Title: **EXPERT JUDGEMENT TO SUPPORT A CLINICAL HYBRID BAYESIAN NETWORK APPROACH ON PANCREATIC CANCER**

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Introduction:
Survival prediction models for pancreatic cancer have poor clinical utility and modest performance [1-2]. Existing tools rely on postoperative data and are based on a traditional non-linear regression technique, failing to include the care process's dynamic nature whereby predicted outcomes evolve as events unfold. Nomograms predict the likelihood of a time-dependent event after weighting the contribution of a fixed number of variables [3]. However, tumor biology is barely based on statistical assumptions. Whether unique patient-and tumor-specific characteristics, already present at the time of diagnosis, may impact survival after surgery and how they interplay is still largely unknown. The project's innovation relies on experts' elicitation process to support a Clinical Hybrid Bayesian Network (CHBN) model capable of unraveling the causal relationship between baseline patient- and tumor-specific predictive parameters and survival [4-11]. The project's primary aim is to translate experts 'opinions into probability distributions and use them to support a novel clinical network to predict pancreatic cancer patients' survival.

Methods:
A CHBN (Figure 1) was designed to reveal variables' connections at diagnosis and to manage continuous and categorical variables not to lose valuable information related to themselves. The nodes chosen are Ca19.9 serum level, gender, Body Mass Index (BMI), year of diagnosis, tumor location, age, diabetes, tumor size in millimeters, symptoms, American Association of Anesthesiology Score (ASA), resectability, and neoadjuvant therapy. The SHeffield ELicitation Framework (SHELF) method combines observed data with academic international experts' opinions in the same clinical CHBN. A two-phase project took place to make the elicitation process easier and to refine the survey and quantities of interest: a pilot phase administered to expert academic surgeons, postdoctoral fellows, and senior residents in surgery at the Pancreas Institute of Verona, Italy, and a final phase which involved nine international academic experts of pancreatic cancer care.
Experts' elicitation of Quantities of Interest was translated to numerical values, interpolated in individual responses, and aggregated. The parametric quantile method was considered to elicitate experts' distribution by interpolating and then performing a linear pooling of experts' opinions. Linear mathematical aggregation was performed to summarize data from the experts' pool. In several sections, results were shared with experts, like graphical format distributions for each variable, until a consensus judgment of better distributions. The pooled optimal fit distribution has been computed as follows: for continuous nodes, the mean and standard deviation of linear distribution have been considered; for categorical values, the transformation of the mean and standard deviation of linear distribution into shape (alpha) and scale (beta) parameters was performed.

Results:
The linear pooled distribution for each node of the CHBN was created according to the SHELF method. The graphs showed a general agreement distribution among the single expert's distribution shapes; however, some discrepancies were found for tumor size, age, and ASA score nodes. Additionally, for each node, the expert's pooling vote, the single best-fit distribution, and the type of prevalent distribution were considered. Tumor size and ASA score variables presented absolute concordance and the maximum expression of the expert's consensus, while serum Ca19.9 levels and resectability status showed very good concordance. Instead, the remaining nodes (gender, BMI, year, location, age, diabetes, symptoms, and neoadjuvant therapy) presented an acceptable concordance.

Conclusions:
In oncology, many important clinical decisions are routinely made even when the supporting literature evidence is weak or not applicable to tumor biology. For the first time, this project proposes a CHBN implemented with experts' elicitation,

including clinical variables already present at diagnosis, to model pancreatic cancer patients' survival. Another novelty is using the SHELF method to translate experts' opinions into a prior probability distribution in a pancreatic cancer clinical setting. This project demonstrates that it is possible to use a formal process for eliciting clinician opinions regarding uncertain variables to build research evidence to support clinical decision-making. This new model may overcome the limits of currently available pancreatic cancer survival prediction models. However, further validation processes will be necessary to evaluate the performance and the clinical applicability.

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Figure 1. The Clinical Hybrid Bayesian Network comprehensive of twelve nodes (Ca19.9 serum level, gender, BMI, year of diagnosis, tumor location, age, diabetes, tumor size, symptoms, ASA Score, resectability, and neoadjuvant therapy) and survival at 36 months