic research to pre-clinical studies, a 25-year journey *Constantinos Deltas*, biobank.cy Center of Excellence, University of Cyprus
12:30	Selected Abstract	Importance of clinical interpretation in the era of massive genomic data, *Sophia Ourani*, Makarios III Hospital
(12:40-13:40) LUNCH BREAK – POSTER VIEWING		
	Session 4	Advances in Sequencing Technologies
13:40	Sponsored talk	Driving the multiomics revolution, the latest innovations from illumina, *Scientronics*
14:00	Sponsored talk	Rapid NGS testing in medical research, *C.Georgiou Lab Supplies*
14:20	Sponsored talk	Nanopore sequencing: Novelty without compromise, *Elta90MGR*
	Session 5	Reproductive genetics, Chairs: *Carolina Sismani*, *Elena Kypri*
14:40	Invited Lecture	Prevalence and inheritance of susceptibility loci with incomplete penetrance and variable expressivity detected by prenatal and postnatal microarray testing, *Vasiliki Chini*, Medicover Genetics
15:00	Invited Lecture	Refining Embryo Selection: Is Preimplantation Genetic Testing (PGT) enough? *Nicole Salameh*, The Cyprus Institute of Neurology and Genetics
15:20	Invited Lecture	Preimplantation Genetic Testing for Monogenic Disorders (PGT-M): Current Practices and Emerging Developments, *Thesallia Papasavva*, The Cyprus Institute of Neurology and Genetics
15:40	Invited Lecture	Optical genome mapping offers precise cytogenomic analysis and reproductive guidance for families with cryptic or complex chromosomal rearrangements *Constantia Aristidou*, The Cyprus Institute of Neurology and Genetics

want to know more?

SATURDAY NOVEMBER 1ST		
(16:00) COFFEE BREAK		
	Session 6	Large data, machine learning and AI in health and disease Chairs: *Kyriaki Michailidou*, *Chrysovalantis Voutouri*
16:20	Invited Lecture	AI-Driven Molecular Prescreening in Digital Pathology: From Morphology to Molecular Signatures, *Andreas Mamilos*, German Medical Institute
16:40	Invited Lecture	Machine learning analyses for identification of causal variants in breast cancer *Denise O'Mahony*, The Cyprus Institute of Neurology and Genetics
17:00	Invited Lecture	A digital kidney tubule twin for ADTKD-MUC1: Bridging multi-omics and mechanistic translation *Andrea Kakouri*, biobank.cy Center of Excellence, University of Cyprus
SELECTED ABSTRACT SESSION III		
17:20	Selected Abstract	ChatMDV: Democratising Bioinformatics Analysis Using Large Language Models *Maria Kiourlappou*, University of Oxford
17:30	Selected Abstract	SCA27B is the first dominant ataxia type identified in the Cypriot population *Ioannis Livanos*, The Cyprus Institute of Neurology and Genetic
17:40	Selected Abstract	Altered serum microRNA expression profiles in female patients with central precocious puberty *Maria Morrou*, The Cyprus Institute of Neurology and Genetics
17:50	Selected Abstract	Proteomic insights into SCAR10: Engineering and analysis of CRISPR-edited ANO10-mutant SH-SY5Y cell lines, *Androniki Chrysanthou*, The Cyprus Institute of Neurology and Genetics
(18:00) CLOSING REMARKS		
(18:30) ANNOUNCEMENT OF BEST POSTER AND BEST ORAL PRESENTATION AWARDS		

KEYNOTE LECTURE 1

Prof. Dr. ANDRÉ UITTERLINDEN
Erasmus Medical Centre, Rotterdam, The Netherlands

Biography

André G. Uitterlinden is a Professor of Complex Genetics and with >50 group members head of the Laboratory of Population Genomics at the Erasmus Medical Centre in Rotterdam. Prof. Uitterlinden has a long standing interest in DNA analysis, both technically as well as applying this to human health related research. He was mostly involved in identifying genetic factors for common traits and diseases, for which he early on initiated Genome Wide Association Studies (GWAS) in the Netherlands and set up global consortia. In 2005 he initiated a service providing facility which is now, as the genomics Core Facility, one of Europe's largest genomics facilities, providing services for DNA isolation, genotyping, sequencing, and data analysis, and is handling millions of samples for a global client portfolio. He is now focused on improving the position of Europe in human genomics projects and implementing genetic information in health care and prevention settings. He is PI of the strategic GOALL project within Erasmus MC ("Genotyping On ALL patients"). In 2020 he became a member of the coordination team of the European 1+ million genomes initiative, and therein leads the "Genome of Europe" project to establish the first 100,000 reference genomes covering the population diversity across Europe. He has co-authored over 1500 papers (H-index 216).

KL1. The genome of Europe: towards using genetic information in health care and preventions

Most -if not all- human diseases and their risk factors have a genetic component, implying that variance among individuals in susceptibility, treatment response and/or progression, is determined -in part- by genetic variation. DNA analysis technology is developing continuously and allows sequencing a human genome in <24hours (expensive), but also analyzing millions of SNPs in millions of DNA samples using arrays (cheap). Human genome sequencing projects have uncovered hundreds of millions of such genetic variants, but it has been array/chip technology -applied in cohort studies and biobanks- that has identified tens of thousands of genetic factors for common diseases by Genome Wide Association Studies (GWAS).

The 1 million genomes (1+MG) initiative is such a human genome sequencing project and is part of the Digital Europe Program (DEP) and was declared in 2018 by (now) 27 signatory EU countries aiming to make at least 1 million whole genome sequences (WGS) accessible for use in research, health care, and prevention. 1+MG Working Group 12 (WG12) named Genome of Europe (GoE), was started in 2019 with many country representatives to establish a European Reference Genome Database of >500k WGS (@30x coverage). From these discussions a proposal was formulated to sequence the first 100,000 genomes which was awarded for funding by DEP and started in October 2024. With a budget of 45 mio euro GoE has now >30 participating countries, 51 institutes and >200 scientists involved, and has defined a strategy to collect the first 100k genomes to be proportional and representative of the diverse European populations. The data collection will adhere to ELSI and ICT guidelines and be made accessible via the Genomics Data Infrastructure (GDI) project which has been previously funded as part of the DEP. Several GoE "use cases" were defined including variant look-ups, genetic diversity analyses, multi-ancestry imputation services, and recalibration of genetic risk profiles, and establish longer term (clinical) applications. GoE will stimulate European genomic research competitiveness, advancing personalized medicine and broader scientific and healthcare objectives and, apart from integrating with European initiatives in health care and prevention, also seek global collaboration with similar genome initiatives.

Altogether, this has led to genetic information now entering the hospital clinic in a broad sense, whereby –in theory- all patients can be assessed for (clinically actionable) DNA mutations and polygenic risk scores, next to pharmacogenomics information and their ancestry, blood groups and HLA profiles, for example. Such genetic information can help clinicians in decision making for diagnosis and treatment, and to provide self-empowerment for patients for prevention. Such a program exploring these opportunities, called GOALL (Genotyping On ALL patients) is running at Erasmus MC in Rotterdam, The Netherlands. However, also outside of the (academic) hospitals, applications of using genetic information are explored, such as in population screening programs, e.g., for breast cancer or Familial Hypercholesterolemia. I will describe aspects of these developments, highlight examples, and provide an outlook to the future.

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want to know more?

KEYNOTE LECTURE 2

Prof. Constanine A. Stratakis
ASTREA Health

Biography

Professor Constantine A Stratakis is an internationally known medical geneticist, endocrinologist, translational investigator and executive leader with a unique combination of skills and experience in science, healthcare, clinical trials, molecular research and genetics, policy, government regulations, and patient advocacy. Prof. Stratakis served as the Chief Scientific Officer of ELPEN Pharmaceuticals, in Athens (GR) and directed the efforts to build a new ELPEN Research Institute that is due to open in 2026-27, while he also runs human genetics and precision medicine at IMBB, FORTH, in Heraklion, GR. Most recently he was selected to coordinate the Hellenic Network for Precision Medicine in Molecular Oncology (EDIMO; https://edimo.gr/) and his laboratory (www.digenia.gr) participates in 3 other funded Precision Medicine programs: the 2 networks for Cardiac and Neurodegenerative diseases in Greece and the Health Hub program for the digital transformation of Medicine (2022-26).

His basic training was in medicine (Athens, GR 1989), pediatrics, endocrinology and medical genetics (Paris, France 1988, Georgetown University, Washington DC, USA 1990-1996) and holds a Medical Doctor's, a Doctorate in Medical Sciences, and two honorary PhD degrees, in addition to being a graduate of the University of Maryland School of Public Policy Executive Leadership program (2012).

As an executive leader, Prof. Stratakis led the National Institutes of Health (NIH/NICHD) genetics and endocrinology programs and the NICHD intramural research program (1,100 employees, $200M/year budget) in the United States, for more than 18 years where he trained more than 200 trainees. He is highly sought as a Mentor, speaker, teacher, a patient advocate, and a trusted and highly respected advisor for a wide-range of issues, across various sectors of the healthcare and innovation in life sciences ecosystem.

As an investigator, Prof. Stratakis has worked on the genetics of solid tumors and has identified a number of predisposing genetic defects, including a disease that bears his name (Carney-Stratakis syndrome). He has authored more than 850 publications and served in major Editorial roles of leading journals. He received the 1999 Award for Excellence in Published Clinical Research and the 2009 Ernst Oppenheimer Award both from the US Endocrine Society, and a number of other honors, including NIH Merit and Director's Awards; he also has been named Visiting Professor in academic centers around the world. He is the recipient of the 2019 Dale Medal from the British Endocrine Society and received the 2018 International Award of the European Society of Pediatric Endocrinology (ESPE). He was named honorary member of the Hellenic Society of Cardiology (2017) and the Hellenic Endocrine Society (2019) for his work on the genetics of hypertension and endocrine diseases, respectively. He holds two honorary doctoral degrees from the Universities of Liege, Belgium (2013) and Athens, Greece (2017).

Prof. Stratakis served as the 2018-2019 President of the Society of Pediatric Research (SPR) in the US. In addition to the SPR, he is an elected member of American Pediatric Society (APS), the American Society for Clinical Investigation (ASCI) and the Association of American Physicians (AAP). Dr. Stratakis most recently was instrumental in the launching of the new NICHD Strategic Plan (2020-2024) that emphasizes Precision Medicine, and the use of large data in predictive healthcare.

Prof. Stratakis is dedicated to advances in Science, and he is an exquisite teacher and a marvelous communicator with many interviews in the lay press supporting Science. He is also a tireless advocate of early-stage investigators, diversity and equity.

Finally, Prof. Stratakis is a constant innovator with 4 patents and already involved in start-ups: ASTREA Health, HealthspanDigital. Sterotherapeutics, are three companies that he is involved or founded, all in the last 3 years (2022-2025).

KL2. New genetic syndromes in endocrine oncology: from the clinic to the lab and back

As medicine is poised to be transformed by incorporating personalized and genetic data in its daily practice, it is essential that we improve our clinical observation skills. Genetic testing is a powerful tool in clinical practice for patients and their families. Identification of the underlying genetic etiology in 4 cases led to the discovery of at least 4 new diseases in endocirne oncology, including "Carney-Stratakis syndrome". In the last 30 years, a tremendous amount of new genetic information has become available, and the technologies involved also change by the day. Yet clinical genetics remains the most important way of discovering new diseases and genes. The talk is a tribute to clinical medicine and its importance in genetics.

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SESSION 1

IL1 The CYPROME Genomics Platform: A Framework for Precision Medicine in Cyprus

IL2 Bioinformatics Insights into Network Roadmaps Linking EBV to Multiple Sclerosis

IL3 Cancer and adaptation: What is the evidence?

IL4 Breast cancer risk prediction

SESSION 2

IL5 A synergistic approach for modulating the tumor microenvironment to improve therapeutic outcomes in cancer

IL6 Liquid Biopsy-Guided Therapy Selection; Insights into Clinical Application in Cancer

IL7 Mapping the Breakome in BRCA1/2 Mutation Carriers Reveals Early DNA Damage Landscapes in Breast Oncogenesis

IL8 Molecular Pathways Driving the Transition from Dormancy to Colonization in Metastatic Breast Cancer

SESSION 3

IL9 Treatment with 4-phenylbutyrate improves the kidney phenotype in a mouse model of Alport syndrome with a pathogenic variant in Col4a3

IL10 Advanced Therapies for Genetic Blood Disorders

IL11 Emerging Therapeutic Approaches for Myotonic Dystrophy Type 1

IL12 Gene therapies for rare neuromuscular disorders

SESSION 5

IL13 Prevalence and inheritance of susceptibility loci with incomplete penetrance and variable expressivity detected by prenatal and postnatal microarray testing

IL14 Refining Embryo Selection: Is Preimplantation Genetic Testing (PGT) enough?

IL15 Preimplantation Genetic Testing for Monogenic Disorders (PGT-M): Current Practices and Emerging Developments

IL16 Optical genome mapping offers precise cytogenomic analysis and reproductive guidance for families with cryptic or complex chromosomal rearrangements

SESSION 6

IL17 AI-Driven Molecular Prescreening in Digital Pathology: From Morphology to Molecular Signatures

IL18 Machine learning analyses for identification of causal variants in breast cancer

IL19 A digital kidney tubule twin for ADTKD-MUC1: Bridging multi-omics and mechanistic translation

IL1. The CYPROME Genomics Platform: A Framework for Precision Medicine in Cyprus.

Apostolos Malatras
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The CYPROME Genomics Platform represents a significant effort to establish a comprehensive, FAIR-compliant infrastructure that captures the unique genetic diversity of the Cypriot population. Led by biobank.cy, the Center of Excellence in Biobanking and Biomedical Research at the University of Cyprus, the platform integrates whole exome and whole genome sequencing data with advanced analytics, visualizations, and machine learning tools. The platform bridges research and clinical practice, enabling high-throughput genomics analysis, and secure data sharing. By generating the first fine-scale genetic map of Cyprus, it supports precision medicine and public health initiatives while representing all Cypriot communities. Aligned with European initiatives such as 1+ Million Genomes and the Genome of Europe, the CYPROME platform will strengthen Cyprus's contribution to the European Health Data Space.

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IL2. Bioinformatics Insights into Network Roadmaps Linking EBV to Multiple Sclerosis.

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Casting biological systems as networks and analysing their topology can be useful in understanding how such systems are organized. Graph theory provides a powerful mathematical framework for the understanding of the organization of such large and complex systems by considering them in the form of graphs. Graphs, also termed as networks, can be used to model the pairwise relations between objects. To provide computational ways for a better understanding of the role of EBV in Multiple Sclerosis (MS) disease progression and highlight underlying mechanisms and candidate repurposed drugs, we construct disease-disease networks around MS with diseases in the spectrum of autoimmunity and neurodegeneration. We construct protein-protein networks that map the virus invasion to host and we are making them cell-specific. We are working separately on several EBV strains and on the various types of MS, to provide comparisons and results per strain and disease.

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IL3. Cancer and adaptation: What is the evidence?

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Mutations in Tumor Suppressor Genes can cause several types of cancer. TP53 gene is mutated in at least 50% of tumors. However, evidence is increasing that these mutations can be adaptive, in human or animal populations, and at the somatic level as well. Germline TP53 carcinogenic mutations have been associated with increased longevity in mouse, drosophila, C. elegans and humans, and with higher fertilization rates in mice. Additionally, p53 amino-acid residues that cause cancer in humans, are part of the normal p53 protein sequence in some mammals, reducing apoptosis potential of their cells. It is assumed that this is the way that their cells resist under extreme cold and high altitude (hypoxia). Laboratory experiments gave evidence that carcinogenic TP53 mutations could be adaptive for zebrafish larvae, contributing to higher survival rate under extreme starvation conditions. Similar evidence exists for humans. Extreme starvation exposure has been associated with some cancer types in humans. Additionally, genetic variants in or close to tumor suppressor genes are under selection in people living in extreme cold and high-altitude environments. These human populations exhibit a very high incidence of cancer. Another study showed that BRCA1/2 mutations are related with increased fertility in Utah women. At the somatic level, NOTCH1 and TP53 carcinogenic mutations were found under selection in a large percentage of somatic cells in healthy humans. It seems that carcinogenic mutations may protect our cells under harmful micro-environments. "Mutator" bacteria use the same mechanism to survive under antibiotic stress or other stressful conditions. On the other hand, studies have shown that multiple TP53 copies in elephants contribute to cancer resistance in those big mammals. These data show that evolution, adaptation, and selection can explain multiple phenomena related with cancer. The available evidence show that antagonistic pleiotropy may explain the dual effects of some driver cancer genes.

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IL4. Breast cancer risk prediction.

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Breast cancer remains one of the most common malignancies among women worldwide, with risk shaped by both environmental and genetic factors. While rare, high-penetrance mutations in genes such as BRCA1 and BRCA2 explain a fraction of hereditary cases, the majority of genetic susceptibility arises from numerous common variants of modest effect identified through genome-wide association studies (GWAS).

Recent GWAS have uncovered thousands of single nucleotide polymorphisms (SNPs) associated with breast cancer risk, providing the foundation for developing polygenic risk scores (PRS). By aggregating the weighted effects of these variants, PRS can stratify individuals across a wide spectrum of genetic susceptibility. Integrating PRS with traditional risk factors, such as family history, reproductive history, and lifestyle, enhances predictive performance, offering opportunities for personalized screening and prevention strategies. Emerging work also emphasizes the importance of model calibration across diverse populations, as most PRS have been derived primarily from European-ancestry cohorts.

Polygenic risk scores represent a transformative tool in precision oncology, bridging GWAS discoveries with clinical implementation. As ongoing studies expand to multi-ethnic datasets and integrate genomic with environmental and epigenetic data, PRS-based risk prediction is poised to refine breast cancer prevention and early detection strategies within diverse populations, including those in Cyprus and the Eastern Mediterranean region.

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IL5. A synergistic approach for modulating the tumor microenvironment to improve therapeutic outcomes in Cancer.

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The lack of properly perfused blood vessels within tumors can significantly hinder the distribution of drugs, leading to reduced treatment effectiveness and a negative impact on the quality of life for cancer patients. This problem is particularly pronounced in desmoplastic cancers, where interactions between cancer cells, stromal cells, and the fibrotic matrix lead to tumor stiffness and the compression of most blood vessels within the tumor and thus, to hypoperfusion, limited drug delivery and hypoxia. To address this issue, two mechanotherapy approaches—mechanotherapeutics and ultrasound sonopermeation—have been employed separately to treat vascular abnormalities in tumors and have reached clinical trials. In this study, we performed in vivo studies in sarcomas and breast cancer, to explore the conditions under which these mechanotherapy strategies could be optimally combined to enhance perfusion and the efficacy of nano-immunotherapy. Our findings demonstrate that, combination of the anti-histamine drug ketotifen as a mechanotherapeutic and sonopermeation effectively alleviates mechanical forces by decreasing collagen and hyaluronan levels and thus, reshaping the tumor microenvironment. Furthermore, the combined therapy normalizes the tumor vasculature by increasing pericytes coverage. This combination not only improves tumor perfusion but also enhances drug delivery. Furthermore, the combinatorial treatment drastically reduce primary tumor growth and in many cases tumors were no longer measurable. Overall survival studies showed that all mice that received the combination treatment survived and rechallenge experiments revealed that the survivors obtained immunological memory. Furthermore, combined strategy increased infiltration and activity of immune cells and altered the levels of immunosupportive chemokines. Finally, using machine learning analysis, we identified that tumor stiffness and immune cells levels were strong predictors of treatment response.

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IL6. Liquid Biopsy-Guided Therapy Selection; Insights into Clinical Application in Cancer.

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Liquid biopsy-based assays have become an important tool in precision oncology. They provide real-time, non-invasive molecular profiling through the detection of circulating tumor DNA (ctDNA). Liquid biopsy tests are increasingly being used in clinical practice to guide treatment decisions and support personalized prognostic insights. ctDNA-based tests can identify clinically actionable variants and immuno-oncology biomarkers that have received approval from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in several cancer types including colorectal. By overcoming some limitations of formalin-fixed paraffin embedded tissue biopsy samples, liquid-biopsy offers the opportunity in capturing the complete molecular profile of the disease and providing clinical insights into dynamic tumor evolution, resistance mechanisms and metastatic progression.

Within this evolving landscape, the non-invasive comprehensive NeoThetis therapy selection liquid biopsy assay was developed. NeoThetis detects genetic alterations (single nucleotide variants, small insertions and deletions, copy number alterations, rearrangements) as well as complex biomarkers for immunotherapy treatment (microsatellite instability and blood tumour mutational burden) in a single assay. As a clinical application, the use of serial liquid biopsy testing in metastatic colorectal cancer will be presented, where first and second lines of therapy often yield limited efficacy. Specifically, in metastatic colorectal cancer, frequently characterized by acquired resistance to anti-epidermal growth factor receptor agents, liquid biopsy can facilitate assessment of therapy re-challenge. Liquid biopsies have the potential to dynamically monitor tumor evolution and ensure that treatment strategies remain aligned with the molecular profile and evolution of the disease.

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IL7. Mapping the Breakome in BRCA1/2 Mutation Carriers Reveals Early DNA Damage Landscapes in Breast Oncogenesis.

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Genome instability in BRCA1/2-mutant cancers arises from defects in homologous recombination repair, yet the earliest DNA lesions that predispose to transformation remain poorly defined. Here, we mapped physiological DNA double-strand breaks (DSBs) at genome-wide resolution in primary mammary epithelial cells from non-malignant BRCA1/2 mutation carriers. Compared to healthy controls, BRCA-mutant cells displayed a distinct breakome signature that closely resembled patterns observed in breast cancer cells. Breaks were enriched at proto-oncogenes and tumor suppressors, and break-prone genes tended to be highly expressed and frequently mutated in breast tumors. Moreover, these loci showed a strong correlation with homologous recombination pathways, underscoring the functional link between BRCA loss and aberrant DSB landscapes. Together, these findings demonstrate that BRCA deficiency reshapes the physiological breakome prior to malignant transformation, providing new insights into the origins of genome instability in BRCA-associated cancers and pointing to opportunities for early detection and prevention.

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IL8. Molecular Pathways Driving the Transition from Dormancy to Colonization in Metastatic Breast Cancer.

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Metastasis is the primary cause of mortality among breast cancer (BC) patients, with many developing macrometastases years or even decades after successful treatment of their primary tumour. This phenomenon, driven by the reactivation of dormant disseminated tumour cells, represents a major obstacle in clinical management and highlights the urgent need to identify molecular mechanisms underlying dormancy escape and metastatic colonization. We hypothesized that dormant metastatic BC cells acquire specific molecular alterations that enable their transition to proliferative outgrowth at secondary sites. To test this, we established a murine model in which metastatic breast cancer cells (MIV-Luc-GFP) were intravenously injected into immunodeficient NOD/SCID mice. Tumour progression was monitored over time by whole-body bioluminescence imaging, providing a dynamic view of colonization. At four defined stages—initiation, dormancy, escape, and outgrowth—metastatic cells were isolated from murine lungs by FACS and characterized using proliferation and apoptosis markers (Ki67-/M30-). RNA was extracted from the sorted cells, and whole-transcriptome sequencing was performed. Bioinformatics analysis identified distinct transcriptional programs associated with each phase of metastatic progression. Differentially expressed genes (DEGs; fold-change > 2 or < 0.5, FDR < 0.05) included ZCCHC3, which may help sustain a dormant state, and P4HA1, PFKP, ATF4, and F11R, which were linked to reactivation and outgrowth. Functional studies demonstrated that conditional knockdown of P4HA1 decreased BC cell viability, induced G1/S cell cycle arrest, promoted apoptosis, and inhibited the ID1 pathway in vitro. In vivo, P4HA1 depletion markedly suppressed tumour growth both in the orthotopic mammary fat pad and at metastatic lung sites. These findings suggest that metastatic dormancy and reactivation are tightly regulated by specific molecular drivers. Temporal targeting of key regulators, such as P4HA1, could therefore limit macrometastatic outgrowth and improve long-term disease control. This work not only provides new insight into the biology of metastatic dormancy but also lays the foundation for the development of therapeutic strategies and potential biomarkers to monitor and reduce relapse risk in breast cancer patients.

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IL9. Treatment with 4-phenylbutyrate improves the kidney phenotype in a mouse model of Alport syndrome with a pathogenic variant in Col4a3

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Alport syndrome is a severe inherited kidney disease caused by pathogenic variants in collagen IV genes, the main structural component of the glomerular basement membrane (GBM). Current treatments are limited to renin–angiotensin–aldosterone system blockade. This study investigates the therapeutic potential of the chemical chaperones 4-phenylbutyrate (4-PBA) and tauroursodeoxycholic acid (TUDCA) in mouse models of later-on set Alport syndrome carrying the Col4a3:p.Gly1332Glu mutation.nTreatment with TUDCA showed no improvement, while 4-PBA significantly ameliorated GBM morphology and structure, reducing ultrastructural lesions by 54% and decreasing interstitial fibrosis and glomerulosclerosis. Proteinuria and hematuria also remained low in treated mice. In-vivo and in-vitro findings on primary podocytes suggest that 4-PBA enhances collagen IV secretion and incorporation into the extracellular matrix, likely by promoting trimer folding and reducing proteasomal degradation of misfolded collagen. These findings highlight the therapeutic potential of 4-PBA in mitigating kidney damage and improving collagen homeostasis in Alport syndrome. Project funded by the Alport Syndrome Foundation, the Pedersen Family, and the Kidney Foundation of Canada; the Cyprus Research and Innovation Foundation (RIF) and by the CY-Biobank (EU Horizon 2020).

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IL10. Advanced Therapies for Genetic Blood Disorders.

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Genetic blood disorders represent a diverse group of conditions that pose significant clinical and societal challenges. Although individually rare, they are collectively common, affecting more than 20 million people worldwide. These disorders are associated with high morbidity and mortality, substantial healthcare costs, and marked global inequities. Many remain underdiagnosed or misdiagnosed, and accurate classification often requires advanced genomic analyses such as whole exome/genome sequencing. Conventional management strategies remain largely supportive, fail to address the underlying genetic defects, and often lead to severely impaired quality of life for patients.

In recent years, the emergence of advanced therapies has transformed the therapeutic landscape of genetic blood disorders, offering realistic prospects for durable and potentially curative interventions. These approaches build upon the accessibility of hematopoietic stem and progenitor cells and include gene addition, gene editing, gene regulation, and emerging in vivo and niche-engineering strategies, each with distinct advantages and challenges. Hemoglobinopathies, particularly sickle cell disease and β-thalassemia, have served as leading models, with major milestones marked by the FDA approvals of Zynteglo (lentiviral gene addition for transfusion-dependent β-thalassemia in 2022), Casgevy (CRISPR-based editing for sickle cell disease and transfusion-dependent β-thalassemia in 2023 and 2024, respectively), and Lyfgenia (lentiviral gene addition for sickle cell disease in 2023). Similar advances are extending to immunodeficiencies, bone marrow failure syndromes, and coagulation disorders, supported by decades of HSCT expertise. Remaining challenges include long-term safety, manufacturing complexity, high costs, and limited global accessibility, particularly in low-resource settings. Future directions focus on safer conditioning, non-viral and in vivo/in utero delivery systems, base and prime editing, epigenome modulation, and equitable implementation of these transformative therapies worldwide.

Our laboratory is actively developing advanced therapeutic strategies for both β- and α-thalassemia, employing viral gene addition for α-thalassemia and CRISPR/Cas9 and base-editing technologies to correct the most prevalent β-thalassemia mutation in our population (IVSI-110) and modulate disease modifiers such as BCL11A to induce γ-globin expression for both β-thalassemia and sickle cell disease. In parallel, we are designing base-editing tools targeting key genetic regulators of iron metabolism to establish a foundation for gene-editing-based iron-restriction therapies. This work aims to generate novel treatments for a wide spectrum of inherited and acquired hematologic disorders characterized by dysregulated iron homeostasis, including thalassemias, congenital dyserythropoietic anemias, sideroblastic anemias, hereditary hemochromatosis, SF3B1-mutant myelodysplastic syndromes, and polycythemia vera. To enhance the safety and translational potential of these approaches, we are performing rigorous off-target analyses to ensure high editing precision and minimize unintended genomic alterations.

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IL11. Emerging Therapeutic Approaches for Myotonic Dystrophy Type 1.

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Myotonic Dystrophy type 1 (DM1) is the most common adult-onset muscular dystrophy and one of the most clinically heterogeneous monogenic disorders. Although classified as a neuromuscular disease, DM1 is a multisystem disorder affecting skeletal muscle, the heart, and the central nervous system, with variability in severity, age of onset, and organ involvement. It is caused by a CTG repeat expansion in the 3′ untranslated region of the DMPK gene. The resulting mutant RNA transcripts form nuclear foci that sequester RNA-binding proteins, particularly MBNL proteins, leading to widespread splicing defects that underlie the multisystemic manifestations of the disease. Therapeutic development in DM1 has advanced substantially and can be grouped into two main approaches. The first category includes approaches that directly target the toxic RNA. Antisense oligonucleotides and ligand-conjugated variants are advancing into clinical trials with the aim of degrading or blocking the mutant transcripts. Additionally, CRISPR interference strategies are emerging as powerful gene-silencing tools with encouraging preclinical data. The second category encompasses strategies that modulate downstream pathways to counteract RNA toxicity including miRNA-based approaches to restore RNA-binding protein function and small molecules to improve splicing. Despite these advances, two major challenges continue to limit translation into effective therapies: the efficient and specific delivery of therapeutic molecules to affected tissues primarily the skeletal muscle and the lack of robust biomarkers that can reliably monitor disease progression and therapeutic efficacy. Circulating muscle-specific miRNAs are emerging as promising biomarkers, while engineered extracellular vesicles also hold potential as therapeutic delivery tools for nucleic acid-based therapies. Together, these advances highlight the significant progress achieved while also emphasizing the ongoing challenges in turning molecular insights into effective therapies

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IL12. Gene therapies for rare neuromuscular disorders.

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Recent advances in gene therapies for other neuromuscular disorders have facilitated the development of novel gene therapy approaches also for Charcot-Marie-Tooth (CMT) inherited neuropathies. CMTs are a group of genetically and phenotypically heterogeneous disorders that predominantly affect the peripheral nervous system. Unravelling the genetic and molecular mechanisms, as well as the cellular effects of CMT mutations, has enabled the development of targeted therapies to address either loss of function or toxic gain of function disease mechanisms. Proposed gene therapy treatments for CMTs include virally or non-virally mediated gene replacement, addition, silencing, modification, and editing of genetic material. For most CMT neuropathies, gene- and disease and even mutation-specific therapy approaches targeting the neuronal axon or myelinating Schwann cells may be needed, due to the diversity of underlying cellular and molecular-genetic mechanisms. The efficiency of gene therapies to improve the disease phenotype has been tested mostly in vitro and in vivo rodent models that reproduce different molecular and pathological aspects of CMT neuropathies. Toxicity and biodistribution studies in bigger animal models, in particular non-human primates, provide important insights into the translatability of the proposed administration and dosing, demonstrating the scale-up potential and safety towards clinical applications for patients with CMT neuropathies.

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IL13. Prevalence and inheritance of susceptibility loci with incomplete penetrance and variable expressivity detected by prenatal and postnatal microarray testing.

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Genetic rearrangements in certain chromosomal regions are associated with disorders that exhibit incomplete penetrance and variable expressivity. These are commonly known as susceptibility loci, such as 1q21.1, 15q11.2, 15q13.3, 16p11.2, 16p13.11, 17p13.3, 17q12, 17q21.31, and 22q11.21. A significant challenge in prenatal diagnosis arises from the fact that these susceptibility loci often lack clear ultrasound manifestations and this often raises difficulties in clinical interpretation and risk assessment. The objectives were to assess retrospectively the prevalence and inheritance of susceptibility loci with incomplete penetrance and variable expressivity detected by chromosomal microarray analysis (CMA) in a private diagnostic laboratory in Greece over a three-year period (2022–2025).

A total of 1,526 prenatal samples were analyzed by aCGH testing. Indications for CMA included mainly ultrasound anomalies, advanced maternal age, high-risk maternal serum screening, high-risk non-invasive prenatal testing (NIPT), and parental anxiety. Recurrent pathogenic and susceptibility CNVs were identified and analyzed. Parental microarray testing was performed when available to determine the inheritance pattern of these CNVs. Additionally, a cohort of 1,250 postnatal samples with well-described phenotypes (developmental delay and ASD) was also analyzed by aCGH.

Among the 1,526 prenatal samples, recurrent pathogenic and susceptibility CNVs were identified in 1.96% of all cases (30/1,526), representing 21% of all CNV findings (30/143). The most frequently observed susceptibility CNVs were 15q11.2 deletion (0.52%), 15q11.2 duplication (0.39%), 22q11.2 duplication (0.33%), and 16p13.11 duplication (0.19%). Parental microarray testing, when performed, revealed that the majority of susceptibility CNVs were inherited. In the postnatal group, susceptibility CNVs were identified in 1.6% (20/1,250), with the most frequently observed being the 16p11.2 duplication (0.32%), followed by the 16p11.2 deletion, 15q11.2 deletion, and 1q21.1 duplication (each 0.24%).

These findings highlight the difficulty in the clinical evaluation of susceptibility loci at the prenatal level, a challenge underscored by their notable frequency in both cohorts and the demonstrated differences in penetrance estimates. The necessity of parental testing is essential for accurate genetic counseling. Furthermore, the importance of postnatal monitoring for early signs, enabling timely developmental intervention when needed, is emphasized. The overall outcome indicates an urgent need for context-specific penetrance data, where locus-specific penetrance estimates are derived from prenatal or large population-based cohorts, rather than relying solely on highly ascertained postnatal studies. This is particularly crucial for improving the accuracy of risk assessment for asymptomatic carriers identified during prenatal testing.

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IL14. Refining Embryo Selection: Is Preimplantation Genetic Testing (PGT) enough?

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Infertility affects approximately 10% of couples worldwide, and assisted reproductive technologies (ART) play a central role in treatment. Implantation success rates, however, remain modest, underscoring the importance of accurate embryo selection. Preimplantation genetic testing (PGT) has significantly improved the ability to detect aneuploidies and inherited disorders, yet questions remain regarding the reliability of trophectoderm (TE) biopsy. In this study, we tried to examine the concordance between inner cell mass (ICM) and TE chromosomal profiles, evaluate the reliability of a single TE biopsy, and investigate associations between ploidy status, mtDNA copy number, and embryo morphology.

We observed a high degree of concordance between ICM and TE ploidy status, supporting the representativeness of TE biopsy in PGT-A. Single biopsy results similarly reflected whole-embryo chromosomal profiles. mtDNA copy number was consistently higher in non-euploid embryos and in TE compared to ICM. No significant correlation was found between overall morphology and ploidy status; however, higher mtDNA copy numbers in A-grade TE suggested a potential biomarker of implantation competence. Our findings support the reliability of PGT-A for embryo chromosomal assessment and highlight mtDNA as a promising complementary biomarker for embryo selection, particularly when multiple euploid embryos are available.

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IL15. Preimplantation Genetic Testing for Monogenic Disorders (PGT-M): Current Practices and Emerging Developments.

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Preimplantation Genetic Testing (PGT) constitutes a critical component of modern reproductive genetics, enabling the selection of embryos free from specific genetic abnormalities prior to transfer. PGT for Monogenic Disorders (PGT-M) focuses on identifying pathogenic variants in single genes responsible for inherited conditions, providing an effective means to prevent disease transmission in at-risk couples.

The Molecular Genetics Thalassaemia (MGT) Laboratory introduced PGT-M for β-thalassaemia in 2004, establishing the first comprehensive PGT-M programs in Cyprus. The conventional approach, based on direct mutation detection combined with short tandem repeat (STR) haplotyping, has proven to be a robust and reliable diagnostic strategy, minimizing the risks of allele dropout and recombination. Over time, the application of PGT-M has expanded to a broad spectrum of single-gene disorders, facilitated by the development of bespoke, family-specific assays tailored to each family's genetic background.

To address the increasing diagnostic demands, improve assay efficiency, reduce turnaround time, and provide access to more at-risk couples, our laboratory has recently developed and integrated novel molecular workflows into our routine PGT-M practice. These workflows incorporate whole-genome amplification (WGA) using Multiple Displacement Amplification (MDA), enabling concurrent analysis of multiple genes, repeat testing using diverse methodologies, and the integrated detection of monogenic disorders, structural rearrangements, and chromosomal aneuploidies in a single embryo.

A key challenge in PGT-M remains the determination of haplotypes in the absence of additional family members or in cases involving de novo pathogenic variants. The adoption of targeted long-read sequencing (T-LRS) using Oxford Nanopore Technology (ONT) effectively addresses these limitations by enabling the direct detection of the targeted pathogenic variant simultaneously with single-nucleotide variation (SNV) polymorphic markers co-inherited with the pathogenic variant. This approach allows accurate haplotype reconstruction independent of family inheritance patterns. The introduction of (T-LRS) technologies in our pipeline provides enhanced haplotyping resolution, improved identification of de novo variants, and improved resolution in complex family structures or cases lacking informative markers. Collectively, these technologies have transformed PGT-M by increasing diagnostic resolution, flexibility, and clinical applicability. This evolution from single-gene testing to comprehensive embryo genotyping under a unified analytical framework aims to broaden accessibility for couples at risk of monogenic or combined genetic disorders, while ensuring rapid turnaround and uncompromised diagnostic precision.

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IL16. Optical genome mapping offers precise cytogenomic analysis and reproductive guidance for families with cryptic or complex chromosomal rearrangements

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Chromosomal rearrangements, such as translocations, inversions, and complex structural variants, represent a significant cause of reproductive failure, congenital anomalies, and genomic disorders. Conventional methods, including karyotyping and array comparative genomic hybridization, provide valuable insights but are limited by their resolution and inability to detect cryptic or highly complex rearrangements. Optical genome mapping (OGM) is a novel single-molecule imaging technology that enables genome-wide detection of structural variants without the need for cell culture. By imaging long DNA molecules labelled at specific sequence motifs, constructing consensus maps and aligning them to a reference genome, OGM accurately identifies any labelling pattern deviations as chromosomal rearrangements at kilobase resolution.

OGM offers transformative advantages for families with unexplained infertility, recurrent pregnancy loss, or affected offspring carrying chromosomal abnormalities. It facilitates the identification of chromosomal rearrangements in carrier parents, supporting refined reproductive counselling and personalized risk assessment. OGM also allows precise delineation of cryptic rearrangements associated with a higher phenotypic risk. Moreover, integration of OGM with complementary technologies, such as long-read sequencing, enhances breakpoint resolution and gene-level interpretation, bridging the gap between cytogenetics and genomics.

Clinical adoption of OGM as a single comprehensive test is expanding, with growing evidence demonstrating its reliability in detecting clinically relevant structural variants. Selected cases from the literature and a departmental research project at the Cyprus Institute of Neurology and Genetics will be presented, supporting OGM as an emerging tool for cytogenomic analysis in reproductive genetics, offering a path toward accurate diagnosis, informed reproductive choices, and improved clinical outcomes.

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IL17. AI-Driven Molecular Prescreening in Digital Pathology: From Morphology to Molecular Signatures.

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German Medical Institute, Director of Pathology

Artificial intelligence is rapidly transforming diagnostic pathology by bridging morphology with molecular biology. Nowadays, deep learning models trained on whole-slide images can predict key molecular alterations, such as MSI, EGFR, or hormone receptor status, directly from routine H&E slides. The current validation strategies, real-world clinical applications, and the integration of AI-driven molecular prescreening into precision oncology workflows must be discussed, as today AI is rapidly entering our clinical practice! The ethical and quality assurance aspects required for clinical implementation, as well as the pivotal role of the pathologist in guiding this transition toward data-driven medicine, are of paramount importance.

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IL18. Leveraging Deep-Learning to Understand Breast Cancer Genetic Susceptibility.

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Genome-wide association and fine-mapping studies have identified numerous breast cancer risk loci. Since most associated variants are non-coding, translating them into biological mechanisms is challenging. To characterize the regulatory landscape of breast cancer susceptibility and identify potentially overlooked functional variants, we applied deep-learning models (DL) to evaluate regulatory potential independent of statistical association strength.

We applied Sei, a DL model trained on 21,907 chromatin profiles from >1,300 cell types, to predict the regulatory impact of 1.7 million variants within fine-mapping breast cancer regions. Unlike overlap-based approaches, Sei predicts the magnitude and direction of regulatory effects across diverse regulatory elements. We focused on breast-relevant cell types (adipose, breast epithelial, immune, fibroblast, endothelial), using chromatin profiles with >1.5-fold enrichment and regulatory effects ≥0.1. ExpectoSC, an independent model predicting gene expression effects, complemented regulatory predictions.

Sei predicted regulatory function for 68,046 variants (45.15%) with breast-relevant regulatory potential. Immune signals dominated: 61.8% showed activity in macrophages, B/T-lymphocytes, or NK cells, while 16.7% were breast epithelial. Among predictions, 42.8% affected enhancers, 23.2% transcription factor binding (ESR1, FOXA1, CTCF), 11.0% active transcription regions, and 2.0% promoters. ExpectoSC revealed gene expression effects for 11,813 variants. Notably, 96.7% of functionally predicted variants fall below genome-wide significance thresholds. Gene annotation revealed among others established cancer drivers (ESR1, BRCA1/2), and immune genes (STAT3, IL4), revealing pathways linked to breast cancer susceptibility.

A large reservoir of functional variants below traditional significance thresholds was identified offering new avenues for understanding breast cancer genetic aetiology.

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want to know more?

IL19. A digital kidney tubule twin for ADTKD-MUC1: Bridging multi-omics and mechanistic translation.

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Autosomal Dominant Tubulointerstitial Kidney Disease caused by MUC1 mutations (ADTKD-MUC1) is a rare genetic disorder characterized by non-specific histopathological features and variable onset of end-stage renal disease (ESRD). Despite its clinical significance, the mechanisms driving progression remain poorly understood, and robust disease models are lacking. This study aims to develop a digital representation of the kidney tubular microenvironment by pairing functional and multi-omics data from urinary extracellular vesicles (uEVs), and matched urine and serum samples to replicate disease progression and uncover molecular mechanisms and therapeutic targets. Through an ongoing observational study, longitudinal clinical, biochemical data and uEV-samples were collected from 46 individuals with ADTKD-MUC1 and 29 healthy relatives. uEVs were profiled by small-RNA-sequencing, and mass-spectrometry-based proteomics, metabolomics, and lipidomics, while urine and serum were processed by metabolomics. Paired data were analyzed to identify biomarkers and pathways associated with progression. Using prior-knowledge from KEGG, STRING, and miRTarBase, a dynamic molecular network was constructed integrating pathway relations, protein-protein interactions, and miRNA-target links. Control expression data defined a baseline model, while patient overlays revealed disease signatures, driver molecules, and perturbation responses. Multi-omics analyses revealed activation of programmed cell death-associated pathways, with potential implication in disease progression currently tested in vitro. Simulated perturbations of key effectors and suppressors induced system-wide shifts, highlighting a novel therapeutic axis. The model will be refined using single-cell and spatial atlases for nephron-segment mapping and validated through clinical correlations. This work establishes a biologically-informed, scalable digital tubule twin, integrating multi-omics and clinical data to elucidate ADTKD-MUC1 pathobiology and explore therapeutic interventions *in silico*.

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27 SELECTED ABSTRACTS

SELECTED ABSTRACTS I

SA1 Improving Risk Prediction through Rare Variant Classification in Breast Cancer Genes

SA2 Fine-mapping in East Asian-ancestry individuals to refine breast cancer risk loci

SA3 An efficient strategy to resolve the structural complexity of the RCCX locus in Congenital Adrenal Hyperplasia

SELECTED ABSTRACTS II

SA4 EDIT-4-IRON: Genome Editing Strategies for Iron Regulation in Hereditary and Acquired Hematological Disorders

SA5 Widespread tissue delivery of antagomiRs via intramuscular administration

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SA8 ChatMDV: Democratising Bioinformatics Analysis Using Large Language Models

SA9 SCA27B is the first dominant ataxia type identified in the Cypriot population

SA10 Altered serum microRNA expression profiles in female patients with central precocious puberty

SA11 Proteomic insights into SCAR10: Engineering and analysis of CRISPR-edited ANO10-mutant SH-SY5Y cell lines

SA1. Improving Risk Prediction through Rare Variant Classification in Breast Cancer Genes.

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Many rare variants identified in breast cancer susceptibility genes remain as variants of uncertain significance (VUS), complicating clinical decision-making. We quantified the impact of hundreds of VUS using data from >12K variants in PALB2, TP53, CHEK2, and ATM using the largest breast cancer case-control dataset to date (>100K cases, >300K controls) from the BRIDGES, CARRIERS, BioBank Japan, and UK Biobank. Under ACMG/AMP guidelines, multiple evidence sources inform variant classification. Case-control likelihood ratio (ccLR) models outperform odds ratios by modelling variant frequency in cases versus controls, incorporating survival and gene-level penetrance. Standard ccLR assumes uniform risk across variants, limiting detection of heterogeneity. We refined ccLR with a scaling parameter that calibrates per-variant risk, enabling identification of variants conferring higher or lower risk than the gene-level average. LRs were computed across scaling values per variant. Pathogenic evidence was based on the maximum LR exceeding gene-level, age-specific risk, while benign evidence was based on the LR at gene-level risk to avoid inflation. This approach improves interpretability while maintaining conservative benign calls. Evidence was generated for 353 rare unclassified variants, a substantial 15% increase over the standard ccLR, while improving concordance with ClinVar assertions. The refined ccLR approach improves rare variant classification in breast cancer genes by accounting for per-variant risk, providing evidence for more variants and showing stronger ClinVar concordance.

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SA2. Fine-mapping in East Asian-ancestry individuals to refine breast cancer risk loci.

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Previous fine-mapping analyses, using genome-wide association data in European Ancestry individuals, have identified potential causal variants and candidate genes in 150 breast cancer risk regions. Here, we analysed GWAS genotype data from the same regions in 19,769 female breast cancer cases and 17,629 unaffected controls of East Asian ancestry. Using stepwise multinomial regression, we identified 61 independent breast cancer signals (22 with high confidence) across 20 previously reported genomic regions. These included two signals that had not previously been reported in European populations. The strong correlation between effect estimates in East Asians and Europeans indicated that most common susceptibility variants are shared by both populations. We applied the INQUISIT pipeline and identified 26 potential gene targets supported by 15 high-confidence signals in 13 regions, including eight breast cancer driver genes. These results should aid studies into the mechanisms underlying these susceptibility loci.

No external funding received.

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SA3. An efficient strategy to resolve the structural complexity of the RCCX locus in Congenital Adrenal Hyperplasia.

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Genetic defects in the CYP21A2 gene cause 95% of Congenital Adrenal Hyperplasia (CAH) cases. CYP21A2 is located within the RCCX locus in the major histocompatibility complex class III on chromosome 6p21.3. Each RCCX module comprises in tandem RP, C4, CYP21 and TNX genes. The functional genes RP2, C4B, CYP21A2, TNXB and the corresponding pseudogenes are RP1, C4A, CYP21A1P, TNXA share high sequence homology. During meiosis, unequal crossing over could create up to seven structural formats.

A total of 928 alleles from previously screened patients with suspected CAH were re-analyzed to assess RCCX modularity. The RCCX modules were characterized using MLPA and long-range PCR, complemented by Sanger sequencing and restriction enzyme digestion. Among the 928 alleles examined, 433 alleles were bimodular (one functional gene and one pseudogene), 169 monomodular (one functional gene), 253 trimodular (one functional gene and two pseudogenes), three trimodular (one functional gene, one pseudogene and one chimeric gene) and 49 trimodular (two functional genes and one pseudogene). Additionally, eleven alleles carried the non-functional CYP21A1P/CYP21A2 chimeric gene, while ten carried the non-functional TNXA/TNXB chimeric gene.

This study highlights the structural complexity of the RCCX locus on chromosome 6p21.3 and the need to characterize its modular composition. Through the applied methodologies, we identified the full spectrum of modular haplotypes, offering insight into unequal crossover, chimeric gene formation and the genomic diversity seen in CAH cohorts. These findings provide a framework for future genotype-phenotype studies and support more accurate molecular diagnosis of CAH.

Project supported by the A.G. Leventis Foundation.

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SA4. EDIT-4-IRON: Genome Editing Strategies for Iron Regulation in Hereditary and Acquired Hematological Disorders.

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Dysregulation of iron homeostasis and ineffective erythropoiesis drive morbidity across a wide range of hereditary and acquired disorders, including β-thalassemia, hereditary hemochromatosis, polycythemia vera, congenital dyserythropoietic anemias (CDAs), Diamond-Blackfan anemia (DBA), pyruvate kinase deficiency (PKD), and SF3B1-mutant myelodysplastic syndromes (MDS). Current hepcidin-inducing small-molecule therapies require lifelong administration, posing safety, compliance, and cost challenges. The EDIT-4-IRON project proposes a durable, one-off genome-editing strategy targeting erythroferrone (ERFE) and matriptase-2 (TMPRSS6) to restore hepcidin activity and normalize systemic iron metabolism.

CRISPR/Cas9 ribonucleoproteins (RGNs) and adenine/cytosine base editors (ABEs/CBEs) were designed to induce functional knockout of ERFE and TMPRSS6 by targeting start codons, splice junctions, and early coding exons in both human and murine genes. On-target activity is assessed by sequencing, qPCR/ddPCR, and immunoblotting in hematopoietic stem/progenitor cells for ERFE and in Hep3B and AML12 hepatocytes for TMPRSS6. Selected editors will be evaluated in β-thalassemia (Hbbth3/+), hemochromatosis (C282Y), and polycythemia vera (JAK2 V617F) mouse models.

Fourteen gRNAs were designed to target ERFE and TMPRSS6 at key functional sites. Nucleofection optimization in Hep3B and AML12 cells identified program EH-100 with SF buffer as optimal, achieving ~70% GFP expression and ~82% editing efficiency with Alt-R HiFi Cas9 in Hep3B. In AML12 cells, GFP expression reached ~30% and editing ~32%, with further improvements underway.

This one-off, iron-restrictive gene-editing platform could benefit patients with iron overload and ineffective erythropoiesis, reducing lifelong treatment burden and accelerating the development of Advanced Therapy Medicinal Products (ATMPs).

Project funded by the Research & Innovation Foundation of the Republic of Cyprus, BILATERAL/ISRAEL(MOST)/0224/0024.

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SA5. Widespread tissue delivery of antagomiRs via intramuscular administration

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Muscles, traditionally recognized for their role in locomotion and breathing, also participate in tissue communication. Extracellular microRNAs (miRNA) have been identified as key players in intercellular and inter-organ communication in muscle and other tissues. We have previously shown that intramuscular administration of an antagomiR led to the repression of target miRNA in neighbouring skeletal muscles.

This study investigated whether antagomiRs could be delivered to distant muscle and other tissues following intramuscular administration. We designed antagomiRs targeting a muscle-specific miRNA, miR-133b; a ubiquitously expressed miRNA, miR-16; and a scrambled oligonucleotide. Although all sequences were detected in neighbouring skeletal muscles and distant tissues following intramuscular administration, antagomiR-133b showed the highest accumulation and efficacy in various tissues.

This is the first study to provide evidence that intramuscular administration of antagomiRs could be utilized to achieve efficient and widespread distribution in tissues. This in turn could form the basis for alternative future therapeutic approaches.

Project supported by the A.G. Leventis Foundation (3317312) and Telethon Cyprus (33173232).

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SA6. From basic research to pre-clinical studies, a 25- year journey

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The Alport spectrum encompasses classical Alport syndrome (AS) and related entities, including inherited forms of focal segmental glomerulosclerosis (FSGS). We investigated families with inherited kidney diseases through clinical and molecular analyses and generated a knock-in mouse model for AS.

Around 2000, studies of families with inherited FSGS failed to identify pathogenic variants in ACTN4 or CD2AP. A crucial observation by KV was the co-occurrence of microscopic haematuria or haematuria with proteinuria, often accompanied by renal function decline. This prompted sequencing of COL4A3 and COL4A4, encoding glomerular basement membrane (GBM) type IV collagen chains. Pathogenic glycine substitutions were identified, including the founder variant COL4A3:p.Gly1334Glu, establishing a dual diagnosis of FSGS and thin basement membrane nephropathy (TBMN). This was the first report linking heterozygous COL4A3/A4 mutations to progressive kidney disease. The founder mutation was subsequently modelled in a Col4a3 knock-in mouse, which, in homozygosity, developed a severe AS phenotype. Later studies by MP and CS demonstrated activation of the unfolded protein response (UPR), indicating endoplasmic reticulum (ER) stress due to collagen IV misfolding. Based on these findings, we hypothesized that synthetic chaperones could ameliorate disease progression. In a preclinical study by CO and PI, two repurposed chaperones 4-phenylbutyrate (4-PBA) and tauroursodeoxycholic acid (TUDCA) were administered to Alport mice for 6–12 months. 4-PBA, but not TUDCA, markedly improved haematuria, albuminuria, fibrosis, and GBM ultrastructure. This integrated research identified 4-PBA as a promising repurposed therapeutic candidate for Alport syndrome.

Project founded by the Alport Syndrome Foundation, Inc. (ASF), Pedersen Family and the Kidney Foundation of Canada (KFOC), and by the Cyprus Research and Innovation Foundation.

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SA7. Importance of clinical interpretation in the era of massive genomic data

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Myotonic dystrophy type 1 (DM1) is a multisystem disorder that affects skeletal and smooth muscle as well as the eye, heart, endocrine system, and central nervous system. The clinical findings, which span a continuum from mild to severe, have been categorized into three somewhat overlapping phenotypes: mild, classic, and congenital. DM1 is caused by expansion of a CTG trinucleotide repeat in the noncoding region of DMPK. CTG repeat length exceeding 34 repeats is abnormal. Brain magnetic resonance findings have been sparsely reported in literature. In some cases, the lesions are considered to be attributed to hypoxic ischemic encephalopathy or neurometabolic disease and precise diagnosis is retarded.
The first patient was born on 36weeks pregnancy as a result of uncontrolled pregnancy. He presented with hypotonia, respiratory distress since the very first days of life. Extensive work up with metabolic work up and molecular karyotype did not reveal pathogenic findings. The brain MRI showed ventriculomegaly and white matter lesions. Thorough study of family history led to the diagnostic hypothesis of DM1 that was molecularly confirmed.

The second patient is the product of pregnancy conceived through IVF due to infertility of the parents. There were no abnormal findings identified in pregnancy. He was born at 36weeks and presented severe hypotonia, respiratory distress and club feet. Extensive work up including also the lab tests mentioned above was non informative. As presented in the first patient, white matter lesions were evident in the brain MRI. Targeted molecular tested revealed that the patient is affected with congenital type DM1. His mother proved to be mildly affected. Additionally, due to infertility, couple karyotype was done and the mother was proved to be carrier of a balanced translocation. Precise genetic counselling permitted the opportunity of combo preimplantation testing for next pregnancy.

In the era of massive genetic testing, clinical examination along with other findings, such as neuroimaging, should guide genetic testing in order to get a precise diagnosis that can rapidly help the management of the patient and the family.

No external funding received.

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SA8. ChatMDV: Democratising Bioinformatics Analysis Using Large Language Models

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The rapid advancement in single-cell sequencing, spatial omics, imaging and genomic technologies has produced complex, high-dimensional biological datasets that demand accessible tools for analysis and interpretation. Existing visualisation platforms, such as the Multi-Dimensional Viewer (MDV), offer comprehensive interfaces for data exploration but often require advanced computational expertise and manual configuration, limiting their use among clinicians and experimental biologists.

We developed ChatMDV, a natural-language interface integrated with MDV, enabling users to generate interactive visualisations and analyses through natural language commands. ChatMDV leverages a retrieval-augmented generation (RAG) architecture combined with large language models (LLMs) to translate user queries into executable, reproducible Python code and interactive output. This conversational layer lowers the technical barrier to data interrogation, allowing domain experts to perform sophisticated analyses and visualisation tasks without coding expertise.

We illustrate how ChatMDV enables efficient and reproducible analysis of single-cell transcriptomic data across three datasets of increasing complexity: (1) the PBMC3K single-cell RNA-seq dataset, (2) the Human Cell Atlas lung cancer atlas, and (3) the longitudinal TAURUS scRNA-seq study. Across all cases, ChatMDV successfully produced high-quality, reproducible visualisations from simple natural language questions, achieving accuracy above 95% in visualising the datasets.

By bridging the gap between natural language processing and bioinformatics visualisation, ChatMDV reduces technical barriers, enhances reproducibility, and supports more inclusive scientific inquiry. Its modular design and adherence to FAIR (Findability, Accessibility, Interoperability, and Reuse) principles make it a scalable and adaptable framework for accelerating biological data analysis.

No external funding received.

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SA9. SCA27B is the first dominant ataxia type identified in the Cypriot population

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Spinocerebellar ataxia type 27B (SCA27B) is a recently described late-onset ataxia caused by monoallelic intronic GAA repeat expansions in the fibroblast growth factor 14 (FGF14) gene. Expansions of (GAA)≥300 repeats are fully penetrant, while expansions of (GAA)250–299 are pathogenic with reduced penetrance. This study assessed the frequency of the GAA repeat expansion and the phenotypic profile of Cypriot patients with unresolved late-onset cerebellar ataxia (LOCA).

The trinucleotide GAA repeat was analysed in 155 patients and 227 controls. The repeat locus was genotyped using long-range PCR, followed by fragment analysis with capillary electrophoresis, agarose gel electrophoresis, and automated electrophoresis. Electrophoresis methods were compared. Expanded alleles were further validated with bidirectional repeat-primed PCR and Sanger sequencing to confirm pure GAA repeats.

The (GAA)≥250 repeat expansion was identified in 12 patients (7.7%). The mean age of onset was 60 ± 13.5 years. One patient carrying a (GAA)287 expansion developed symptoms at 25 years, the earliest onset in our cohort. All patients with (GAA)≥250 exhibited gait and appendicular ataxia. Nystagmus was observed in 41.7% of the patients, while 58.3% exhibited dysarthria.

SCA27B is the first dominantly inherited ataxia identified in the Cypriot population. FGF14 GAA repeat expansion testing is now included as a first-tier genetic diagnostic test for patients with ataxia.

Project supported by Cyprus Telethon (Grant no. 73285 to K.C.). Long Read Sequencing of the calibrator samples used in this study was supported by the Canadian Institutes of Health Research (Grant no. 189963 to B.B.), the Foundation Groupe Monaco (to B.B.), and the National Institutes of Health (NIH), National Institutes of Neurological Disorders and Stroke (NINDS) (Grant no. 2R01NS072248-11A1 to S.Z.). D.P. holds a Fellowship award from the Canadian Institutes of Health Research (CIHR).

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SA10. Altered serum microRNA expression profiles in female patients with central precocious puberty

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Puberty is the physiological process of sexual maturation, governed by the hypothalamic-pituitary-gonadal (HPG) axis. It begins with the pulsatile release of gonadotropin-releasing hormone (GnRH), which stimulates pituitary secretion of gonadotropins and initiates the development of secondary sexual characteristics. Premature activation of GnRH secretion is defined as central precocious puberty (CPP). GnRH expression is regulated by genetic and epigenetic factors, including microRNAs (miRNAs), which silence gene expression post-transcriptionally. Alteration in their levels may therefore contribute to the pathogenesis of CPP by dysregulating puberty-related genes. This study investigates the differential serum miRNA expression profile in female CPP patients.

Serum samples were collected from twelve female CPP patients and twelve age-matched healthy female controls. Total RNA extraction and small RNA sequencing was performed, using next-generation sequencing. Selected findings were validated by Real-Time PCR in an expanded sample cohort.

Bioinformatic analysis identified ten miRNAs with significant differential expression levels (adjusted p-value < 0.05, $|\log_2 FC| > 0.5$). Six miRNAs were downregulated and four were upregulated in CPP patients. Pathway enrichment analysis of the miRNA's validated target genes highlighted several biological processes, including regulation of nervous system development and axonogenesis.

The differential serum expression profile of these miRNAs in female CPP patients encompasses their potential role as disease-associated biomarkers. These alterations may either reflect direct mechanisms contributing to CPP or secondary effects related to the advanced physical growth of patients. Their involvement in key biological pathways provides new insights into the molecular mechanisms underlying CPP and related pubertal disorders.

Project supported by Telethon Cyprus.

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SA11. Proteomic insights into SCAR10: Engineering and analysis of CRISPR-edited ANO10-mutant SH-SY5Y cell lines

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Autosomal recessive spinocerebellar ataxia type 10 (SCAR10) is a rare neurodegenerative disorder characterised by cerebellar atrophy, oculomotor abnormalities, and ataxia, caused by variants in the ANO10 (anoctamin 10) gene. The ANO10 protein exhibits calcium-dependent chloride channel and phospholipid scrambling activity, and is proposed to contribute to SCAR10 through dysregulation of calcium signalling in Purkinje neurons. However, the precise mechanism underlying SCAR10, and the role of ANO10, remain largely unknown.

Four SH-SY5Y mutant cell lines carrying known SCAR10-associated ANO10 variants were engineered using CRISPR/Cas9 technology, expanded through clonal isolation, and characterised using flow cytometry. Mass spectrometry (MS)-based proteomic analysis was employed to identify differentially expressed proteins between control and mutant lines, and bioinformatic analyses were used to uncover candidate pathways involved in disease pathogenesis.

Comparative proteomic analysis revealed disruptions in synaptic function, cell cycle regulation, extracellular matrix organisation and cell adhesion, and immune homeostasis as potential contributors to SCAR10 pathogenesis. All four processes are functionally linked to calcium signalling, consistent with previous reports implicating aberrant calcium homeostasis in spinocerebellar ataxias.

This study, for the first time, utilises cell-based models to investigate the proteomic landscape of SCAR10 and identifies specific molecules and pathways that may underlie disease pathogenesis. These findings provide a foundation for further investigation and experimental validation, with potential implications for the development of new therapeutic approaches.

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POSTER ABSTRACTS

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PA1. Liquid- and tissue-biopsy based genotyping for efficacy determination of anti-EGFR re-challenge in RAS wild-type advanced colorectal cancer (A-REPEAT study)

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Despite therapeutic advancements, metastatic colorectal cancer (mCRC) remains a leading cause of death, with a 5-year survival rate of 14%. Treatment for RAS wild-type mCRC patients includes chemotherapy and an anti-epidermal growth factor receptor (anti-EGFR) agent as first-line therapy, followed by second-line treatment with chemotherapy plus an anti-vascular endothelial growth factor (anti-VEGF) agent. However, patients eventually progress with limited therapeutic options for successive lines. The A-REPEAT study (NCT03311750) evaluated the efficacy of anti-EGFR re-challenge as third-line therapy.

Twenty-three RAS wild-type mCRC patients were recruited upon progression to second-line treatment. The primary objective was to evaluate the response rate (RR) to third-line treatment with panitumumab plus chemotherapy. Blood was serially obtained at diagnosis and every 2 months and subjected to the NeoThetis Colorectal cancer liquid biopsy assay (Medicover Genetics) while tissue samples were tested using a custom Ampliseq assay, to identify factors predictive of response to anti-EGFR re-challenge.

The objective RR was 13% while disease control rate was 52%. NGS genotyping of tissue and liquid biopsies revealed TP53, APC, KRAS and NRAS as the most frequently altered genes. About half of the patients tested via liquid biopsy had RAS mutations prior to anti-EGFR re-challenge. Patient response or control of disease did not correlate with the plasma RAS status, possibly due to the small cohort size.

Liquid biopsies have the potential to guide anti-EGFR re-challenge in mCRC patients. Larger cohorts are required to determine the role of RAS and other biomarkers in response to anti-EGFR re-challenge.

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want to know more?

PA2. Histopathology Characteristics As Predictors Of Pathogenicity In Breast Cancer Risk Genes

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Breast cancer (BC) is divided into different subtypes based on their histological and molecular characteristics. Genetic testing in a clinical setting aims to detect pathogenic variants (PVs) in genes associated with BC susceptibility. Previous work has shown that the histopathological features of breast tumours seem to differ between carriers and non-carriers of PVs, which can be used to aid variant classification. In this study, we aimed to evaluate the predictive effect of different breast tumour histology characteristics in respect to variant pathogenicity, or benignity for the established BC susceptibility genes (BRCA1, BRCA2, PALB2, ATM, CHEK2, BARD1, RAD51C, RAD51D and TP53). We included 88,071 breast cancer cases from the BRIDGES study of the Breast Cancer Association Consortium and the CARRIERS consortium, analyses were conducted independently for each dataset and then combined in pooled analyses. Likelihood Ratios (LR) were calculated for each gene and each subtype of estrogen receptor (ER) and histological grade in carriers and non-carriers and aligned to code strength levels, according to the guidelines of the American College of Medical Genetics and Association for Molecular Pathology (ACMG/AMP). Evidence in favour of pathogenicity were observed for most genes, with some differences between the two datasets. Conversely, evidence against pathogenicity was identified for other genes and subtypes, with largely consistent findings across studies. Our results provide refined LR estimates for the association of the different histopathology features in breast cancer risk genes and are aligned to the ACMG/AMP thresholds. These results can be combined with other evidence to inform variant classification.

Project supported by Telethon Cyprus.

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PA3. Unravelling the diagnostic power of whole-exome sequencing for copy number variant detection

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Whole-exome sequencing (WES) has emerged as a powerful tool for detecting single nucleotide variants (SNVs) and insertions/deletions (indels). Recent studies have shown that WES, paired with advanced computational methods, can also provide high-resolution copy number variant (CNV) detection, often surpassing traditional techniques in terms of accuracy and efficiency. Here we present four cases of CNV detection by WES in patients with various neurodevelopmental disorders and/or congenital anomalies, who remained undiagnosed after karyotyping and array-CGH (resolution 100kb).

WES was performed on Illumina NextSeq 2000 platform using Illumina DNA Prep with Exome Enrichment. Bioinformatic analysis, annotation and interpretation were performed on Franklin by Genoox platform using the human genome assembly hg19. Array-CGH results were retrospectively re-evaluated and quantitative Real-Time PCR (qRT-PCR) was used to validate WES findings.

In 4/136 family trios, pathogenic or likely pathogenic CNVs, consistent with the patients' phenotype, were identified from WES: i) a ~6.15kb copy number gain in SLC12A3 (exons 9-14) found in trans with a pathogenic missense SNV, ii) a de novo heterozygous ~793bp deletion in POGZ (exons 11-12), iii) a homozygous ~140bp deletion in IFT74 (exon2), and iv) a homozygous ~84kb deletion in PGM2L1 (exons 6-14). None of the CNVs were detectable by array-CGH, but all were successfully confirmed by qRT-PCR.

This study supports that detection of CNVs <100kb yields an additional ~3% of resolved cases. Hence, CNV analysis incorporation into WES diagnostic pipelines is of utmost importance for comprehensive evaluation of patients and discovery of novel disease-associated variants.

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PA4. Optical genome mapping: a novel cytogenomic tool for revealing cryptic complexity in patients with neurodevelopmental disorders

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Structural Variants (SVs) contribute significantly to the development of neurodevelopmental disorders (NDDs) due to direct/indirect disruption of causal genes and/or the presence of complex rearrangements. Detailed SV delineation is of utmost importance for explaining the carriers' phenotypes, yet it may be challenging using conventional workflows. This study exploits the utilization of a novel cytogenomic technology, Optical Genome Mapping (OGM), to address the limitations of previous testing in detecting cryptic complexity in undiagnosed SV carriers with unexplained NDD phenotypes.

The OGM procedure included ultra-high molecular weight DNA extraction, fluorescent labelling at specific sequence motifs, construction of consensus maps and comparison against a reference genome. Any labelling pattern deviation was indicative of the presence of an SV.

OGM detected cryptic complexity in 3/18 (16.7%) referred SV carriers with NDDs. In a patient with intellectual disability, seizures, dysmorphic features, 46,XY,t(4;9)(q25;q21.1)dn and del(7)(p13p12.2), OGM revealed additional complexity on der(9), while der(4) disrupted ankyrin-B, a protein involved in neuronal functioning recently associated with NDD. In another patient with intellectual disability, hydrocephaly, epilepsy, dysmorphism and 46,XY,t(2;3;15)(2pter->2q31::15q21.1->15q21.3::3q23->3qter;3pter->3q23::15q21.3->15qter;15pter->15q21.1::2q31->2qter).arr 2q31.1(170063405_172450547)x1,3p24.1p23(28048310_31108971)x1, OGM revealed an extra chr3 fusion event mapping upstream TRIM71 associated with Hydrocephalus, congenital 4. Finally, in a patient with attention deficit hyperactivity disorder, several congenital anomalies and 46,XX,t(2;3)(q35;q27), OGM indicated the additional involvement of chr15 in the rearrangement.

Collectively, this project offers new perspectives in revealing the potential role of cryptic complexity as an underlying mechanism, as well as supporting novel candidate genes implicated in NDDs especially after further validation and additional evidence by functional studies.

Project supported by Telethon Cyprus and internal funding from the Cyprus Institute of Neurology and Genetics.

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PA5. Generation of α^0-thalassemia hudep cell line models for gene therapy development using CRISPR/CAS9

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Alpha thalassemia is an inherited hemoglobin disorder caused by deletions or mutations in the HBA1 and HBA2 genes, which encode α-globin chains essential for hemoglobin function. Mutations reduce or eliminate α-globin production, causing an imbalance with β-globin chains and ineffective erythropoiesis. The most severe form, α^0-thalassemia (hydrops fetalis) is fatal, and results from mutations in all four α-globin genes. Due to limited access to primary cells from affected patients, alternative models are needed for research. To address this, we generated CRISPR/Cas9-edited in vitro α^0-thalassemia model cell lines using HUDEP-2 erythroid progenitor cells, which predominantly express adult hemoglobin (HbA). CRISPR/Cas9 gene editing was employed to delete both HBA1 and HBA2 genes in HUDEP-2 cells. Two gRNAs flanking the deletion region and Cas9 were introduced via electroporation. Successful deletions were confirmed by gap-PCR and Sanger sequencing. Single cells were isolated by FACS, and clones were screened using duplex PCR to identify biallelic, heterozygous, and non-deleted clones. Functional assays, including erythroid differentiation and globin profiling by RP-HPLC, were conducted. Six biallelic α^0-thalassemia clones were identified. Flow cytometry showed delayed erythroid maturation in biallelic clones compared to controls. RP-HPLC confirmed absence of α-globin in one biallelic clone, validating its applicability as a disease model. HUDEP-2 α^0-thalassemia model cell lines were successfully generated and characterized, offering a valuable platform to study disease mechanisms and evaluate gene therapies. Further functional validation is required before their application.

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PA6. Functional correction and genome integrity with duplex base editing of β-thalassemic hematopoietic stem cells

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Beta-thalassemia is one of the most common monogenic disorders worldwide and remains a major health challenge. Editing genetic regulators such as the BCL11A erythroid enhancer and HBG promoters can reactivate fetal hemoglobin (HbF) expression and represents a promising therapeutic approach. Double-strand break (DSB)-independent base editors (BEs) offer safer and more versatile genome editing than DSB-dependent CRISPR/Cas systems; however, the risk of unwanted on- or off-target effects, including undetected chromosomal rearrangements, requires thorough evaluation. We assessed simplex and duplex BE-mediated editing of the BCL11A erythroid enhancer and HBG promoter (BCL11A binding site, -115 bp) using primary patient-derived CD34+ hematopoietic stem cells from three donors. Comprehensive DNA, RNA, protein, and morphological analyses were performed, alongside direct comparisons with DSB-based editing. CAST-seq was applied to detect recombination events and evaluate genomic safety. RNA-seq profiling across all conditions revealed maximal HBG activation with duplex BE, accompanied by similar apoptotic and immune response signatures among treatments. Duplex BE achieved robust γ-globin and HbF induction, improved functional correction compared to simplex editing, and a low frequency of genomic alterations in both target loci. Simultaneous base editing of the BCL11A erythroid enhancer and HBG promoter enables efficient HbF reactivation with minimal genomic impact. The duplex BE strategy demonstrates strong efficacy, safety, and translational potential as a therapeutic approach for beta-thalassemia.

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PA7. Long-read-amplicon haplotyping for β-thalassaemia preimplantation genetic testing for couples with no additional family members.

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Preimplantation Genetic Testing for Monogenic Disorders (PGT-M) screens embryos for single-gene disorders before implantation. In Cyprus, β-thalassaemia is the most prevalent monogenic disorder, accounting for > 80% of PGT-M procedures annually. A key challenge in PGT-M is determining haplotypes without additional family members or in cases of de novo mutations. Long-read sequencing (LRS), using Oxford Nanopore Technology (ONT), addresses these limitations by enabling accurate detection of polymorphic markers co-inherited with the pathogenic variants, independent of family history. This study introduces an HBB-targeted LRS workflow that identifies β-thalassaemia pathogenic variations, across a region exceeding 10 kb, in a single read. Ten previously diagnosed families at risk for β-thalassemia, were enrolled in this study. Genomic DNA samples were subjected to long-range PCR (LR-PCR) using HBB-flanking primers and targeted (T-LRS) was performed on the MinION platform. Variant calling and haplotyping identified the pathogenic variants and informative single nucleotide variants (SNVs), linked to the disease-associated allele. LR- PCR was successfully performed on all samples, followed by T-LRS. High-quality data enabled comprehensive HBB locus haplotyping, detecting the β-thalassaemia pathogenic variations directly and co-inherited SNVs. Consequently, all disease- or healthy alleles with supporting SNVs in parents were traced back in the offspring with consistent results with the previous diagnosis. This study underscores the effectiveness of LRS, utilizing the ONT MinION platform for PGT-M, begining with β-thalassaemia and potentially expanding to other conditions.

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PA8. Genetic concordance between the trophectoderm and inner cell mass of day-5 preimplantation embryos using next generation sequencing

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Preimplantation genetic testing for aneuploidies (PGT-A) is used for embryo selection, on a 5-10 cell biopsy from the trophectoderm (TE) which later forms the placenta. Whether this biopsy reflects the inner cell mass (ICM) which develops into the fetus, is still questionable. Additional viability biomarkers were proposed, including mitochondrial DNA (mtDNA) copy number.

Thirty-two donated blastocysts were dissected into TE and ICM and tested with low-pass whole-genome sequencing using the Embgenix PGT-A Core kit (CE-IVD, Takara Bio Inc.). For 14 of these 32 embryos, TE biopsy was previously performed for PGT-A. Ploidy status, mtDNA copy number and the morphology of, the TE and the ICM were evaluated.

81% of blastocysts showed full ploidy concordance and 19% showed partial concordance between their ICM and TE. Out of the 14 embryos with previous PGT-A result, 86% showed full concordance and 14% partial concordance with the TE ploidy. Non-euploid blastocysts showed a significantly higher but variable mtDNA copy number both in ICM and TE. No significant correlation was found between the mtDNA copy number and the morphology of the whole blastocyst, the TE or the ICM.

These results show that TE ploidy correctly reflects the ICM and a TE biopsy is accurate for embryo status prediction. Also, a high mtDNA copy number in TE or ICM alone may also be indicative of aneuploidy. Our data supports the connection between TE ploidy and embryo ploidy and thus the clinical utility of PGT-A, especially when combined with additional biomarkers.

Project supported by the Internal Research Fund of The Cyprus Institute of Neurology and Genetics.

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PA9. HAPLONID: A high-density NGS panel for the Non-Invasive Determination of Paternal Inheritance in β-Thalassaemia

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Non-invasive prenatal testing (NIPT) has been widely adopted for the screening of chromosomal abnormalities; however, its adoption for monogenic disorders, such as β-thalassaemia, has proven challenging. Haemoglobinopathies are the most common monogenic disorders globally, with β-thalassaemia being particularly prevalent in Cyprus. This study introduces a non-invasive prenatal haplotyping (NIPH) assay for β-thalassaemia, utilizing cell-free DNA (cfDNA) from maternal plasma. The assay determines paternal inheritance by analyzing highly heterozygous single-nucleotide variants (SNVs) in the β globin gene cluster. To identify highly heterozygous SNVs in the population, 96 randomly selected samples were processed using Illumina DNA-prep NGS chemistry. A custom, high-density NGS genotyping panel, named HAPLONID, was designed with 169 SNVs, including 15 common pathogenic ones. The AmpliSeq for Illumina assay was then applied to cfDNA to evaluate the panel's efficiency in performing NIPT for β-thalassaemia. Analysis revealed 219 highly polymorphic SNVs, and the sequencing of 17 families confirmed successful paternal allele determination. The NIPH assay demonstrated 100% success in diagnostic interpretation. This study achieved the advancement of an integrated NGS-NIPT assay for β-thalassaemia, bringing it one step closer to being a diagnostic assay and thereby enabling a reduction in the number of risky invasive prenatal sampling procedures in Cyprus and elsewhere.

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PA10. A multi-omics analysis of effector and resting Treg cells in pan-cancer

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Regulatory T cells (Tregs) are critical for maintaining the stability of the immune system and facilitating tumor escape through various mechanisms. Resting T cells are involved in cell-mediated immunity and remain in a resting state until stimulated, while effector T cells promote immune responses. Here, we investigated the roles of two gene signatures, one for resting Tregs (FOXP3 and IL2RA) and another for effector Tregs (FOXP3, CTLA-4, CCR8 and TNFRSF9) in pan-cancer.

Using data from The Cancer Genome Atlas (TCGA), The Cancer Proteome Atlas (TCPA) and Gene Expression Omnibus (GEO), we focused on the expression profile of the two signatures, the existence of single nucleotide variants (SNVs) and copy number variants (CNVs), methylation, infiltration of immune cells in the tumor and sensitivity to different drugs.

Our analysis revealed that both signatures are differentially expressed across different cancer types, and correlate with patient survival. Furthermore, both types of Tregs influence important pathways in cancer development and progression, like apoptosis, epithelial-to- mesenchymal transition (EMT) and the DNA damage pathway. Moreover, a positive correlation was highlighted between the expression of gene markers in both resting and effector Tregs and immune cell infiltration in adrenocortical carcinoma, while mutations in both signatures correlated with enrichment of specific immune cells, mainly in skin melanoma and endometrial cancer. In addition, we reveal the existence of widespread CNVs and hypomethylation affecting both Treg signatures in most cancer types. Last, we identified a few correlations between the expression of CCR8 and TNFRSF9 and sensitivity to several drugs, including COL-3, Chlorambucil and GSK1070916, in pan-cancer.

Overall, these findings highlight new evidence that both Treg signatures are crucial regulators of cancer progression, providing potential clinical outcomes for cancer therapy.

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PA11. Assessing case-control likelihood ratios for ovarian cancer risk variants in UK Biobank

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Ovarian cancer is highly heritable and shares key moderate/high-penetrance genes with breast cancer, including BRCA1, BRCA2, and PALB2. Still, many variants in these genes remain of uncertain significance, complicating clinical management. Using UK Biobank, we computed case-control likelihood ratios (ccLRs) for the association between ovarian cancer diagnosis and exonic variants in BRCA1, BRCA2, and PALB2. Clinical variant classifications were compared with logistic regression results and cross-checked against ClinVar. We analyzed 6,298 rare variants (MAF < 0.001) across 1,933 cases and 227,708 controls (mean follow-up: 56 ± 8 years). Of these, 1,242 variants met the benign supporting threshold (ccLR < 0.48: 37% BRCA1, 16% BRCA2, 2% PALB2), with 377 absent from ClinVar; 154 variants met the pathogenic supporting threshold (ccLR > 2.08: 2% BRCA1, 3% BRCA2, 2% PALB2), with 21 absent from ClinVar. Among 356 variants with |ccLR| > 2.08 and expert-reviewed ClinVar classifications, concordance was almost perfect for BRCA1 (Cohen's $\kappa = 0.90$) and substantial for BRCA2 ($\kappa = 0.71$). ccLRs were highly correlated with logistic regression odds ratios (ORs; Spearman's $\rho = 0.82$). However, OR-based classification (pathogenic strong if OR > 4 and lower 95% CI > 2) missed 104 variants with ccLR > 2.08, while only 11 of the 61 variants meeting these criteria lacked ccLR evidence. Notably, three BRCA1 and one BRCA2 variant classified as pathogenic by both methods were missing from ClinVar. We show that ccLRs can reliably identify rare ovarian cancer risk variants, demonstrating high concordance with ClinVar.

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PA12. Determining NGS quality control metrics to inform the orthogonal validation procedures in diagnostic settings

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Next Generation Sequencing has provided deeper insights into the human genome, bridging genetic variation to phenotype manifestations. Although extensively used in clinical settings and research, its output often requires additional validation for ambiguous calls, since multiple errors can be introduced during sequencing. Thus, clinical laboratories cannot always rely 100% on NGS output, often proceeding to orthogonal validation procedures through conventional methods to confirm the presence or absence of a variant. We aimed to address this challenge by implementing additional analysis steps to further characterise calls reducing the need for unnecessary wet lab confirmation to save time and resources. To this end, initially, we ran the Nf-core/Sarek pipeline to generate VCFs containing germline SNPs and Indels from both Whole Exome Sequencing (WES) and Hereditary Cancer Panels (HCP) results. Then, we performed benchmarking with hap.py tool to obtain labels of the detected variants, extracted their quality metrics and introduced them as features into machine learning models. Notably, five different models were generated for four distinct analysis pipelines, such as DeepVariant, HaplotypeCaller, Dragen and Varsome concerning WES, and only Varsome for HCP. All models demonstrated high performance during training and upon evaluation using independent datasets, and we concluded that adjusting the probability threshold can improve predictions of the variant class with the highest clinical impact. The endpoint of this study was a user-friendly interface that accepts new VCFs, processes them by employing all models for the specified analysis pipeline, and finally outputs prediction probabilities for each call, displaying also their quality metrics distributions.

No external funding received.

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PA13. A novel missense variant in ERCC4 gene associated with late onset progressive neurological decline

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The ERCC4 (Excision repair cross-complementation group 4) gene on chromosome 16p13.1–p13.2, encodes a protein involve in the nucleotide excision repair (NER) pathway. ERCC4 mutations are associated with autosomal recessive Xeroderma Pigmentosum (XP) Group F, Fanconi Anemia (FA) and XFE Progeroid Syndrome (XFEPS). XP-F-patients may present with adult-onset neurologic impairment, including hypersensitivity to UV radiation, chorea syndrome, cerebellar ataxia, dysarthria and bilateral hearing loss. In Cordts et al. cohort, eight patients with ERCC4 variants developed adult-onset neurological signs without skin cancer or marked UV sensitivity [PMID: 35699229].

A 69-year-old patient presented with progressive chorea movements, tremor, involuntary movements, muscle weakness, dysarthria, unstable gait, ataxia and cognitive decline. MRI revealed significant generalized cerebral atrophy (including cerebellum) with ventricular dilation. No ischemic/hemorrhagic stroke or malignant-appearing lesions were observed.

Whole-exome sequencing was performed from peripheral blood DNA (SureSelect Exome V8 panel).

A homozygous c.2248C>T variant in ERCC4 gene, p.Arg750Cys (NM_005236.3), was detected. The variant is extremely rare, observed in 0.005% in gnomAD. Interestingly, this variant has been reported in another two individuals in compound heterozygosity state with another missense mutation (p.Arg799Trp) and in homozygous state presenting with spastic paraparesis, cerebellar syndrome and cognitive impairment.

To our knowledge this is one of very limited cases with neurodegeneration without significant dermatological involvement, except dry skin and excessive freckling, or UV sensitivity reported to date harbouring a homozygous ERCC4 variant. These findings strengthen the contribution of ERCC4 gene to adult-onset neurological disorders.

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PA14. Serum muscle-specific miRNAs as potential monitoring biomarkers of muscle wasting progression in Myotonic Dystrophy type I

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Myotonic Dystrophy type 1 (DM1) is the most common muscular dystrophy in adults characterized by muscle wasting and weakness. DM1 muscle wasting progression is highly variable, thus creating the need to develop reliable non-invasive biomarkers for its evaluation. We previously reported that four muscle-specific miRNAs, miR-1, miR-133a, miR-133b and miR-206 are increased in DM1 patients compared to controls and correlate with the disease progression. Our aim was to associate these miRNAs with muscle wasting during the disease course and suggest them as monitoring biomarkers. In this study, serum samples from patients participating in 'PhenoDM1' study (Newcastle, UK) and from the Creation Biobank (Canada) were used. Specifically, participants provided serum samples at multiple follow-up intervals and the four miRNA levels were analyzed at different time points. DM1 patients were characterized as stable or progressive at the time of blood collection based on the change of their outcome measures. Total RNA, including miRNA, was extracted from the serum samples followed by Real-Time PCR analysis specific for the four miRNAs. Our results showed that the four muscle-specific miRNA levels can be used to monitor the disease progression in two independent biobanks. Particularly, their levels remain stable or decreased in stable DM1 patients, following monitoring, whereas they follow an increasing trend in stable patients that became progressive. Our study demonstrated that the circulating levels of the four muscle-specific miRNAs reflect the progression status of the patients and these molecules could be used as monitoring biomarkers in DM1.

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PA15. Robust and specific RNA biomarkers for Systemic Sclerosis

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Systemic Sclerosis (SSc) is an autoimmune rheumatic disease (ARD) with unclear aetiopathogenesis. The diagnosis, prognosis and treatment of the disease are challenging, thus mandating the discovery of reliable biomarkers to improve patient care. Candidate biomakers have been proposed in the literature, and this study aimed to validate some of them in an easily accessible tissue.

Blood samples were collected from healthy controls (HC), patients with SSc, as well as patients with other ARD, and RNA extraction was performed. Fifteen candidate biomarkers of SSc reported in previous proteomic studies were selected for further validation. The expression levels of these molecules were assessed using real-time PCR, and statistical analysis was performed to identify statistically differentially expressed molecules among the study groups. Pathway analysis was performed to identify pathways that are implicated in the disease.

This approach confirmed overexpression of two out of the fifteen selected molecules in patients with SSc compared to HC or other patients with ARDs. Pathway analysis revealed that the validated molecules are implicated in pathways that might be involved in disease pathogenesis and clinical manifestations (e.g., cardiac muscle contraction).

We conclude that these two molecules are reliable and specific biomarkers for SSc, when measured in blood at RNA levels, conferring minimal risk to patients, thereby facilitating a cost-effective and timely diagnosis.

No external funding received.

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PA16. Urine-Derived Tubular Cells as means of Liquid Biopsy for Biomarker Validation in MUC1 Kidney Disease

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Autosomal Dominant Tubulointerstitial Kidney Disease caused by MUC1 mutations (MKD/ADTKD-MUC1) is a rare inherited disorder. In this disease, the mutant MUC1-frameshift (MUC1-fs) protein accumulates in cytoplasmic vesicles of tubular epithelial cells, leading to stress and cell death. Multi-omics profiling of urinary extracellular vesicles (uEVs) has highlighted ferroptosis, a regulated form of cell death, as a key mechanism. This study aimed to use urine-derived tubular cells as a liquid biopsy to validate biomarkers associated with MKD. Cells isolated from urine samples of patients with MKD and healthy individuals, were used for cytospin preparations or cultured as primary tubular cells. Expression of the ferroptosis marker 4-hydroxynonenal (4HNE) and the system xc^- transporter subunits CD98 and SLC7A11 were examined by immunofluorescence and western blotting. MDCK and MCF7 cells were used as high and low 4HNE expression controls, while HeLa and A549 cells served as positive controls for CD98 and SLC7A11. Urine-derived tubular cells with high 4HNE expression were more frequently detected in MKD patients than in healthy controls. Moreover, patients with more severe disease exhibited higher levels of 4HNE-associated proteins. No significant differences in CD98 and SLC7A11 expression was observed between groups. Urine-derived tubular cells could offer a promising liquid biopsy approach for identifying biomarkers in MKD. Primary urine-derived cells from patients and healthy controls also provide a comparative in vitro model for investigating the molecular pathways underlying MUC1-related kidney pathology.

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PA17. 3-methylglutaconic aciduria associated with deficiency in the mitochondrial i-AAA protease YME1L1

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3-methylglutaconic aciduria (3-MGA) is a biochemical feature of several inherited metabolic disorders. Primary 3-MGAs arise from defects in the leucine catabolism, resulting in 3-methylglutaconyl-CoA accumulation. Secondary 3-MGAs comprise a more heterogeneous group of disorders, unrelated to leucine metabolism, but associated with compromised mitochondrial function. Impaired mitochondrial respiration and consequent elevation of mitochondrial NADH/NAD+ ratio is thought to attenuate the Krebs cycle, resulting in the diversion of acetyl-CoA to 3-methylglutaconyl-CoA formation, the precursor of 3-methylglutaconic and 3-methylglutaric acid. Two siblings presented with sensorineural hearing loss and neurological abnormalities were subjected to metabolic and genetic investigation. To assess the effects related to the identified variant, patient-derived fibroblasts were subjected to western blot analysis, immunofluorescence staining, measurement of oxygen consumption rate and evaluation of the Krebs cycle enzymatic activity. We report 3-MGA in the two siblings associated with a novel, homozygous missense variant (c.1999C>G, p.Leu667Val) in the YME1L1 gene which encodes a mitochondrial ATP-dependent metalloprotease. We show that this variant is associated with compromised YME1L1 function, as revealed by abnormal proteolysis of the YME1L1 substrates OPA1 and PRELID1 in patient-derived fibroblasts. Consistent with the aberrant processing of OPA1, a key regulator of mitochondrial dynamics, patient's fibroblasts display fragmentation of the mitochondrial network. Our results further indicate that YME1L1L667V is associated with compromised mitochondrial respiration and attenuated activity of the rate-limiting Krebs cycle enzymes. Our findings classify YME1L1 deficiency as a new type of secondary 3-MGA and suggest that it should be considered in the diagnostic evaluation of 3-MGA patients presenting with sensorineural hearing impairment and neurological manifestations. Project supported by the Internal Fund of The Cyprus Institute of Neurology and Genetics, 2024-21, the Ministry of Health Czech Republic (grant number: DRO-VFN64165), and General University Hospital Prague, the Charles University, Cooperation Paediatrics and UNCE /24/MED/022. Urine-derived tubular cells could offer a promising liquid biopsy approach for identifying biomarkers in MKD. Primary urine-derived cells from patients and healthy controls also provide a comparative in vitro model for investigating the molecular pathways underlying MUC1-related kidney pathology.

Project supported by the Internal Fund of The Cyprus Institute of Neurology and Genetics, 2024-21, the Ministry of Health Czech Republic (grant number: DRO-VFN64165), and General University Hospital Prague, the Charles University, Cooperation Paediatrics and UNCE /24/MED/022.

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PA18. Investigating TNNC1 Gene Inheritance and Clinical Outcomes Through a Comprehensive Familial Study

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Hypertrophic cardiomyopathy (HCM) and restrictive cardiomyopathy (RCM) have significant phenotypic overlap and a similar genetic background. This study focuses on the genetic testing of two interconnected families with four infants diagnosed with fatal RCM associated with bi-ventricular hypertrophy, three decades ago. Biological samples of the deceased infants were analysed with exome sequencing, while direct ancestors and siblings of the deceased infants were analysed using the Ventrilia Cardiovascular NGS test (Medicover Genetics), that analyzes 292 genes that can cause multiple cardiovascular conditions with complex phenotypes. The rest of the family members were tested using Sanger sequencing.A pedigree spanning six generations was created, involving 56 individuals participating in this study. Our genetic analysis revealed that homozygosity for NM_003280.3(TNNC1):c.23C>T(p.Ala8Val) results in HCM which evolves into a severe RCM phenotype, leading to fatal outcomes during infancy. Identified heterozygous individuals were predominantly asymptomatic or exhibited later onset of HCM, inherited in an autosomal dominant manner. Our study provides strong evidence that the homozygous expression of A8V TnC exacerbates disease progression, leading to the transition from HCM to RCM, ultimately culminating in death. This indicates that variants in the TNNC1 gene associated with HCM can also lead to severe RCM in infancy, showing different inheritance patterns. Overall, this study underscores the complex nature of genetic inheritance in cardiomyopathies and emphasizes the vital role of genetic testing in providing essential insights crucial for diagnosis, prognosis, early intervention, and the development of potential treatment strategies.

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PA19. Genetic Variants and Parenting Behaviors: Gene–Environment Interactions in Child Psychopathology

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This study examined the role of genetic variants and gene–environment (GxE) interactions in shaping child psychopathology and parenting behaviors. We focused on 68 single-nucleotide polymorphisms (SNPs) across key neurobiological pathways, including serotonin, dopamine, noradrenaline, oxytocin, vasopressin, acetylcholine, glutamate, HPA axis, and neurotrophic genes. Behavioral outcomes (externalizing and internalizing psychopathology) and parenting measures (positive parenting, sensitivity to punishment, sensitivity to reward, and parental sensitivity) were assessed. The sample included 167 parent reports for SNP–behavior associations and 137 reports for SNP–environment associations. Child outcomes were measured with the Child Symptom Inventory for Parents-4 (CSI-4), including ADHD, conduct disorder (CD), oppositional defiant disorder (ODD), anxiety, and depression. Parenting factors were measured with the Sensitivity to Punishment and Reward Questionnaire (SPRQ) and the Highly Sensitive Person (HSP) Scale. Genotyping was conducted using amplicon-based next-generation sequencing. Linear regression analyses revealed significant associations between several SNPs and psychopathology. Serotonin receptor HTR2C rs6318 C allele carriers and HTR2A rs6314 A allele carriers showed higher externalizing and internalizing symptoms ($p = 0.04$; $p = 0.02$), while the oxytocin OXTR rs2268490 T allele carriers had lower conduct problems ($p = 0.02$). Moreover, dopamine receptor DRD1 rs4532 T allele carriers showed lower levels of externalizing traits, whereas serotonin receptor HTR2C rs6318 C allele carriers were predictive of higher levels of both externalizing and internalizing traits, including anxiety ($p = 0.005$) and depression ($p = 0.03$). Parenting measures were not significantly associated with positive parenting behaviors but were related to children's sensitivity to punishment and reward, involving variation in dopamine, serotonin, and oxytocin pathway genes. These findings highlight the interplay of genetic predispositions and environmental responsiveness in shaping behavioral outcomes and parenting, underscoring the importance of integrating GxE approaches in child psychopathology research.

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BIOGRAPHS - INVITED LECTURES

1. Dr. Apostolos Malatras, PhD

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Dr. Apostolos Malatras leads the digital and bioinformatics infrastructure of biobank.cy, focusing on the integration of genomic, phenotypic, and clinical data within FAIR-compliant frameworks. He has contributed to several national and EU-level initiatives, including Cyprus's participation in the Genome of Europe, and Genomic Data Infrastructure projects. His research interests include omics analysis, federated, scalable, and secure data infrastructures, and management systems.

2. George Spyrou, PhD

Dr. George M. Spyrou is the Bioinformatics European Research Area Chair Holder and the Head of the Bioinformatics Department at the Cyprus Institute of Neurology and Genetics. He holds a BSc on Physics, an MSc on Medical Physics and an MSc on Bioinformatics as well. During his PhD he worked on algorithms and simulations focusing on breast cancer imaging. At the very beginning of the Biomedical Research Foundation of the Academy of Athens (BRFAA), Dr. Spyrou was selected to drive and supervise the design and development of the whole informatics infrastructure at BRFAA, being appointed as a Research Scientist of level B. Since 2001 and for over 10 years he worked on the strategic plan and implementation of IT development at BRFAA, acting as the Head of the Department of Informatics and New Technologies of BRFAA. In parallel, he was organizing his research group and was running his own research on bioinformatics and medical informatics. In 2007 Dr. Spyrou was promoted to Senior Research Scientist (Level A) at BRFAA after successful evaluation. For the years 2009-2016 he was coordinating a full semester course (Simulation Methods in Medicine and Biology) in the Postgraduate Program "Information Technologies in Medicine and Biology" (in both directions: Bioinformatics and Medical Informatics) at the University of Athens. Since 2017 Dr. Spyrou is the Bioinformatics Course Coordinator at the Cyprus School of Molecular Medicine. He is also a visiting instructor on Systems Bioinformatics and Network Analysis in other two postgraduate courses, namely the Master program on "Complex Systems and Networks" at the Aristotle University of Thessaloniki and the Master program on "Translational Research in Molecular Biology and Genetics" at the Democritus University of Thrace. Further to them, Dr. Spyrou has been an instructor at the Greek National Centre for Public Administration and Local Government (EKDDA) for the period 2005-2014, with over 300 lecture hours. Through his teaching activities Dr. Spyrou has the opportunity of supervising/mentoring a number of MSc and PhD students. His work includes computational methods that act as bridges between molecular biology, systems biology and molecular medicine, exploiting computational intelligence and high performance computing for multi-omics network analysis, systems bioinformatics and in silico drug discovery. Some of his in silico experiments are executed in Super-Computing Centers after successful evaluation of the proposed research projects. Dr. Spyrou is the Representative of Cyprus in the Management Committee of the COST Action CA15120 entitled: "Open Multiscale Systems Medicine (OpenMultiMed)". Up to now, he has served as Reviewer, Invited Speaker, Chairman and Scientific Advisory Board Member in topics related to Biomedical Informatics topics while he has authored over 160 scientific publications in peer reviewed journals and international conference proceedings.

3. Konstantinos Voskarides, PhD

Konstantinos Voskarides is an Associate Professor of Genetics and Molecular Biology at the University of Nicosia Medical School and at the School of Veterinary Medicine of University of Nicosia. Dr Voskarides holds a BSc in Biology from Aristotle University of Thessaloniki and a PhD in Molecular Biology and Genetics from University of Cyprus. He is currently a Senior Editor at the Springer journals "BMC Medical Genomics" and "Journal of Molecular Evolution". Dr Voskarides has expertise on medical genetics and evolutionary medicine. He contributed to the discovery of new genes causing familial renal diseases and he also deciphered the genetic origins of Greek-Cypriots. Between 2010-2015 he contributed to the establishment of the first Biobank in Cyprus and afterwards the first zebrafish facility in Medical School of University of Cyprus. He also discovered a possible link between cancer incidence and previous evolutionary adaptations, a study that gained a lot of attendance by news media in 2018. His current research is mainly focused on comparative and evolutionary genetics of cancer genes, having introduced zebrafish as an animal model to experimental evolution. He is also interested on analysis of GWAS data regarding rheumatic and psychiatric diseases. Dr Voskarides has authored 68 articles since 2024 in prestigious journals, he has an h-index 27, and he is the Editor of the book "Genomic Elements in Health, Disease and Evolution" in Springer Publishing Group.

4. Kyriaki Michailidou, PhD

Dr Kyriaki Michailidou is Associate Professor and Head of the Biostatistics Unit at the Cyprus Institute of Neurology and Genetics. She holds a PhD in Genetic Epidemiology from the University of Cambridge, an MSc in Applied Statistics from the University of Oxford, and a BA in Mathematics from the Aristotle University of Thessaloniki. Her research focuses on the genetic and statistical underpinnings of complex diseases, with a particular emphasis on cancer susceptibility. Dr Michailidou is a leading member of international consortia such as the Breast Cancer Association Consortium (BCAC) and ENIGMA, where her work has contributed to the identification of numerous genetic risk loci for breast cancer. She leads research and training in biostatistics and genetic epidemiology, fostering interdisciplinary collaborations that bridge statistical innovation with biomedical research. She also holds a visiting researcher position at the Centre for Cancer Genetic Epidemiology at the University of Cambridge.

5. Fotios Mpekris, PhD

Dr. Fotios Mpekris earned a BS degree (with an excellent GPA) in Physics from the University of Cyprus in 2012 and the same year, he joined with a scholarship the Department of Mechanical Engineering at the at the University of Cyprus and the Cancer Biophysics Laboratory in particular, as a PhD student. He defended his PhD thesis in November 2016, and since then with funding coming mostly from his own grants, he had been a postdoctoral fellow at the Cancer Biophysics Laboratory and a part time lecturer at the University of Cyprus and the University of Nicosia until October 2023. In 2023, he secured a highly selective research grant by the European Research Council (ERC Starting Grant, MMSCancer, 1.5M euros, started at November 2023) and he took over a faculty position as a Research Assistant Professor at University of Cyprus since April 2025. Since April 2025, he is the Head of the Cancer Genetics, Therapeutics & Ultrastructural Pathology Department at the Cyprus Institute of Neurology and Genetics. During his research career, Dr. Mpekris has secured 2.5M euros in research funding as a Principal Investigator. The implementation of his research has led to the publication of a remarkably large number of articles in high impact journals and the development of scientific expertise that is internationally competitive. He has co-authored more than 50 scientific articles in peer-reviewed journals (h-index=23, >3,000 citations, Google Scholar). As a recognition of this scientific contribution, Dr. Mpekris has been awarded the Young Researcher Award by the Research and Innovation Foundation of Cyprus in 2023 as well as the Youth Researcher Award in Sciences by the Youth Board of Cyprus in 2024. His research activity focuses on the study of the abnormal tumor patho-physiology, the barriers that these abnormalities pose to the effectiveness of cancer therapies and the development of new therapeutic strategies to overcome these barriers and enhance the efficacy of therapies for cancer.

6. Chrysa Soteriou, PhD

Chrysa completed her studies in the UK and the USA and obtained her PhD in the field of membrane and cancer biology from the University of Leeds through an interdisciplinary collaboration that combined molecular biology, molecular dynamics simulations and atomic force microscopy. Since 2022, she has been an R&D Scientist at Medicover Genetics, focusing on the development and validation of liquid biopsy products in oncology using NGS.

7. Rami Aqeilan, PhD

Prof. Rami I. Aqeilan is a biomedical scientist specializing in cancer biology and genome stability. He is a Full Professor at the Hebrew University of Jerusalem (HUJI) and a Group Leader at the Cyprus Cancer Research Institute (CCRI). His research focuses on tumor suppressor genes, DNA damage response, and fragile sites, with recent efforts devoted to mapping the breakome of cancer cells and uncovering its role in cancer initiation. Prof. Aqeilan has published more than 150 research articles with an h-index of 61, and his scientific leadership has been recognized through major awards, including the ERC Consolidator Grant, the Kaye Innovation Award, and the Yodim Award.

8. Christiana Neophytou,PhD

Dr. Christiana Neophytou is an Assistant Professor at the EUC. She earned a BSc degree in Biology from the University of Athens in 2008 and an MSc degree in Molecular Biology from the University of Cyprus in 2010, graduating with the highest GPA in her class. She obtained a PhD from the University of Cyprus in 2014 where she remained as a Post Doctoral Researcher. Her PhD and post-doctoral work focused on breast cancer research. She was involved in the discovery of critical mediators of breast cancer metastasis which could also represent feasible targets for therapy. Concurrently, she worked on European Commission-funded projects including “GRANATUM-FP7” that aimed to identify natural anticancer compounds and “HMB4EU-Horizon2020”, investigating exposure to environmental chemicals and disease. In addition to acquiring extensive experience in a wide variety of in vitro molecular and cell biology techniques, she became familiar working with NOD/SCID immunodeficient mice to perform in vivo tumorigenesis assays using the UVP animal imaging system. In 2019 she obtained an RIF “Excellence” grant to study mechanisms of breast cancer metastatic dormancy as a Post Doctoral Researcher at the EUC. She currently is an Assistant Professor of Cancer Biology in the Department of Life Sciences at the European University and Head of the “Apoptosis and Cancer Chemoresistance Group” which currently consists of 1 PhD student, 2 MSc students and 1 BSc student. She is a member of several professional bodies, including the American and European Associations for Cancer Research. She is also the first recipient of the “Early Career Woman Researcher Award” for 2023 from the European University of Cyprus. She currently participates in two RPF-funded projects investigating novel markers of breast cancer metastatic dormancy and novel cancer immunotherapies in pancreatic cancer. She is also the recipient of two privately funded grants by Alpinamed AG to investigate the effects of natural extracts in breast, liver and brain cancers. She has earned 6 awards for presenting her work at international conferences. She has published over 30 papers, including some in high-impact journals as well as 2 book chapters, with more than 2000 citations and h-index 19. Her overall research interests include the deregulation of apoptosis in cancer and cancer chemoresistance. Her long-term goal is to develop novel strategies to improve the efficacy of chemotherapeutic approaches and reverse resistance through drug combination as well as the discovery of novel cancer chemopreventive agents. She is an active Management Committee member in two EU-funded COST actions (CA22125, CA23119). Dr. Neophytou currently maintains active collaborations with different research groups both locally as well as internationally.

9. Christoforos Odiatis

Dr Christoforos Odiatis is a Postdoctoral Researcher at biobank.cy, the Center of Excellence in Biobanking and Biomedical Research at the University of Cyprus. His research focuses on Alport syndrome, a genetic kidney disorder, with a particular interest in understanding its molecular mechanisms and identifying potential therapeutic targets.

10. Panayiota Papassava, PhD

Dr. Panayiota Papasavva is a Hematologist at the Cyprus Institute of Neurology and Genetics (CING). She earned her Medical Degree from the National and Kapodistrian University of Athens and completed her specialization in Hematology at the Hematology Clinic of the General Hospital of Athens "G. Gennimatas." She holds an MSc and a PhD in Medical Genetics from CING, where her doctoral and postdoctoral research focused on genome editing for β-haemoglobinopathies. Her clinical work focuses on the diagnosis and management of rare genetic hematological disorders, including rare red blood cell defects, bone marrow failure syndromes, immune disorders, rare bleeding and coagulation disorders, and syndromes with genetic predisposition to hematological malignancies.

11. Andrie Koutsoulidou, PhD

Dr. Andrie Koutsoulidou is an Assistant Professor at the Department of Molecular Genetics, Function and Therapy of the Cyprus Institute of Neurology and Genetics. She has over 13 years of research experience in muscular disorders, focusing on biomarker discovery and the development of therapeutic approaches for Myotonic Dystrophy type 1. Dr. Koutsoulidou has contributed to several international and national projects funded by the Association Française contre les Myopathies (AFM-Telethon) and the Research and Innovation Foundation. She has co-authored numerous scientific publications and serves as a reviewer for leading journals.

12. Kleopas Kleopa, MD, PhD, FAAN, FEAN

Prof Kleopas A. Kleopa, MD, PhD, FAAN, FEAN, is a Consultant Neurologist at the Cyprus Institute of Neurology and Genetics. He studied medicine and trained in neurology and neuromuscular disorders in Germany and the USA. Dr. Kleopa has a long track record as a clinician-scientist with expertise in neurological and neuromuscular disorders, neuroscience, and gene therapy. He coordinates the Centre for Neuromuscular Disorders delivering multidisciplinary clinical care and cutting-edge therapeutics. He is also Head of Neuroscience Department and coordinates the Neuroscience MSc/PhD Graduate Program at CING. His translational research has made significant contributions to the understanding of mechanisms of neurogenetic, neuroinflammatory and neuromuscular disorders and to the development of innovative cell-targeted gene therapies for inherited neuropathies and leukodystrophies, with results currently being developed for clinical translation in collaboration with industry. His work has been published in more than 130 peer-reviewed high-impact scientific papers and has been recognized by numerous prestigious Awards, including the EAN Investigator Award and the National Distinguished Researcher Award. He is a Board Member of the Peripheral Nerve Society (PNS) and Vice-Chair of the CMT and Related Disorders (CMTR) special interest group. He serves in Scientific Advisory Boards of the USA CMT Association, the Gilbert Foundation Neurofibromatosis-1 Gene Therapy Initiative, and the PMD Foundation. He co-chairs the Working Groups on Gene Therapies, Neuropathies, and Leukodystrophies of the European Reference Networks for rare neuromuscular and rare neurological disorders.

13. Vasiliki Chini, PhD

Dr. Vasiliki Chini is the Laboratory Director at Medicover Genetics in Greece. She brings almost two decades of expertise in clinical genomics and molecular diagnostics, specializing in rare genetic disorders. Dr. Chini earned her Degree in Biology from the University of Athens (2002) and a PhD in Clinical-Laboratory Medical specialties from the University of Patras (2007). From 2009 to 2020, she was a registered Clinical Scientist at Hamad Medical Corporation in Qatar, where she led the molecular diagnosis of Rare Mendelian Disorders using Whole Exome Sequencing (WES) and managed metabolic syndrome diagnosis for the Newborn Screening Program. During this time, she was a key contributor to the Qatar Genome Project and the Autism Project, focusing on bioinformatics analysis and clinical interpretation of genomic data for the Qatari population. Returning to Greece, she served as the Head of the NGS Unit at the University of Athens Medical School and led the Molecular Genetics Laboratory at "Aghia Sofia" Children's Hospital. Since July 2022, she has overseen all laboratory operations and quality assurance at Medicover Genetics, specializing in NGS tertiary analysis, clinical interpretation, and the development and validation of new diagnostic assays.

14. Nicole Salameh, PhD

Nicole Salameh, Senior Laboratory Scientific Officer at the Cytogenetics and Genomics Department of the Cyprus Institute of Neurology and Genetics, where she has been working since 2002. She holds a Bachelor of Science from the Kapodistrian University of Athens and a Master's degree from the University of Cyprus. She is currently pursuing her PhD at the Medical School of the Kapodistrian University of Athens. Her work focuses on cytogenetics, molecular cytogenetics, and molecular analyses related to human disorders and conditions such as intellectual disability, learning difficulties, autism, congenital abnormalities and infertility. She has been an active member of the Cyprus Society of Human Genetics since 2004, serving twice as a board member.

15. Thessalia Papasavva, PhD

Thessalia Papasavva has been with the Cyprus Institute of Neurology and Genetics (CING) since 1996 and holds the position of Group Leader of the Hemoglobinopathies Diagnosis and Development Unit, as well as Quality Manager of the Department. She holds a BSc in Microbiology from the University of Arizona (USA), an MSc in Applied Molecular Biology and Biotechnology from University College London (UK), and a PhD in Medical Genetics from the University of Athens in collaboration with CING. Her research and diagnostic work focus on the diagnosis, prenatal, and preimplantation genetic diagnosis of hemoglobinopathies, hemolytic anemias, and other monogenic disorders. She has extensive experience and expertise in the development and application of innovative, state-of-the-art methodologies aimed at advancing genetic analysis in both prenatal and diagnostic contexts. In addition, she is actively involved in the development of customized preimplantation genetic testing (PGT) analyses and in promoting comprehensive PGT applications for a wide range of monogenic disorders. As a Research Fellow of the CING School, she lectures in the postgraduate program and supervises MSc and PhD students. She has authored publications in international scientific journals, participated in research projects, and presented at conferences in Cyprus and abroad. She also serves as a reviewer for international scientific journals in the fields of hemoglobinopathies and prenatal diagnosis. Her specialized expertise and scientific contribution to diagnostic and research strategies in hemoglobinopathies and anemias represent a significant asset to the advancement of medical genetics.

16. Constantia Aristidou, PhD

Dr Constantia Aristidou holds a BSc in Biochemistry and an MSc in Toxicology from the University of Surrey, UK. She subsequently completed her PhD in Medical Genetics at the Cyprus Institute of Neurology and Genetics (CING). Her doctoral research, conducted at the Department of Cytogenetics and Genomics, focused on accurately mapping breakpoints in apparently balanced translocation carriers using whole-genome mate-pair sequencing (WG-MPS). During her PhD, she also completed an Erasmus+ traineeship at the University of Copenhagen, Denmark, where she received specialized training in WG-MPS. In 2019, she joined the High-Throughput Arrays team at the Oxford Genomics Centre, Wellcome Centre for Human Genetics, University of Oxford, UK. Currently, Dr Aristidou is an Associate Scientist at the Department of Clinical Genetics and Genomics of CING and continues to collaborate closely with the Department of Cytogenetics and Genomics. Her research interests focus on the genetic aetiology of rare diseases and the application of novel cytogenomic tools for the detection and precise characterization of structural variants in patients with neurodevelopmental disorders or couples with infertility.

17. Andreas Mamilos, Dr

Prof. Dr. med. Andreas Mamilos began his medical studies at Johannes Gutenberg University in Mainz, Germany, where he commenced his specialty training in Pathology under the guidance of Prof. Dr. Kirkpatrick. He advanced his expertise at the University of Regensburg, Bavaria, under Prof. Dr. Evert, where he not only honed his clinical skills but also contributed to pivotal research projects as an academic associate. With comprehensive training spanning medical autopsies, histopathology, cytology, and molecular pathology, Prof. Mamilos brings a rare breadth of expertise to his role. His doctoral thesis, which explored the pathomechanisms of macrophages in peritoneal adhesions, exemplifies his commitment to translational research that bridges bench and bedside. His research contributions at Regensburg, including work in Graft-versus-Host Disease (GvHD) and the tumor microenvironment, underscore his dedication to advancing medical knowledge in complex disease areas and achieving new therapeutic implementations. Prof. Mamilos has also conducted research on the applications of artificial intelligence (AI) in breast cancer, focusing on tailoring personalized treatment approaches through the evaluation of predictive and prognostic factors of breast carcinoma. After 17 years of distinguished work and study in Germany, Prof. Mamilos returned to his homeland to lead the Pathology Department as its new director. In addition to his diagnostic leadership, he is committed to ongoing research collaborations and continues his role as a scientific assistant and lecturer at the University of Regensburg. Prof. Mamilos frequently lectures in Germany, sharing his expertise with students in medicine, dentistry, and molecular biology, and remains an active member of the research community. He also lectures in Pathology at the European University of Cyprus.

18. Denise O'Mahony, PhD

Dr. Denise O'Mahony is a genetics graduate who completed her PhD at the Biostatistics Unit of the Cyprus Institute of Neurology and Genetics (CING), specializing in breast cancer genetic epidemiology. Her doctoral research focused on interpreting BRCA1 and BRCA2 variants of uncertain significance through novel assessment of ovarian tumour characteristics and development of novel methods for analysing large-scale case-control data, alongside applying Bayesian fine-mapping approaches to identify causal variants in breast cancer. Following her PhD studies, she worked as a postdoctoral fellow at the Department of Medical Genetics, Oslo University Hospital, where she investigated the subclonal reconstruction of tumours in association with aromatase inhibition treatment and evaluated polygenic modelling for breast cancer risk assessment and patient outcomes in Norway. Her work also included implementing AI-driven pipelines for identifying functionally-impactful variant predictions in breast cancer. Dr. O'Mahony is currently a postdoctoral researcher at the Biostatistics Unit of the CING, where she is working on the DISARM project, focusing on the use of polygenic risk scores for early ovarian cancer risk prediction. Dr. O'Mahony is also an active member of the BCAC (Breast Cancer Association Consortium) international consortium and serves as a committee member of the International Genetic Epidemiology Society.

19. Andrea Kakouri, PhD

Dr Andrea Kakouri is a post-doctoral researcher at biobank.cy, Center of Excellence in Biobanking and Biomedical Research at the University of Cyprus. Her research focuses on the integration of multi-omics, clinical, and biochemical data to investigate rare genetic kidney diseases, with a particular focus on ADTKD-MUC1. Her work aims to study the disease's natural history, identify biomarkers, elucidate mechanisms, and uncover therapeutic targets, while also applying computational approaches to develop a digital kidney tubule twin, modeling healthy and disease states to enhance clinical translation. She also studies rare glomerulopathies, aiming to identify prognostic biomarkers and progression drivers. Beyond nephrology, Dr Kakouri has expertise in liquid biopsy, using next-generation sequencing of circulating tumour DNA to identify biomarkers of immunotherapy response in non-small cell lung cancer. She holds a BSc in Biological Sciences (University of Leicester), an MSc in Cell and Gene Therapy (UCL), and a PhD in Medical Genetics (Cyprus Institute of Neurology and Genetics).

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