Predictive Models for Cancer Risk in TP53 Germline Mutation Carriers

Germline mutations in the TP53 gene (Li-Fraumeni syndrome), is a rare inherited cancer predisposition syndrome characterized by a very high lifetime risk of multiple cancers at young ages. Despite the clear genetic risk, the expression of cancer among carriers shows large variability.

This heterogeneity is only partly explained, and clinical management remains challenging. Improved quantitative models are needed to estimate individual risk, optimize surveillance strategies.

Objectives

1. To build and validate statistical (and machine learning models) for cancer risk prediction in TP53 germline mutation carriers.
2. To assess/estimate how demographic, clinical, and lifestyle factors influence age-specific penetrance and cancer types.
3. To explore the potential benefit of surveillance strategies (e.g. MRI screening) on early detection and survival outcomes using simulation studies.
4. To explore the potential role of cfDNA in cancer surveillance in a group of TP53 mutant carriers
5. To explore the psychological effects of the current used screening techniques.

Data

The project can make use of available, published datasets from other countries from clinical cohorts of TP53 mutation carriers, complemented by published penetrance estimates and simulated data when necessary. Data sources may include family registries, clinical follow-up information, and survival outcomes

Methodology

• Survival analysis and competing risks models to estimate age-specific cancer incidence.
• Regularized regression and machine learning techniques (e.g. random survival forests, neural networks for survival data) for prediction.
• Simulation studies to evaluate potential surveillance strategies in terms of cancer detection rates and cost-effectiveness.

Expected Results

The project will deliver a validated statistical framework for predicting cancer risk in TP53 mutation carriers, with potential applications in personalized medicine and genetic counseling. The findings will also provide methodological contributions to survival modeling in rare diseases.