# Γεφυρώνοντας μεγάλα ομικά, γενετικά και ιατρικά δεδομένα για την ευρεία εφαρμογή της Ιατρικής Ακριβείας στην Ελλάδα

## *ΠΑΡΑΔΟΤΕΟ Π6.2*

## *«Προσαρμογή Μοντέλων Μηχανικής Μάθησης σε Ελληνικές Κοόρτες»*

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| ***Τίτλος Παραδοτέου*** | Προσαρμογή Μοντέλων Μηχανικής Μάθησης σε Ελληνικές Κοόρτες |
| ***Ενότητα Εργασίας*** | ΕΕ6: Ανάπτυξη Μοντέλων Μηχανικής Μάθησης για Εξόρυξη Γνώσης και Κατηγοριοποίησης Ασθενών |

Ελλάδα 2.0
ΕΘΝΙΚΟ ΣΧΕΔΙΟ ΑΝΑΚΑΜΨΗΣ ΚΑΙ ΑΝΘΕΚΤΙΚΟΤΗΤΑΣ
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# Σύνοψη Ενότητας Εργασίας 6, Δράσης 6.2 Πανεπιστήμιο Πατρών

**Παραδοτέο 6.2**

**Τίτλος Παραδοτέου:** Προσαρμογή Μοντέλων Μηχανικής Μάθησης σε Ελληνικές Κοόρτες

Η δεύτερη δράση της ΕΕ6 εστιάζει στη μετάφραση των θεωρητικών μοντέλων του Π6.1 σε κλινικά εφαρμόσιμα εργαλεία, προσαρμοσμένα στα δεδομένα του ελληνικού πληθυσμού. Η στρατηγική βασίζεται στην αξιοποίηση δύο εθνικών πόρων: της βάσης δεδομένων CanVaS (γενετική ποικιλομορφία Ελλήνων ασθενών με καρκίνο) και της μελέτης Epirus Health Study - EHS (πολυ-ωμικά δεδομένα γενικού πληθυσμού).

1) Προσαρμογή στα Ελληνικά Δεδομένα (CanVaS): Η χρήση της βάσης CanVaS επιτρέπει την αντιμετώπιση της «μεροληψίας εξακρίβωσης» (ascertainment bias) που προκύπτει από τη χρήση παγκόσμιων βάσεων δεδομένων, οι οποίες συχνά υποεκπροσωπούν τοπικές μεταλλάξεις (founder mutations). Το μοντέλο ταξινόμησης παραλλαγών BRCA1/2, το οποίο βασίζεται στη δομή της πρωτεΐνης (structure-informed), επικυρώθηκε σε δεδομένα του CanVaS επιτυγχάνοντας ισορροπημένη ακρίβεια 95%. Αυτό επιβεβαιώνει ότι το σύστημα αναγνωρίζει τον πραγματικό βιοφυσικό αντίκτυπο των μεταλλάξεων και είναι κατάλληλο για τον ελληνικό πληθυσμό.

2) Στρωματοποίηση Ασθενών (EHS): Για την κατηγοριοποίηση ασθενών με μεταβολικά νοσήματα, κατασκευάστηκε ένα «πολυεπίπεδο ετερογενές δίκτυο» (multiplex heterogeneous network) που συνδυάζει γονιδιωματικά, μεταβολιμικά και κλινικά δεδομένα από 959 άτομα της μελέτης EHS. Χρησιμοποιήθηκε ο αλγόριθμος Random Walk with Restart (RWR) για τη διάδοση σήματος μέσα στο δίκτυο. Η μέθοδος πέτυχε να διακρίνει με ακρίβεια ασθενείς με Σακχαρώδη Διαβήτη Τύπου 2 από ασθενείς με Οικογενή Υπερχοληστερολαιμία, παρά την κοινή μοριακή βάση των δύο παθήσεων, αναδεικνύοντας τοπολογικά αποτυπώματα που δεν εντοπίζονται με απλές αναλύσεις βιοδεικτών.

Το GoMedPrecision επιτυγχάνει τη σύνδεση της καινοτόμου υπολογιστικής έρευνας με την κλινική πράξη στην Ελλάδα. Ο συνδυασμός της ερμηνείας παραλλαγών (μέσω CanVaS) και της στρωματοποίησης ασθενών (μέσω EHS) παρέχει μια ολοκληρωμένη οδό για την εφαρμογή ιατρικής ακριβείας, προσαρμοσμένης στα γενετικά χαρακτηριστικά του ελληνικού πληθυσμού.

# Deliverable 6.2: Adaptation of Trained Models to Greek Cohorts and Integrated Pipelines

## Strategic Adaptation to Greek Datasets

Crucially, the translational strength of GoMedPrecision is anchored in two Greek resources that provide population-specific depth and clinical relevance: the Epirus Health Study (EHS) [1] and the CanVaS cancer-variation resource [2]. The EHS is an ongoing, deeply phenotyped population cohort of residents from the Epirus region that collects detailed clinical, lifestyle, and molecular data; its prospective design and rich phenotyping make it ideally suited to discover and validate multi-omics disease signatures that are representative of the Greek population. The CanVaS repository documents germline genetic variation and curated clinical metadata from thousands of Greek cancer patients, including recurrent (founder) pathogenic variants observed in Greece. Together, these resources supply both the population-level context and the disease-focused variant catalogues necessary for responsible, locally relevant precision medicine.

Within GoMedPrecision we exploit these datasets in three concrete ways. First, CanVaS supplies population- and disease-specific germline variation that we use to mitigate ascertainment bias when training and calibrating structure-informed VUS classifiers; using a large, locally derived variant set reduces misclassification that can arise from solely global training sets and improves clinical relevance for Greek patients. Second, the EHS cohort provides the deeply phenotyped, multi-omics patient data (genotype, metabolome, clinical measures) required to construct the multiplex heterogeneous networks used by our Random Walk with Restart (RWR) and diffusion-based stratification pipelines; the cohort's local demographic and environmental context ensures that discovered patient subtypes and topological disease footprints are applicable to the target population. Third, the integrated pipeline — from node-level VUS classification to edge/topology analysis and patient-level diffusion — enables end-to-end validation: predicted vari ant pathogenicity can be cross-checked against CanVaS clinical annotations and the downstream patient stratifications can be assessed and refined using EHS clinical outcomes and biomarkers.

## Clinical Application & Stratification

### Classifying BRCA1 and BRCA2: Validation on Population-Specific Data

A critical distinction between our approach and existing tools, such as MARGINAL [3], lies in the selection of input features. Tools relying on ACMG-AMP criteria as input features risk circularity, as these same criteria are often used to define the ground-truth clinical labels in databases like ClinVar [7]. By contrast, our model relies exclusively on physicochemical and structure-informed properties. This provides a more objective, ab initio classification that predicts biological impact based on molecular first principles rather than automating pre-existing curation rules.

Beyond avoiding circularity, our emphasis on the CanVaS dataset addresses the limitations of global classifiers in handling population-specific genetic heterogeneity. Global tools are typically trained on aggregated datasets dominated by major ethnic groups, potentially leading to ascertainment bias where founder mutations or variants specific to the Greek population are misclassified or designated as VUS due to low global frequency. By integrating CanVaS data with ab initio structural modeling, our approach decouples pathogenicity prediction from global prevalence statistics. This ensures that the classification is driven by the intrinsic biophysical impact of the mutation—such as stability loss or functional disruption—making the model particularly robust for specific populations where global predictors may lack sensitivity or applicability.

A critical step in adapting computational models for clinical utility is rigorous validation against population-specific data. The performance metrics presented in Table 1 below demonstrate the robustness of our structure-informed variant classification pipeline when applied to data enriched with Greek founder mutations from the CanVaS database. By achieving high precision and recall (95% balanced accuracy) on this specific cohort, we confirm that the model does not merely learn global statistical trends but captures genuine biophysical constraints relevant to the local population. This validation is a prerequisite for integrating the tool into the GoMedPrecision diagnostic workflow, ensuring that the "node" inputs for our downstream network analyses are both accurate and locally valid.

Table 1: Classification metrics after applying PCA for dimensionality reduction. The same model's performance is evaluated at different confidence thresholds

(a) No threshold applied

| Class | Prec. | Rec. | F1 | Support |
|---|---|---|---|---|
| benign | 0.96 | 0.87 | 0.91 | 174 |
| pathogenic | 0.74 | 0.90 | 0.82 | 71 |
| Accuracy | | | 0.88 | 245 |
| Macro Avg | 0.85 | 0.89 | 0.85 | |
| Weighted | 0.89 | 0.88 | 0.88 | |

(b) Confidence threshold at $> 80\%$

| Class | Prec. | Rec. | F1 | Support |
|---|---|---|---|---|
| benign | 0.98 | 0.97 | 0.97 | 122 |
| pathogenic | 0.90 | 0.93 | 0.91 | 40 |
| Accuracy | | | 0.96 | 162 |
| Macro Avg | 0.94 | 0.95 | 0.94 | |
| Weighted | 0.96 | 0.96 | 0.96 | |

$$\begin{bmatrix} 152 & 22 \\ 7 & 64 \end{bmatrix} \qquad \begin{bmatrix} 118 & 4 \\ 3 & 37 \end{bmatrix}$$

# A Graph-Based Multi-Omics Approach for Patient Stratification in the Epirus Health Study

## Context and Challenge

The ultimate goal of the GoMed Precision program is to improve patient care. This work applies the network medicine principles developed in the preceding papers to a real-world clinical cohort, the Epirus Health Study. The challenge addressed is the stratification of patients with chronic metabolic diseases, specifically distinguishing between Type 2 Diabetes Mellitus and Familial

Hypercholesterolemia. These conditions often co-occur and share overlapping molecular pathways, making precise differential diagnosis and patient stratification difficult using standard clinical markers alone.

## Methodological Innovation

We constructed a "multiplex heterogeneous network" that integrates genomics, metabolomics, and clinical phenotype data. Data from 959 individuals were processed, including genotype data imputed via TOPMed [4] and metabolomic profiles.

The network architecture consists of distinct layers: a gene co-expression layer and a metabolite co-expression layer, both constructed using WGCNA (Figure 1). These layers are connected to a disease similarity network through bipartite associations derived from public databases like OMIM [5] and HMDB [6].

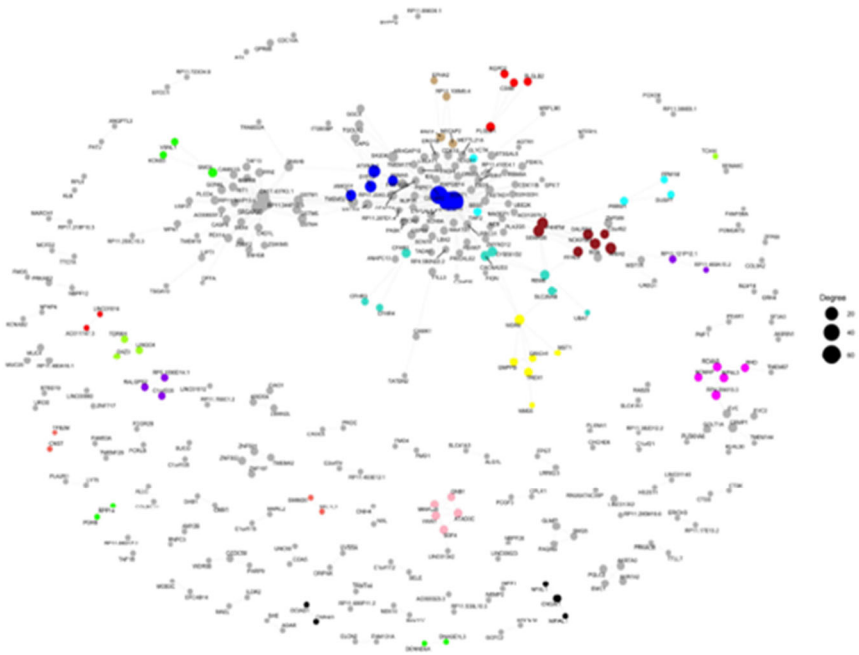

Figure 1: Network representation of gene associations showing the 1,000 most significant edges.

The core analytical tool employed is a Random Walk with Restart (RWR) algorithm adapted for this multiplex structure. For each patient, significant genes and metabolites (identified via Z-scores relative to a healthy baseline) serve as "seed" nodes. The random walker propagates these patient-specific signals across the multi-omics network to generate a ranked list of associated diseases. This "diffusion" process allows the algorithm to identify the topological footprint of a patient's disease, capturing indirect associations that simple biomarker lists would miss. The model utilizes optimized transition and restart parameters to generate robust disease-gene association scores.

Key Findings

The study presents a proof-of-concept demonstrating the algorithm's ability to correctly classify patients. In the presented test cases, the RWR scores accurately prioritized "Type 2 Diabetes Mellitus" for a diabetic patient and "Familial Hypercholesterolemia" for a patient with the corresponding condition, despite the high biological overlap between the two metabolic disorders. The algorithm successfully differentiated the molecular signatures of these diseases by leveraging the full topology of the multiplex network.

We conclude that this graph-based multi-omics integration provides a more granular patient stratification than single-omics approaches, offering a promising avenue for precision medicine in diagnosing complex, multifactorial diseases within the Greek population. This work represents the translational endpoint of the GoMedPrecision pipeline, demonstrating how the theoretical and computational tools developed in the earlier papers can be applied to real-world patient data to improve diagnostic precision. It validates the utility of multiplex networks in capturing complex biological relationships that traditional single-layer analyses often miss (see Table 2).

Table 2. Disease scores for classifying each patient according to their disease status.

DISEASE SCORES FOR PATIENT WITH DIABETES

| Disease Name | Score |
|---|---|
| TYPE 1 DIABETES MELLITUS | 2.065964e-03 |
| HYPERCHOLESTEROLEMIA, FAMILIAL, 4 | 8.632750e-06 |
| TYPE 2 DIABETES MELLITUS | 8.335352e-06 |
| HYPERCHOLESTEROLEMIA, FAMILIAL, 3 | 7.984983e-06 |
| MATURITY-ONSET DIABETES OF THE YOUNG | 8.594573e-07 |
| HYPERCHOLESTEROLEMIA, FAMILIAL, 2 | 5.775218e-07 |

DISEASE SCORES FOR PATIENT WITH HYPERCHOLESTEROLEMIA

| Disease Name | Score |
|---|---|
| HYPERCHOLESTEROLEMIA, FAMILIAL, 4 | 1.547662e-05 |
| TYPE 1 DIABETES MELLITUS | 8.705014e-06 |
| HYPERCHOLESTEROLEMIA, FAMILIAL, 3 | 8.060045e-06 |
| TYPE 2 DIABETES MELLITUS | 7.784217e-06 |
| HYPERCHOLESTEROLEMIA, FAMILIAL, 2 | 5.713896e-07 |
| MATURITY-ONSET DIABETES OF THE YOUNG | 2.165624e-07 |

# Conclusion

The GoMedPrecision research portfolio represents a significant and comprehensive advancement in the field of network medicine. By systematically addressing the challenges of data noise, biological complexity, and patient heterogeneity, we have developed a complete suite of computational tools. From the structure-informed classification of BRCA variants to the ILP-based control of Boolean networks and the deep learning analysis of complex transcriptomes, this work demonstrates the power of integrating theoretical rigor with biological intuition.

In summary, GoMedPrecision achieves both methodological novelty and translational readiness by combining rigorous algorithmic development with Greek-specific data assets. The synergy between structure-informed variant interpretation (anchored on CanVaS) and multi-omics patient stratification (anchored on EHS) provides a pathway toward clinically actionable, population appropriate precision medicine in Greece. Continued engagement with these national resources will be essential for clinical validation, for addressing population-specific genotype–phenotype relationships (including founder effects), and for responsibly moving candidate interventions toward clinical deployment.

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