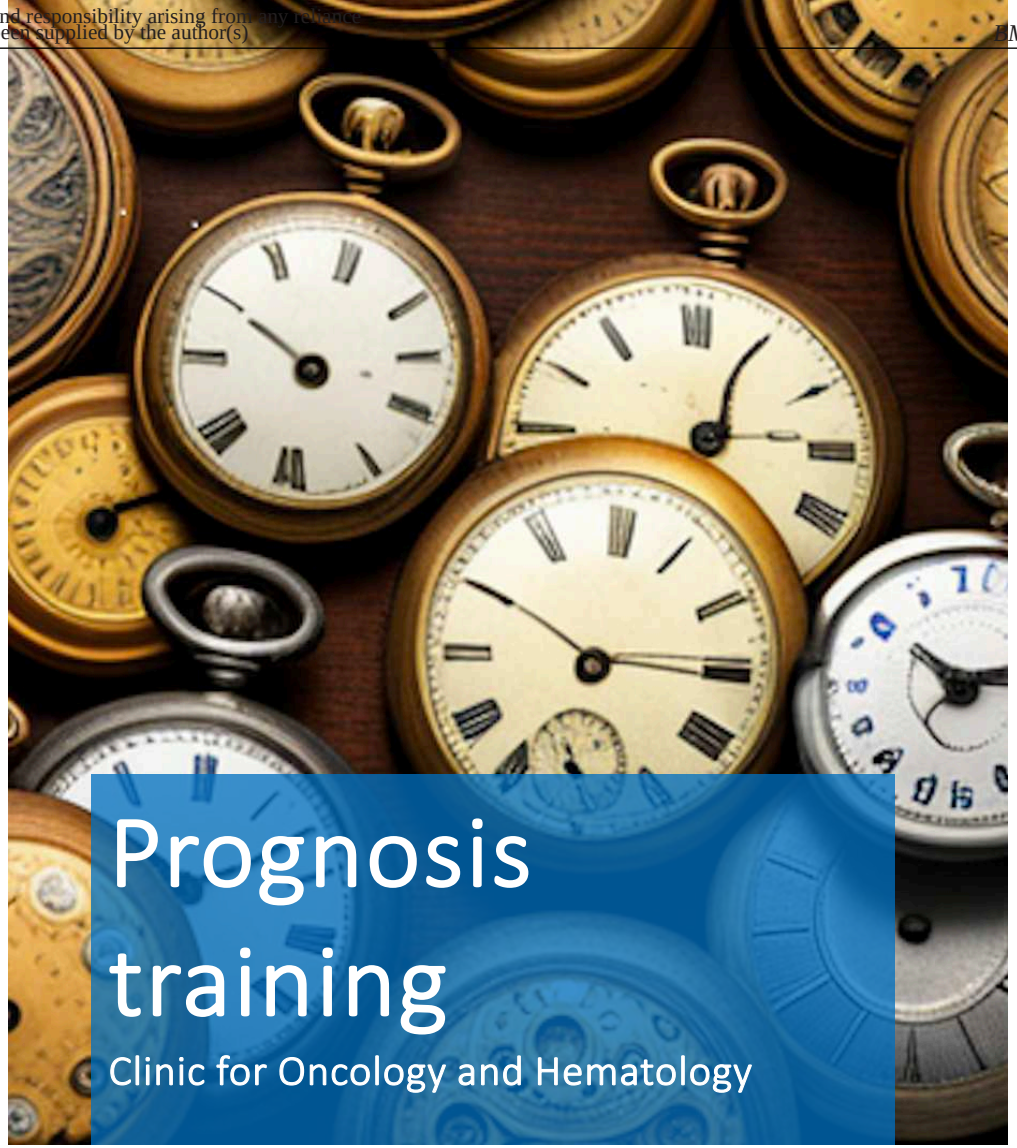
Supplementary file 2: Prognosis training brochure and training programme

The following are impressions of the brochure including the cover page, the final page with the "anchor numbers", survival (“actuarial”) tables, 2 examples of diseases, and a written explanation of how to use this information from the brochure within a focused prognosis training for clinicians.

”Anchor Numbers“ in months

1.1. Lung cancer - SCLC	10
1.2. Lung cancer - NSCLC	11
2. Glioblastoma	9
3. Urinary bladder carcinoma - local / IV	42 / 11
4. Colon carcinoma - all / IV	78 / 13
5. Acute myeloid leukemia	15
6.1. CLL – Binet C	30
6.2. Diffuse large B lymphoma	120
6.3. Follicular lymphoma	180
6.4. Mantle cell lymphoma	66
7. Gastric carcinoma - III / IV	18 / 7
8. Breast cancer – IV	30
9. Myelodysplastic syndromes	34
10. Renal cell carcinoma IV	9
11. Esophageal carcinoma	12
12. Ovarian carcinoma - all / Figo IV	37 / 15
13. Pancreatic carcinoma - all / after R0	8 / 15
14. Plasmocytoma	46
15. Prostate carcinoma – all / IV	168 / 30
16. Rectal cancer - all / IV	80 / 18
17. Soft tissue sarcoma - local / IV	24 / 12



BARMHERZIGE BRÜDER
Krankenhaus Regensburg

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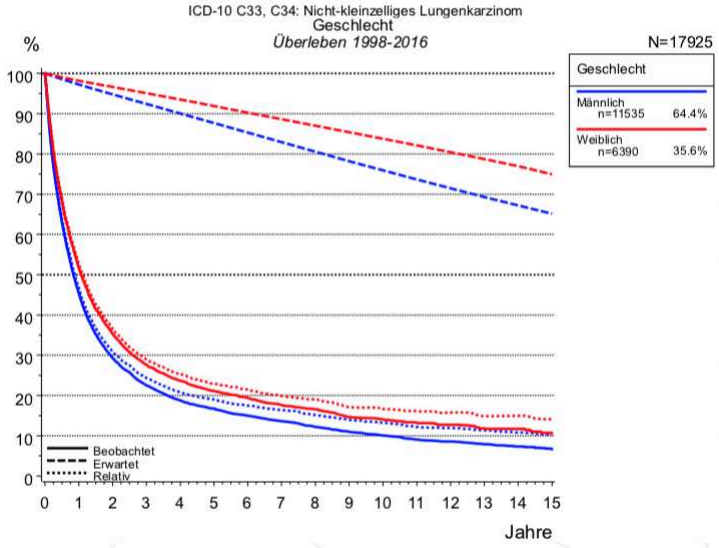
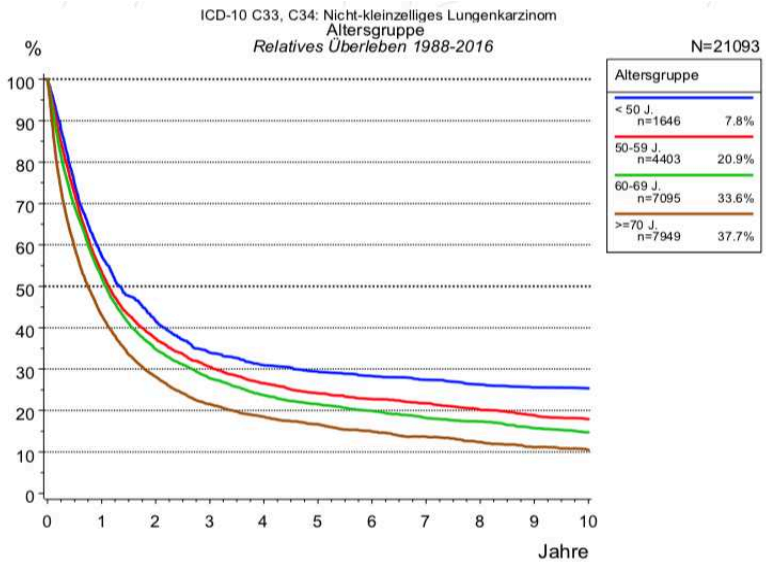
Average life expectancy in Germany in years by age

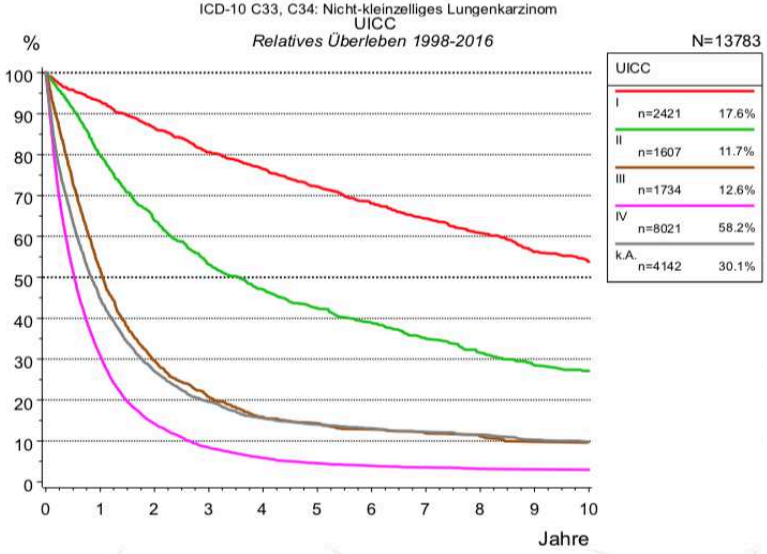
AGE	LIFE EXPECTANCY MEN	LIFE EXPECTANCY WOMEN
50 years	29.65	34.04
51 years	28.77	33.11
52 years	27.9	32.19
53 years	27.03	31.28
54 years	26.18	30.37
55 years	25.34	29.46
56 years	24.51	28.57
57 years	23.69	27.67
58 years	22.87	26.78
59 years	22.07	25.9
60 years	21.28	25.03
61 years	20.5	24.15
62 years	19.72	23.29
63 years	18.96	22.43
64 years	18.21	21.58
65 years	17.46	20.74
66 years	16.73	19.9
67 years	16	19.07
68 years	15.28	18.25
69 years	14.57	17.42
70 years	13.87	16.61
71 years	13.18	15.8
72 years	12.5	14.99
73 years	11.83	14.2
74 years	11.18	13.43
75 years	10.54	12.67
76 years	9.92	11.92
77 years	9.33	11.2

1. Lung cancer:
1.2. <u>Non-small</u> lung cancer

Median survival across all groups:	women: 12 months men: 10 months
Median survival in stage IV:	7 months
Relevant subgroups	
- EGFR mutation	31 months
- ALK mutation	>36 months
- MET alterations	24 months
- BRAF-V600 mutations	24 months
- with good response to immunotherapy	30 months



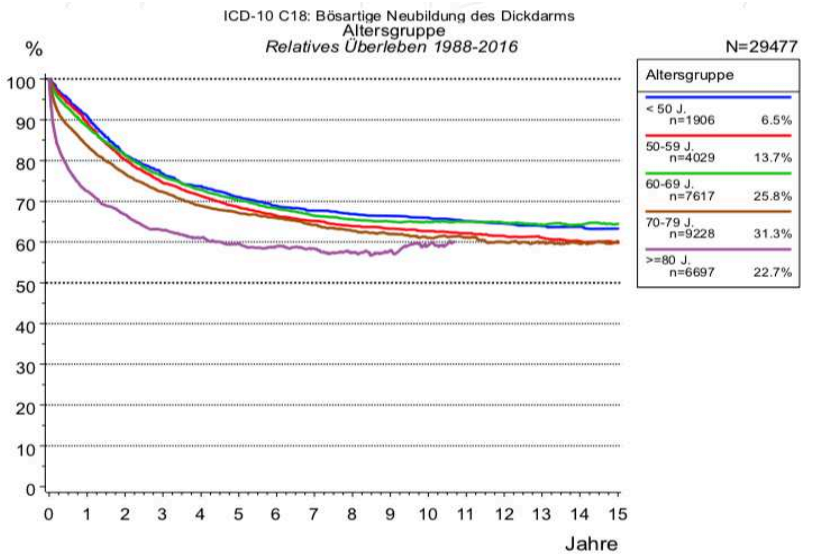


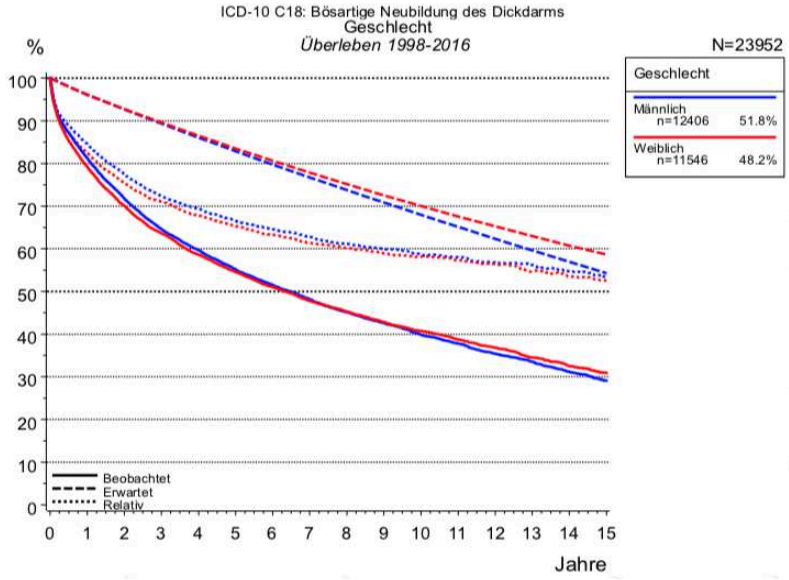


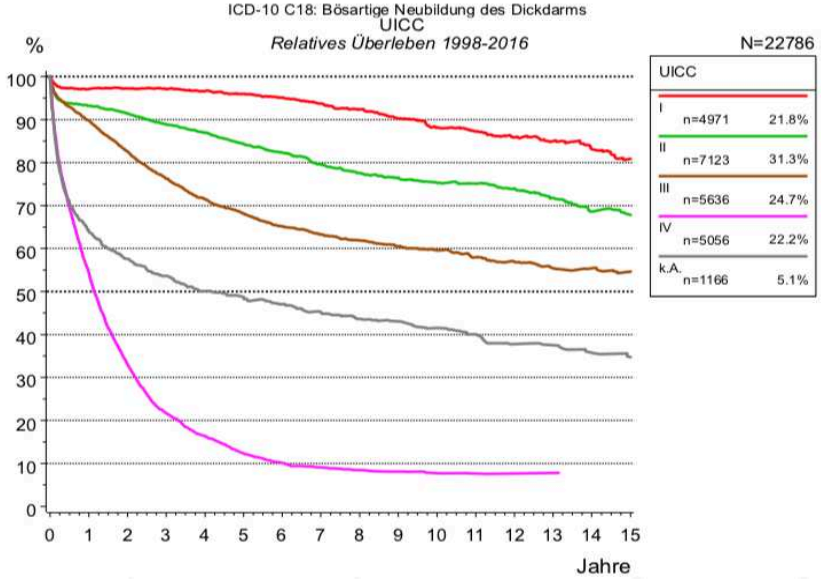
sources: Tumorregister München 2019, UptoDate 2019, Onkopedia 2019, Kris et al. 2014, other

4. Colon carcinoma

Median survival across all groups:	6.5 years
Curation also possible in stage IV, if R0 resection	
Median survival in stage IV:	13 months
Median survival if fit for all lines of therapy:	30 months
Relevant subgroups	
- BRAF mutation	12 months







sources: Tumorregister München 2019, other

The 21 most frequent oncological and malignant hematological diseases were described in the brochure in the way demonstrated above for lung cancer and colon cancer. The whole brochure is copyrighted and can be obtained from the authors.

Prognosis Training

The prognosis training consisted of two components – 1.) epidemiological data of the 21 most frequent malignant diseases of the department and life tables of the general (German) population, which were provided in a brochure and 2.) a general concept how to approach clinical prognostication.

The general concept was to first establish an "outside view" onto the patient by abstracting as much as possible. In order to clarify this process of abstraction the following six topics were discussed with the participating physicians – leading from "extreme abstraction" (1.) to the situation realistically encountered in the clinic (2.-6.):

1. If you only know age (e.g. 78 years) and sex (e.g. male) of your patient (but nothing else) then look into the life tables provided in the brochure and find an average overall survival of 8.7 years for this constellation.

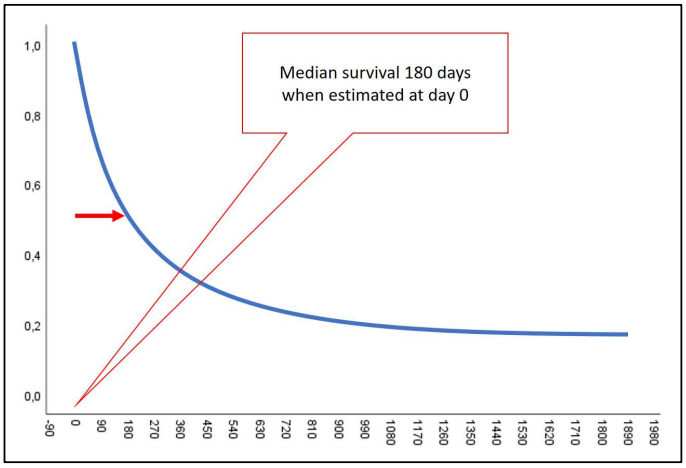
2. If you also know the malignant disease (e.g. gastric cancer) of the patient and preferably the stage of the disease (e.g. stage III) use the epidemiological data provided in the brochure and find an average survival 18 months after diagnosis.

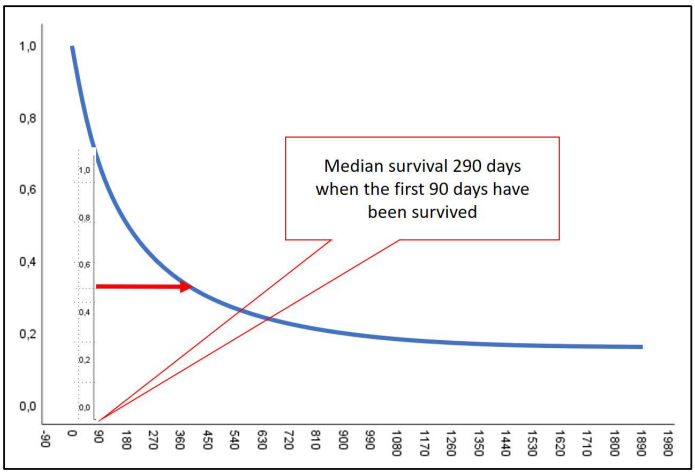
3. Find these data on the backside of the brochure for rapid access ("anchor" data). Consult the respective chapter within the brochure for more detailed prognostic information.

4. Use this approach to have an "anchor" number for your prognostic estimate that has an epidemiological foundation.

5. If the malignant condition is generally lethal and treatment has no curative potential the Kaplan Meier curves show no plateau. The "anchor" number that you obtained above gives the expected survival <u>after diagnosis</u>. Therefore if your patient has already lived with the oncological condition for several months and has received one or more lines of palliative systemic therapy subtract the months lived from the first estimate.

6. If the malignant condition is potentially curable the Kaplan Meier curves will have a plateau. If your patient is being treated with curative intent and has so far not failed therapy then visually construct a new Kaplan Meier curve for the patient´s present time point in his course of the disease (see below). Use the new Kaplan Meier curve to obtain a new (and "better") conditional survival.





This "actuarial" or "outside view" onto the patient is – of course – completely impersonal (except for malignant disease type and stage). Most of the time substantially more information is available for an individual patient (time since diagnosis, genetic risk groups, number of prior therapies, response to therapy, general condition, comorbidities, social

support etc.). This additional information needs to be integrated into the prognostic estimate by adjusting the "outside view" upward and downward.

The multitude of perspectives onto the prognosis of a given patient can be likened to the view of the multifaceted eye of a dragonfly. Different aspects (= views) onto a prognostic constellation need to be integrated into "one" prognostic estimate. Quite clearly, these adjustments are made with a high degree of uncertainty. E.g. "no family support" is a bad thing and – qualitatively - will most likely be detrimental for prognosis – but – quantitatively - how much so? The same is true for virtually all other components that might have prognostic impact, in which hardly ever the "exact" prognostic contribution in this very situation is known.

We take as granted that there is no option "not to prognosticate" – a clinician is faced with the never-ending task of clinical decision making that always takes place in the "foreground" with a "background" of a prognosis estimate – that has been made by the clinician - either consciously or unconsciously, deliberately or intuitively. To illustrate this: The same clinical symptom (severe respiratory insufficiency) may lead to very different courses of action (e.g. transfer to the ICU versus best supportive care measures) depending on the estimate of the patient´s prognosis by the treating physician.

Therefore – if the exact contribution of a potential prognostic component is not (quantitatively) known – should it be used at all – or better be ignored? Let us consider the alternative: If we do not use these "unquantified" prognostic components then an all-encompassing "holistic guess" would be the alternative. However, in other settings – different from medicine – a process called "Fermization" – has been shown to provide better results than an "uneducated guess".

"A Fermi problem or Fermi question is a quantitative estimation for a problem where initially there is practically no or insufficient data available. It is named after the nuclear physicist Enrico Fermi, who was known for being able to provide good estimates spontaneously despite limited information. For example, during the first atomic bomb test (Trinity Test), he threw paper scraps into the air and observed how far they were blown away by the shockwave, which allowed him to estimate the approximate explosive power of the bomb on the spot, long before sensor measurements were evaluated. The challenge with such problems is that there are no direct empirical values from a similar problem or the necessary data available for

direct calculation. However, one has a good understanding of the relationships in the problem's environment and can use them to indirectly arrive at a solution.

The prerequisite for solving a Fermi problem is, therefore, a certain general knowledge and "common sense." Since this prior knowledge cannot be directly used for the solution, one must quantify this prior knowledge and justify the respective assumptions. The overall result is then determined from these partial estimates, often in several stages. The lack of empirical values for the entire problem is compensated by the availability of empirical values for the partial problems, and the absence of data for calculation is compensated by these estimates for the partial problems. The overall result is often surprisingly accurate (at least in the correct order of magnitude). As the partial problems are well known (or could be further broken down), their estimates are quite good and hover around the actual values. Furthermore, no systematic errors occur throughout; instead, estimation errors likely cancel each other out – if one quantity was overestimated, another might have been underestimated." (quote (translated) from "Fermi Problem" - *https://de.wikipedia.org/wiki/Fermi-Problem*)

In the medical context of our study we used the Fermization concept by avoiding to adjust the "outward view" with a single all-encompassing holistic step that integrates everything we seem to know about our patient. Instead we advised the participating physicians to consider the components that are most likely relevant for the prognosis of the patient. Some examples that physicians were advised to consider during prognostication are listed in table 1 below.

Table 1: Clinical Information to consider during prognostication

Clinical Information	Prognostic Estimate
unfavorable genetics	adjust downwards
severe comorbidities	adjust downwards
cachectic	adjust downwards
"failed" prior therapies	adjust downwards
insufficient family support	adjust downwards
severe language barrier	adjust downwards
long travel to provider	adjust downwards
lack of insurance	adjust downwards
….	adjust downwards
favorable genetics	adjust upwards
"good" health	adjust upwards
prior "exceptional" responses to therapy	adjust upwards
prior long remissions	adjust upwards
unusual long survival since diagnosis	adjust upwards
good family support	adjust upwards
short travel to provider	adjust upwards
…..	adjust upwards