

Generalized Net Model of the Prostate Cancer Early Stages of Development



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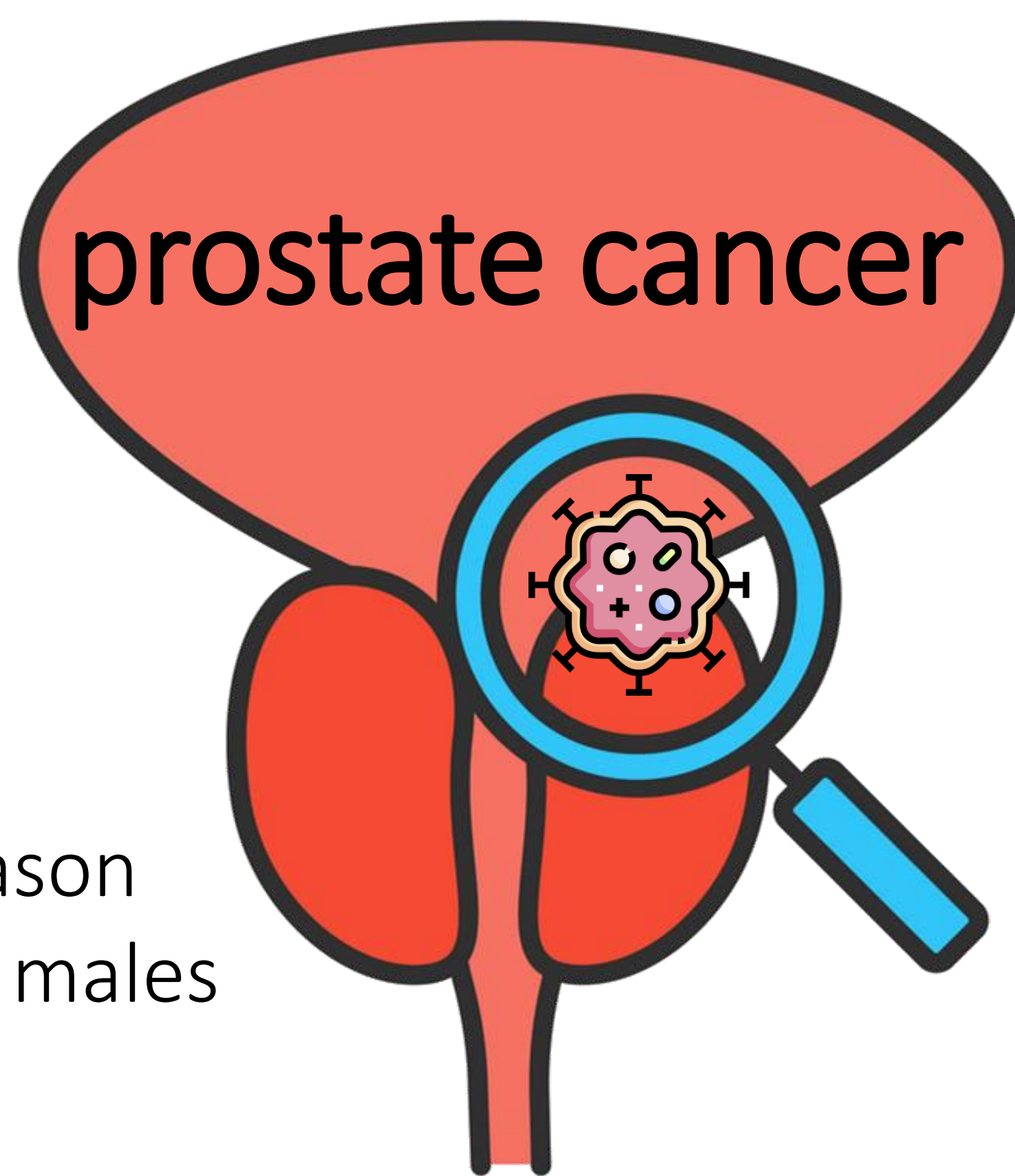
Facts about prostate cancer and its treatment



The most frequent non-skin cancer diagnosed in males
1 600 000 cases annually



The second most common reason for cancer-related death in males
366 000 deaths annually

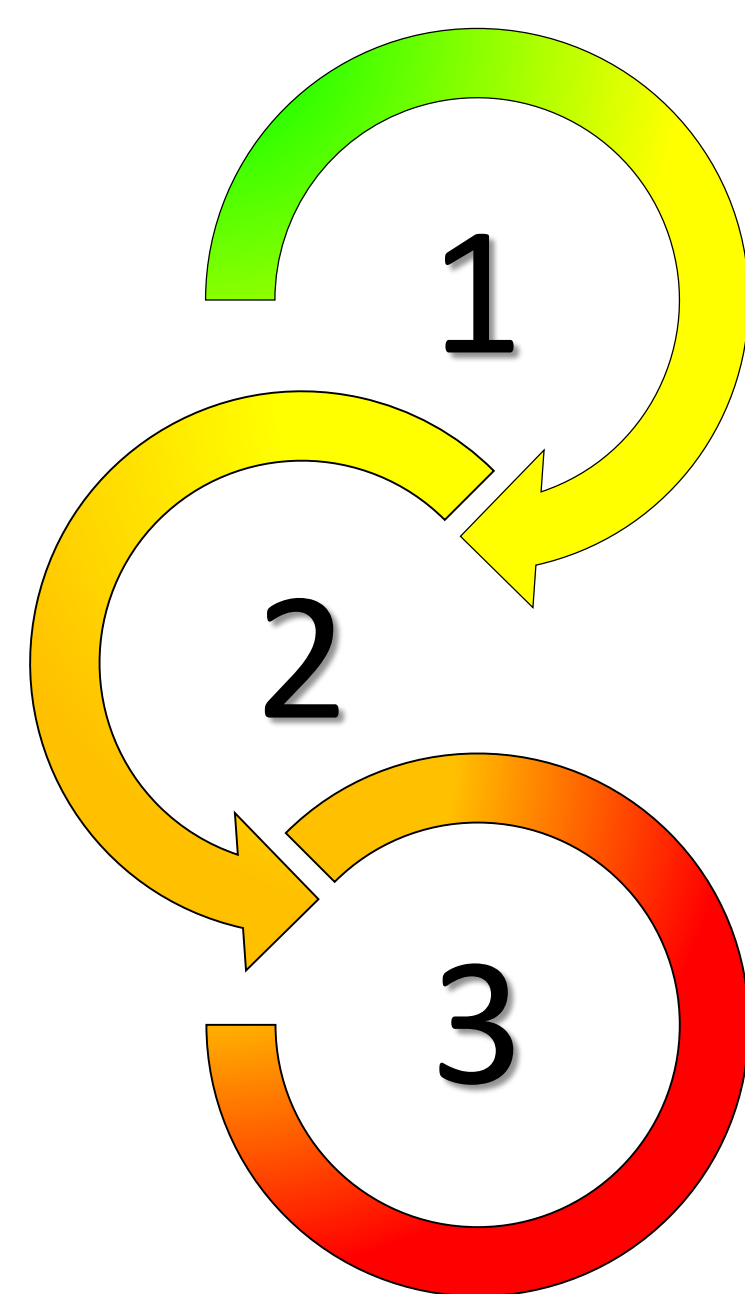


The two main obstacles in front of major advances in prostate cancer research:

- the **limited efficacy** in cases of metastatic disease, and
- the observed **significant overtreatment** for clinically indolent cases, that never have clinical consequences during the life-time of the patient.



Three different stages of development of prostate cancer, identified on the basis of molecular, pathological, clinical and imaging characteristics



Precancerous states such as **atypical small acinar proliferation (ASAP)** and **high-grade intraepithelial neoplasia (HGPIN)**, defined by the hyperplasia of acinar luminal cells and progressive disruption and loss of basal cells layer;

Androgen-dependent prostate cancer, characterized by the complete loss of basal cells layer and the overt malignant microscopic phenotype; because at this stage prostate cancer is still androgen-dependent, it is sensitive to androgen deprivation therapy (ADT); and

Androgen-independent (castration resistant) prostate cancer, which is an inevitable step in natural progression of prostate cancer and is insensitive to ADT.

ASAP and HGPIN are believed to be precursor lesions of prostate cancer owing to two facts, based on significant evidence:

- 1) epidemiological data that connects their existence with following finding of invasive carcinoma during follow-up, and
- 2) microscopic structural resemblance of epithelial cells of precancerous lesions and prostate cancer; and their colocalization in the prostate tissue, as well as shared genetic changes, vastly investigated in the last decade.

Generalized net model

In the paper, we propose a generalized net model of the early stages of prostate cancer development through the different stages of precursor lesions, incorporating the influence of endocrine, respiratory, gastro-intestinal and circulatory system on this process.

The GN model contains 8 transitions, 26 places and 12 types of tokens.

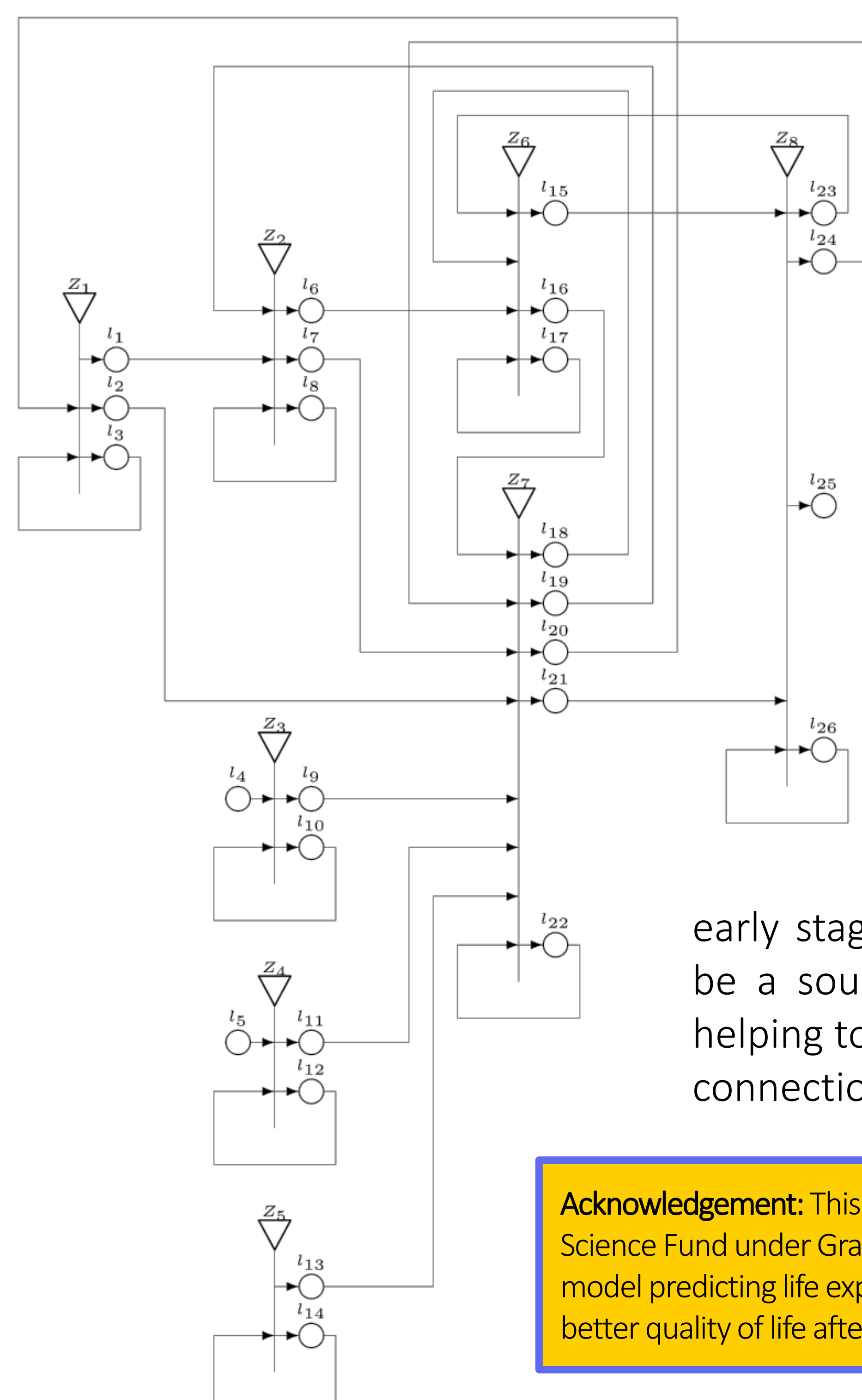
$$Z_1 = \langle \{l_3, l_{20}\}, \{l_1, l_2, l_3\}, \begin{array}{c|ccc} l_3 & l_1 & l_2 & l_3 \\ \hline W_{3,1} & true & true & true \\ l_{20} & false & false & true \end{array} \rangle$$

$$Z_2 = \langle \{l_1, l_8, l_{19}\}, \{l_6, l_7, l_8\}, \begin{array}{c|ccc} l_1 & l_6 & l_7 & l_8 \\ \hline W_{8,6} & false & false & true \\ l_{19} & false & false & true \end{array} \rangle$$

$$Z_3 = \langle \{l_4, l_{10}\}, \{l_9, l_{10}\}, \begin{array}{c|cc} l_4 & l_{10} \\ \hline l_{10} & false & true \\ & true & true \end{array} \rangle$$

$$Z_4 = \langle \{l_5, l_{12}\}, \{l_{11}, l_{12}\}, \begin{array}{c|cc} l_5 & l_{12} \\ \hline l_{12} & false & true \\ & true & true \end{array} \rangle$$

$$Z_5 = \langle \{l_{14}\}, \{l_{13}, l_{14}\}, \begin{array}{c|cc} l_{13} & l_{14} \\ \hline l_{14} & true & true \end{array} \rangle$$



$$Z_6 = \langle \{l_6, l_{17}, l_{20}\}, \{l_{15}, l_{16}, l_{17}\}, \begin{array}{c|ccc} l_6 & l_{15} & l_{16} & l_{17} \\ \hline W_{17,15} & false & false & true \\ l_{20} & false & false & true \end{array} \rangle$$

$$Z_7 = \langle \{l_2, l_7, l_9, l_{11}, l_{13}, l_{16}, l_{20}, l_{22}, l_{24}\}, \{l_{18}, l_{19}, l_{20}, l_{21}, l_{22}\},$$

$$\begin{array}{c|ccccc} & l_{18} & l_{19} & l_{20} & l_{21} & l_{22} \\ \hline l_2 & false & false & false & false & true \\ l_7 & false & false & false & false & true \\ l_{11} & false & false & false & false & true \\ l_{13} & false & false & false & false & true \\ l_{16} & false & false & false & false & true \\ l_{20} & false & false & false & false & true \\ l_{22} & W_{22,18} & W_{22,19} & W_{22,20} & W_{22,21} & true \\ l_{24} & false & false & false & false & true \end{array} \rangle$$

$$Z_8 = \langle \{l_{15}, l_{21}, l_{24}\}, \{l_{23}, l_{24}\}, \begin{array}{c|cc} l_{15} & l_{24} \\ \hline l_{21} & false & true \\ l_{24} & true & true \end{array} \rangle$$

This GN model represents a broad frame in which different genetic events and the influence of the surroundings as well as regulatory systems in the human body can define their interactions in early stages of prostate cancer development. This model should be a sound basis for gaining additional insight on the subject, helping to elucidate multiple and complex connections and correlations.

Acknowledgement: This research is supported by the Bulgarian National Science Fund under Grant Ref. No. KP-06-N43/7 “Creating a prognostic model predicting life expectancy in prostate cancer patients and providing better quality of life after definitive surgical treatment”.

