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Challenges and chances of the new EU-Regulation on Health Technology Assessment

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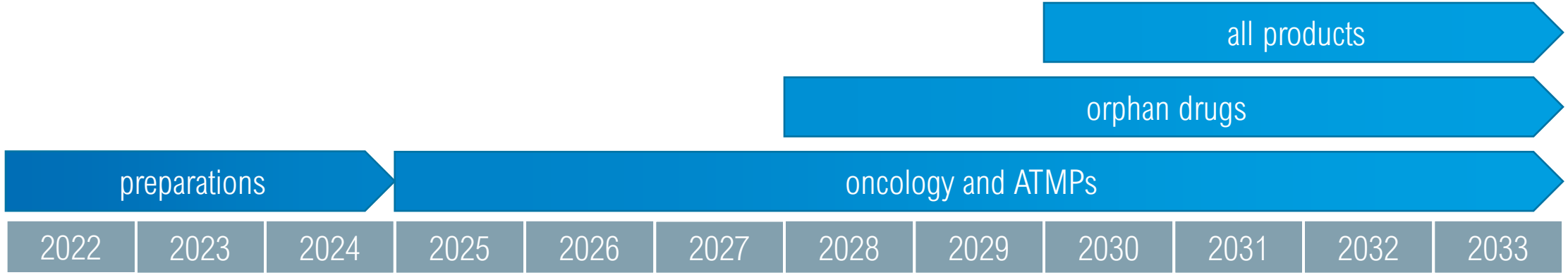
Regulation (EU) 2021/2282

- → Aim: Health technology assessments (HTA) on the level of the European Union instead of national level
  - → "The assessment scope for joint clinical assessments [JCAs] should be inclusive and should reflect all Member States' needs in terms of data and analyses to be submitted by the health technology developer [HTD]"[1]
  - → "any information, data, analyses and other evidence required for the JCA should be submitted only once …" [1]
- → Facilitate market access for patients in the EU
- → Guarantee fair prices



[1] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU

Oncologics and orphan drugs – overview AMNOG 2011-2020

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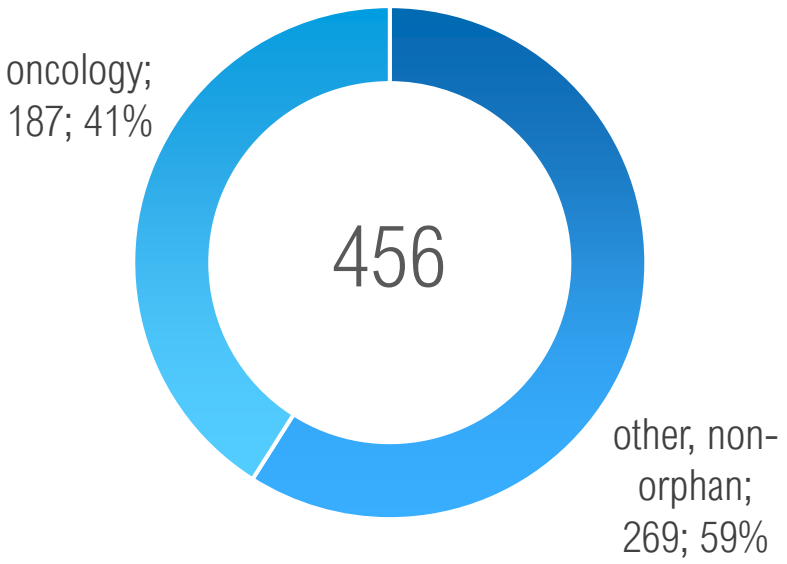
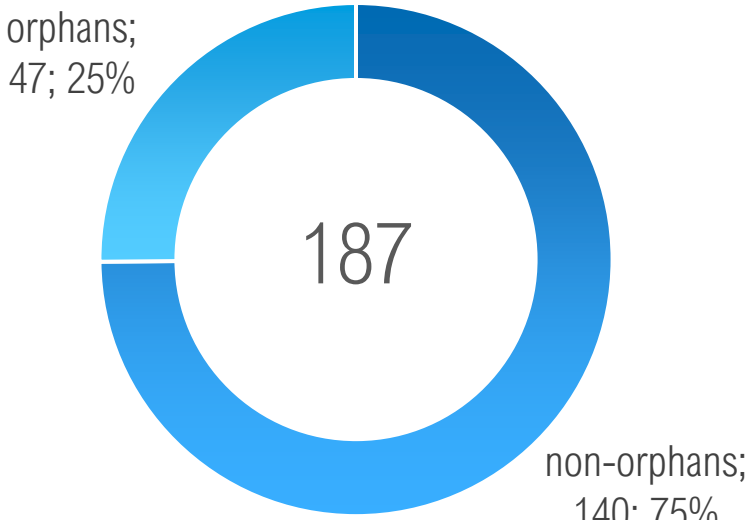
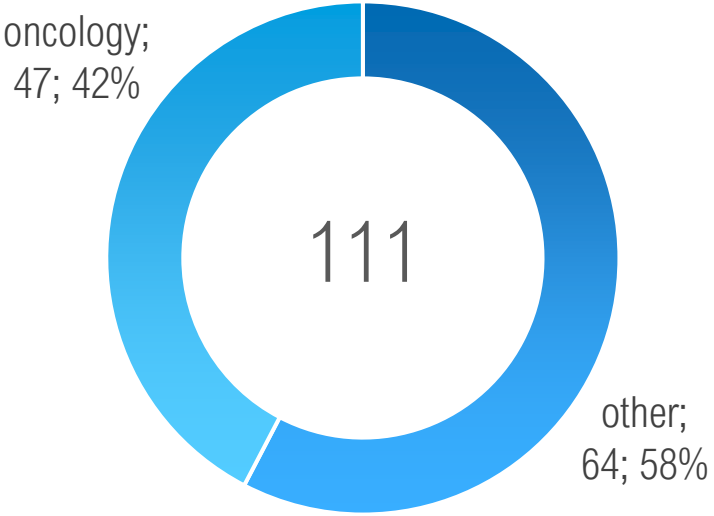
Completed assessments



Oncology



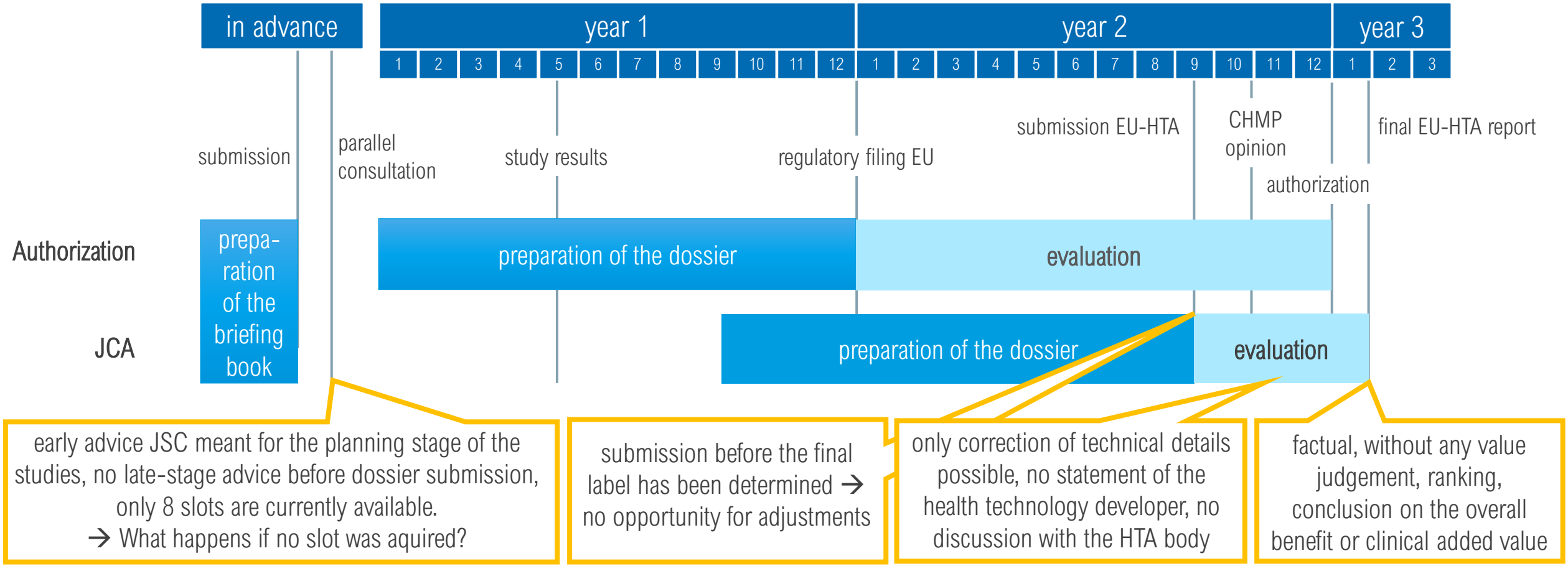
Orphan drugs



41 % of the products will be assessed in JCAs starting in 2025.
Even if orphan drugs are first scheduled for 2028, approx. 40 % are used in oncology.

own illustration according to Bundesverband pharmazeutischer Industrie – AMNOG Daten 2021

Joint Clinical Assessments - procedure



own illustration according to Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU

PICOS scheme – Population & intervention

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Population

Intervention

- Population, indication, dosage, titration are defined in the label
- The JCA dossier is submitted prior to the positive opinion / marketing authorization

→ *What happens if there is a change of label and adjustment of the dossier will not be possible?*

Comparator

Outcome

Study

PICOS scheme - Comparators

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Population

Intervention

Comparator

Outcome

Study

Choice of comparator should be strictly defined:

- Standard of care[1]
- Based on available clinical evidence[1]
- Marketing authorization for the respective indication and line of treatment[1]
- *Exclusion of off-label products*

What happens if no uniform comparator across the Member States exists?

- Differences in standard of care or legislation (e. g. most economic option, ATC class)[1]
- Large multi-comparator study may be necessary to meet all requirements of the member states[1]
- *Best case scenario: choose 1 out of many*

Indirect comparisons need to be feasible and realistic

[1] EUnetHTA Guideline Comparators & Comparisons. Adapted version 2015.

PICOS scheme - Outcomes

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Population

Intervention

Comparator

Outcome

Study

Commonly accepted endpoints in oncology:

- Mortality[1] (overall survival)
- Morbidity[1] (symptoms, pain, fatigue, etc.; time to worsening of symptoms, responder analyses)
- Health-related quality of life[1,2]
- Safety[3]

Surrogate endpoints should be validated:

- Biomarkers[4]
- Intermediate endpoints (e. g. progression-free or disease-free survival)[4]

→ *Acceptance of surrogates according to EMA*

Primary VS secondary endpoints:

- *Which endpoints are considered for the determination of an added benefit?*

[1] EUnetHTA Guideline Endpoints used in Relative Effectiveness Assessment: Clinical Endpoints. Adapted version 2015.
[2] EUnetHTA Guideline Endpoints used in Relative Effectiveness Assessment: Health-related Quality of Life and Utility Measures. Adapted version 2015.
[3] EUnetHTA Guideline Endpoints used in Relative Effectiveness Assessment: Safety. Adapted version 2015.
[4] EUnetHTA Guideline Endpoints used in Relative Effectiveness Assessment: Surrogate Endpoints. Adapted version 2015.

PICOS scheme - Studies

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Population

Intervention

Comparator

Outcome

Study

Trial design:

- Randomized controlled trials (RCTs) as the gold standard[1]
- When are non-randomized trials acceptable (best available evidence)[2],
- Especially for third-line therapy in oncology or orphan drugs
- *Minimal study duration is unclear*

Internal validity:

- Risk of bias

→ ***Studies that have been accepted by the EMA for the authorization should also be accepted for the JCA***

[1] EUnetHTA Guideline Internal validity of randomided controlled trials. Adapted version 2015.
[2] EUnetHTA Guideline Internal validity of non-randomised studies (NRS) on interventions. July 2015.

PICOS scheme – Potential issues

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Population

Intervention

Comparator

Outcome

Study

Potential for disagreements between JCA and national HTAs:

- Impact of the orphan drug status[1]
- Additional subgroup analysis / post hoc analysis on national level[1,2]
- Assignment of different comparators (also influenced by subgroups)[1,2]
- Acceptance of indirect comparisons[1,2]
- Acceptance of surrogate / intermediate endpoints[1,2]
- Risk of bias assessments[2]

[1] Giuliani et al., *Health Economics Review* (2018)
[2] Kisser et al., *The European Journal of Health Economics* (2021)

Further considerations

→ Parallel assessments on EU and national level are still possible

→ Health-economic analysis not included in the JCA

→ Joint Clinical Assessments without benefit rating to be used on national level[1]

→ Determination of the added benefit will remain in the sovereinity of the Member States[1]

→ The Member States will remain responsible for market access and reimbrusement[1]

Benefit assessments as instrument for price negotiations:
Will the unification of the HTA system also lead to a unification of the pricing system on a European level (see European reference price)?

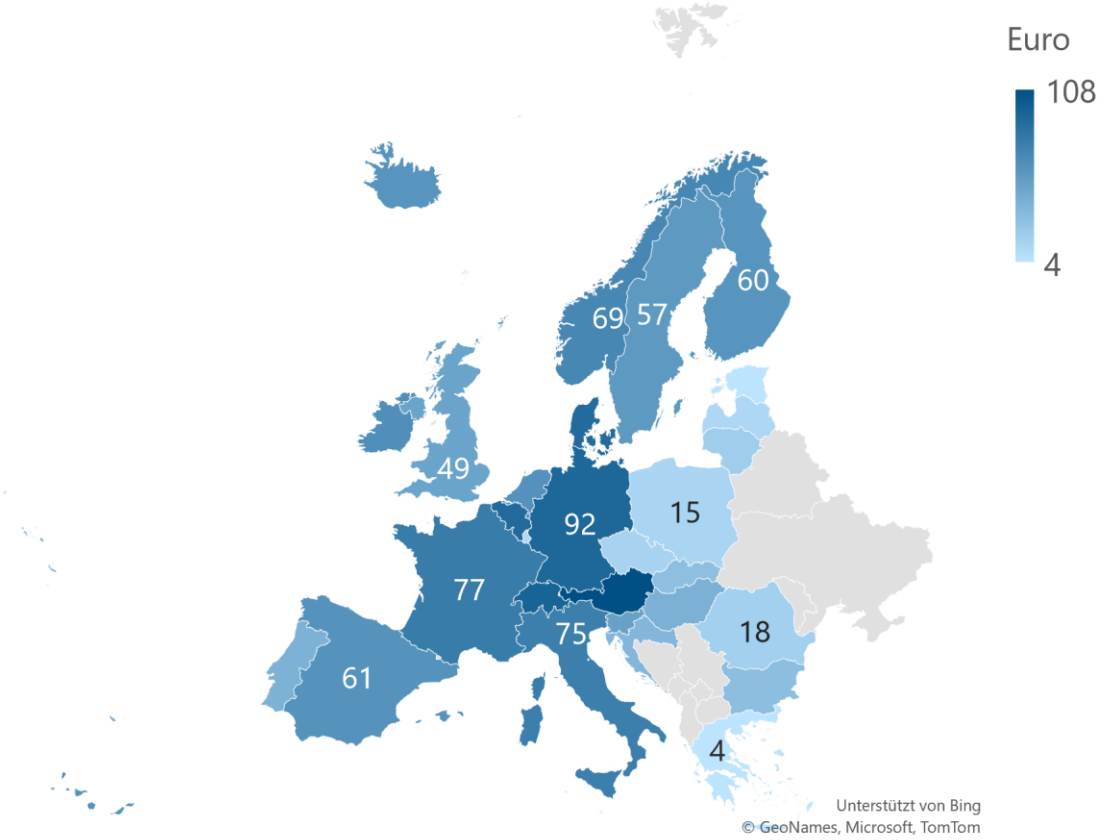
[1] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU

Expenditures for oncology per capita in Europe

→ Prices for drugs used in oncology vary greatly across the European countries

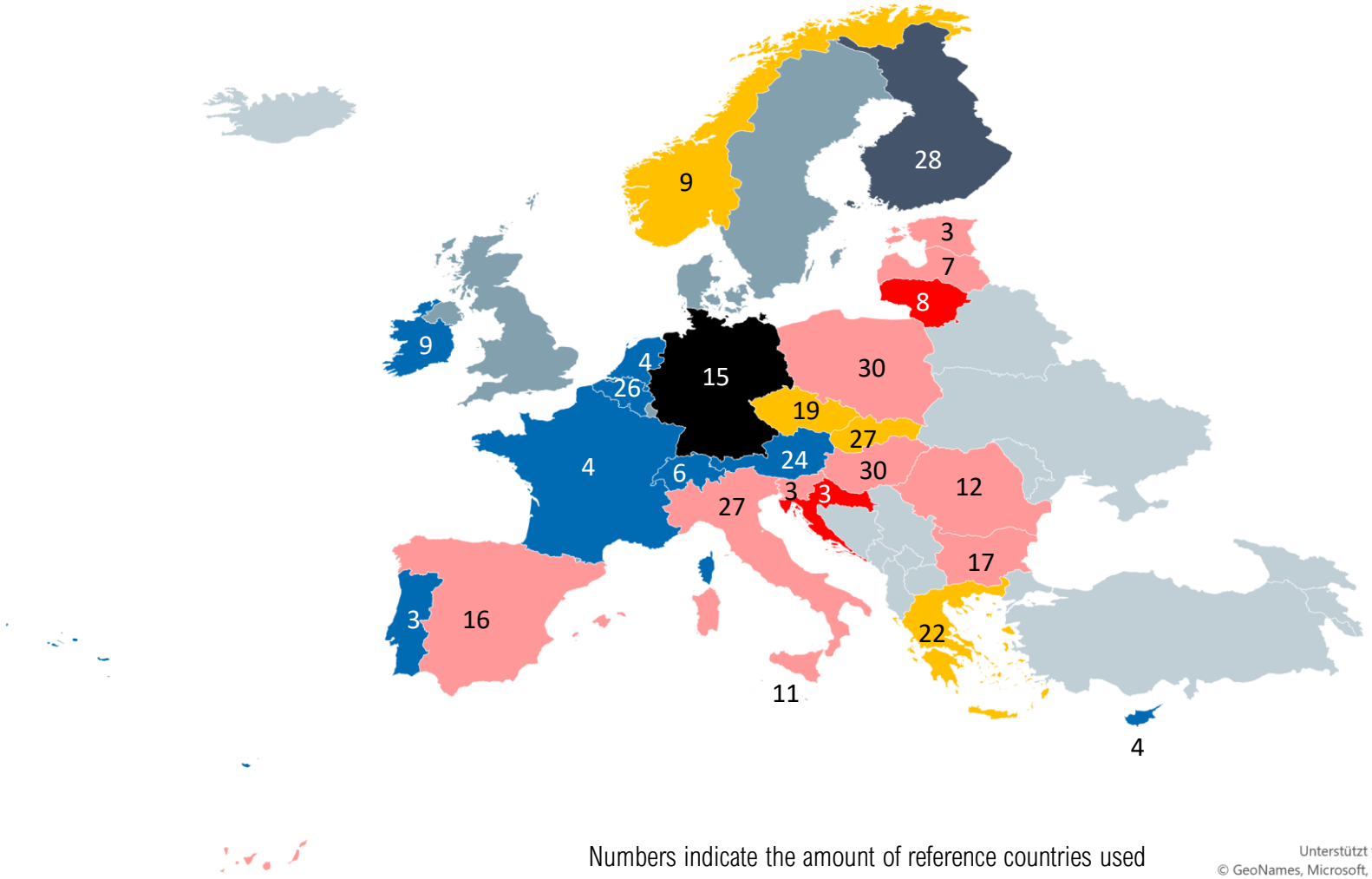
→ From the perspective of the HTD it would be desirable to retain the opportunity for differential pricing

Total cost of cancer drugs per capita (in €) in Europe in 2018



own illustration according to Hofmarcher et al., *European Journal of Cancer 2020*

European Reference Price System compatible with EU HTA?



- Median
- Average
- Average of the lowest 3 prices
- Lowest price
- Below the lowest price
- With purchasing power parity and sales weighted average
- No reference price system
- Not included

Numbers indicate the amount of reference countries used

own illustration

Summary – Challenges and Chances of the EU-HTA

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When setting up a uniform HTA on EU level, special emphasis needs to be put on:

→ Active participation in terms of JSCs and hearings

→ Alignment of national and European HTA

→ Consistent methodology in terms of studies, comparators & endpoints

→ Studies accepted by the EMA for market authorization should also be accepted for HTA

→ Improved harmonization and transparency

→ Accelerated market access based on EU-HTA

→ Pricing and reimbursement should remain in the souvereignty of the member states

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