Patient Reported Outcome Measures Are of Profound Importance for the Success of Health Technology Assessments in Oncologic Indications in Germany.

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Objectives

Patient reported outcome measures (PROM) are most suitable to demonstrate an added benefit in patient-relevant dimensions such as morbidity, quality of life and safety. The German Institute for Medical Documentation and Information (DIMDI) claims that "PROM is used as an umbrella term for different concepts aiming at the measurement of subjectively perceived [...] treatment effects. Their common characteristic is that the appraisal of the health status is reported by the patient himself."

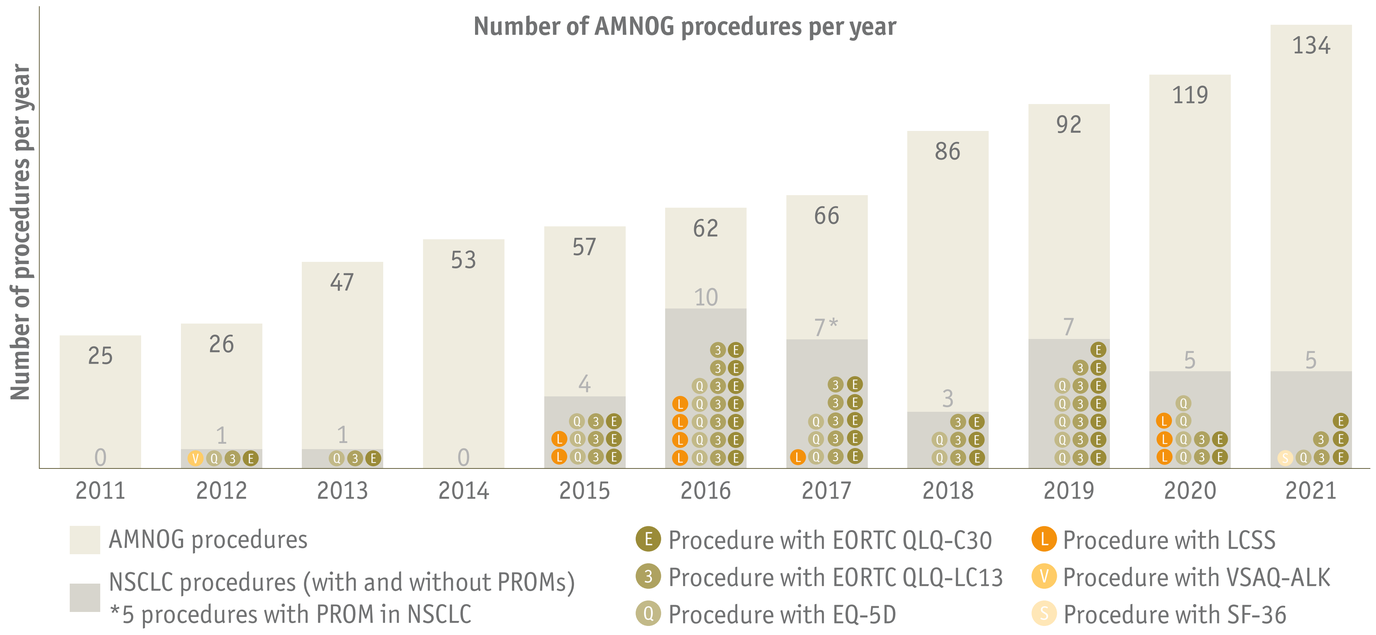
We aimed to investigate the role of PROM in the German AMNOG assessment with a focus on oncologic indications. In which way are PROM evaluated and how do they affect the G-BA's added benefit decision?

Methods

We have screened the relevant documents of the German authorities for specifications regarding PROM. Subsequently, we performed a database analysis to validate the requirements found. The analysis encompassed all conducted benefit assessments in Germany up to 06/2022. Thus, we have evaluated the number of PROM used for each procedure starting until December 2021 and their corresponding consideration by the G-BA. For deeper analyses, we focused on investigating on Non-Small-Cell Lung Carcinoma (NSCLC), which was the most evaluated indication in oncology.

Results

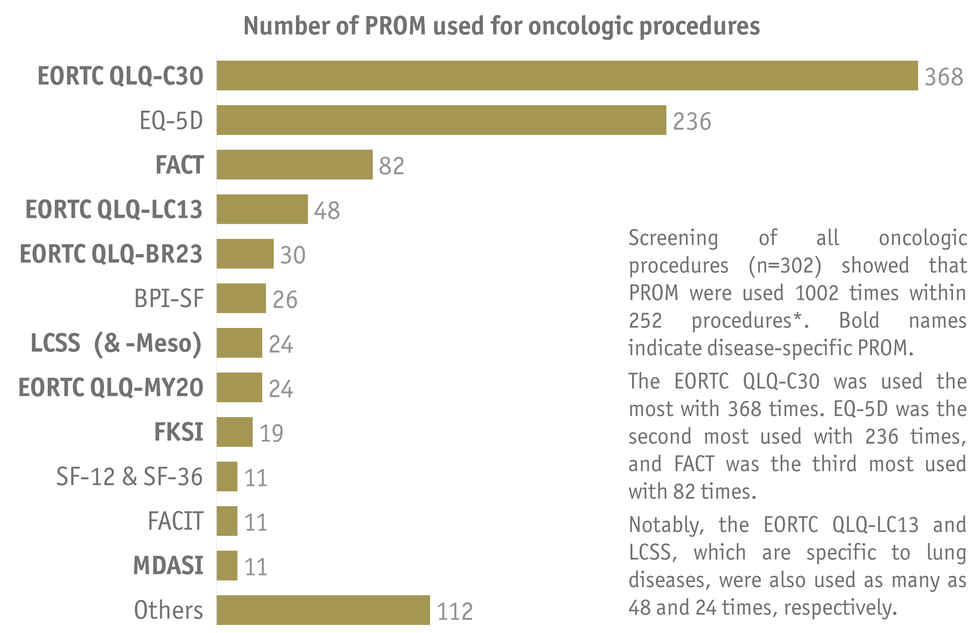
The proportion of PROM utilized in AMNOG procedures for NSCLC indicates their importance



A total of 43 procedures in the indication NSCLC have been assessed in the AMNOG, of which 41 (95%) included at least one PROM. A total of 259 procedures in oncologic indications other than NSCLC have been assessed in the AMNOG, 211 (81%) of them included at least one PROM.

Thus, most of the oncologic procedures used PROM to provide patient-relevant data to support the added benefit claim of the medicinal product.

Disease-specific PROM were most often used, aiming for cancer in general but also specific oncologic entities



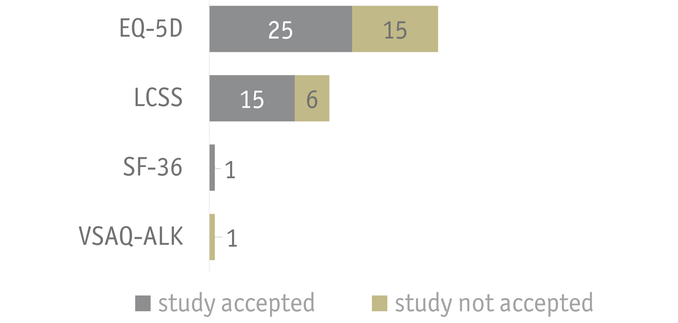
Screening of all oncologic procedures (n=302) showed that PROM were used 1002 times within 252 procedures*. Bold names indicate disease-specific PROM.

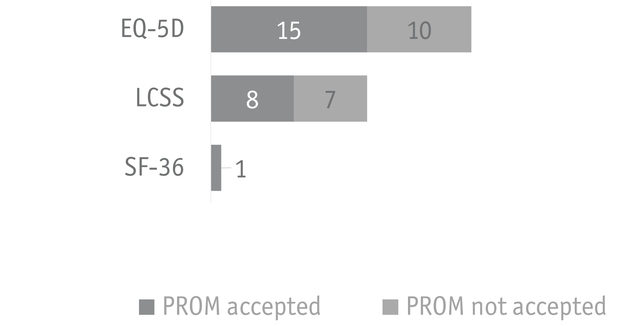
The EORTC QLQ-C30 was used the most with 368 times. EQ-5D was the second most used with 236 times, and FACT was the third most used with 82 times.

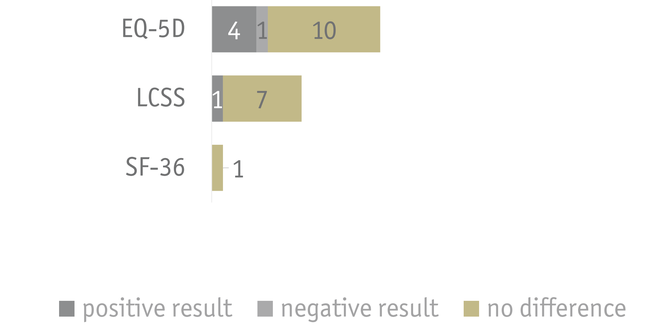
Notably, the EORTC QLQ-LC13 and LCSS, which are specific to lung diseases, were also used as many as 48 and 24 times, respectively.

EQ-5D includes EQ-5D, EQ-5D VAS, EQ-5D-5L, EQ-5D-3L ;
FACT includes FACT-An, FACT-B, FACT-B (TOI-PFB), FACT-BP, FACT-BRM, FACT-C, FACT-Cog, FACT-G, FACT-Leu, FACT-Lym, FACT-M, FACT-O, FACT-P, FACT/GOG-Ntx;
FKSI includes FKSI-19, FKSI-DRS; FACIT includes FACIT-D, FACIT-Dys-SF, FACIT-F;
MDASI also includes MDASI-MM, MDASI-THY;
*a procedure can include a PROM more than once in each study; endpoints were assessed separately.

If NSCLC-studies were accepted by the G-BA in AMNOG procedures, PROM were likely also accepted and underlined a positive effect of the investigated therapeutic in approximately 50% of the cases







Reasons for rejection of studies by the G-BA were that

- the appropriate comparative therapy was not used
- the single-arm study was not appropriate

Reasons why PROM were not accepted by the G-BA were that

- return rates were too low (< 70%)
- the EQ-5D utility index is not accepted in general
- subgroup analyses were missing
- the LCSS is not suitable for measuring HR-QoL in general

The EORTC QLQ-C30 was considered both for the domain morbidity and HR-QoL and gave positive outcomes in 50% of the cases.

Conclusion

- The G-BA and the IQWiG consider the four patient-relevant dimensions of benefit mortality, morbidity (symptoms and complications), (health-related) quality of life and safety in the benefit assessment. To assess the effect of a therapeutic intervention, the German HTA bodies prefer PROM, but there is no privilege or special status for PROM in comparison to other outcome measures during the AMNOG process.
- Most studies in oncologic indications, such as the most prominent NSCLC, use PROM to provide evidence for an added benefit. If the clinical trial is accepted by the G-BA, it is likely that the PROM utilized in the respective trial is also accepted by the G-BA. If accepted, the PROM can have significant impact on the G-BA decision regarding the added benefit, for example outweighing the overall survival:
  - Negative example: dacomitinib (Vizimpro®) as a first-line treatment for NSCLC with activating EGFR mutations → The overall survival showed a statistically significant advantage (HR=0,76; 95%-CI=[0.58; 0.99]; p=0.044). However, PROM in the EORTC QLQ-C30, EQ-5D VAS data showed significant disadvantages leading to no added benefit in the resolution.
  - Positive example: brigatinib (Alunbrig®) for the treatment of ALK-positive advanced NSCLC → for patients without brain metastases, there was no statistically significant difference between the study arms (HR=1.41; 95%-CI=[0.77; 2.60]; p=0.272). But since there were statistically significant advantages in symptom scales of the EORTC QLQ-C30 and the EORTC QLQ-LC13, the G-BA acknowledged a minor added benefit in this patient sub-population.

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All analyses have been conducted with our own comprehensive MAIS database that contains and links AMNOG information of all completed and ongoing benefit assessment procedures according to §35a SGB V of the German Federal Joint Committee (G-BA).