Cytel

Surrogacy and health economic modeling

Background

- Regulatory agencies approve treatments based on early surrogate outcomes when they believe that a treatment effect on the surrogate is likely to predict a treatment effect on the late outcome.
- Formal proof of surrogacy, however, is often lacking.
- Health technology assessment (HTA) bodies need to assess the value for money based on the surrogate and/or immature data on the late outcome.
- Economic models capture all economic and humanistic consequences and uncertainties of novel therapies over the entire disease course.
- Predicted overall survival (OS) benefit is typically a key driver in HTA decision-making.

Aim

The aim is to discuss survival extrapolation approaches typically used in health economic models considering the surrogacy theory.

Surrogacy conditions

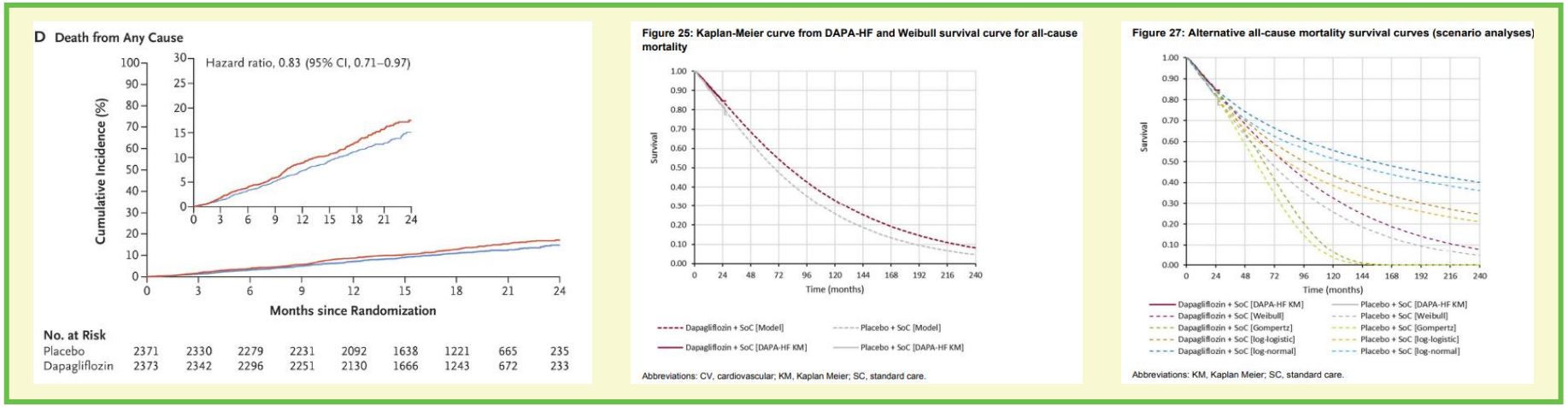
- Clinical/biological plausibility
- Correlation between early and late outcomes
- Association between treatment effects on early and late outcomes

Extrapolation of early or immature late outcomes in economic models

1. Directly extrapolating immature survival data from the trial
2. Risk equations linking early outcomes to late outcomes
3. (Semi-)Markov models linking early outcomes to late outcomes
4. Surrogacy analyses for estimating treatment effects over late outcomes based on treatment effect on early outcomes

1. Directly extrapolating immature survival data from the trial

- Dapagliflozin in heart failure showed significant survival benefit on immature survival data (figure shown below).[1]
- Guidance on survival extrapolations includes:
  - National Institute for Health and Care Excellence (NICE) Technical Support Document (TSD) 14[2] on standard parametric survival extrapolations: some guidance on treatment effect estimation over time
  - NICE TSD 21[3] on flexible parametric survival extrapolation: no guidance on treatment effect estimation over time
- For technology appraisal (TA)679, significant but immature survival benefits were extrapolated using standard distributions[4] assuming a constant lifetime treatment effect.
- Despite guidance, substantial uncertainty exists over extrapolation of immature survival data and its treatment effect.
  - What is survival on standard of care?
  - Given immaturity of data, what is the level of certainty that treatment effect is truly proportional/constant over a lifetime?



1. McMurray JJV et a; DAPA-HF Trial Committees and Investigators . Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995-2008 ; 2. https://www.sheffield.ac.uk/nice-dsu/tsds/survival-analysis; 3. ttps://www.sheffield.ac.uk/nice-dsu/tsds/flexible-methods-survival-analysis; 4. https://www.nice.org.uk/guidance/ta679/documents/committee-papers

2. Risk equations linking early outcomes to late outcomes

- In eight studies on type 2 diabetes, empagliflozin showed benefits in HB1Ac, blood pressure and weight.
- Risk calculators like the UK Prospective Diabetes Study (UKPDS) correlated early and late outcomes.[1]

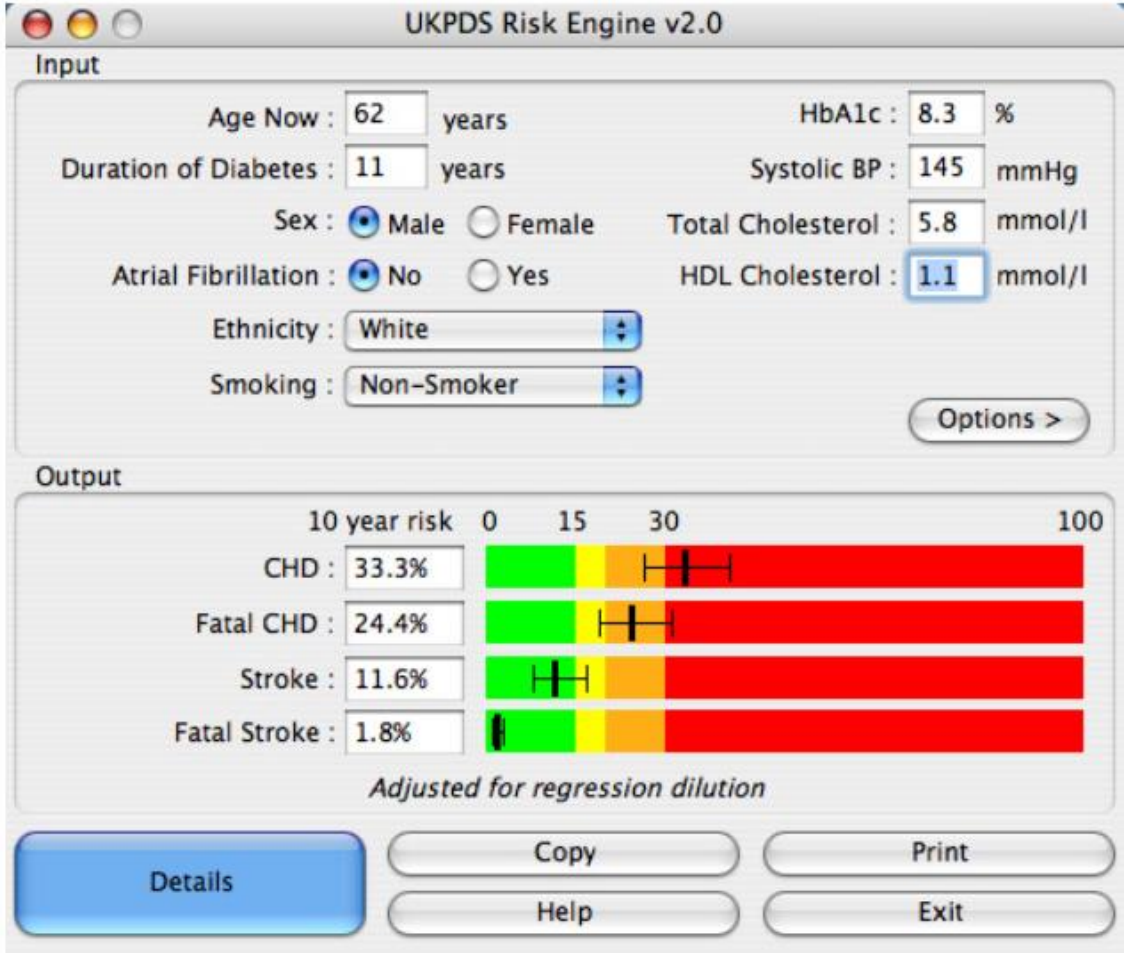
Short-term outcomes

- HbA1c
- Systolic blood pressure
- Cholesterol
- Body mass index

Long-term outcomes

- Coronary heart disease
- Stroke
- Fatal events

- Several NICE HTA submissions in diabetes were informed by economic models using UKPDS risk equations.[2]
- In these submissions, the long-term complications were linked to costs and quality of life to estimate incremental cost-effectiveness ratios.



1. https://www.dtu.ox.ac.uk/ukpds/; 2. https://www.nice.org.uk/guidance/ta336/chapter/3-The-companys-submission#cost-effectiveness

2. Risk equations linking early outcomes to late outcomes (cont.)

Daly 2022 review of economic diabetes models submitted to NICE stated[1]:

- *"HbA1c's accuracy as a predictor of macrovascular complications or mortality is strongly disputed."*
- Risk equations are often dated and do not represent current quality of care.
- *"In the case of gliflozins, follow-up studies are required to determine whether weight losses are sustained or transient, confirming or disproving the different TA committees' preferred assumptions."*

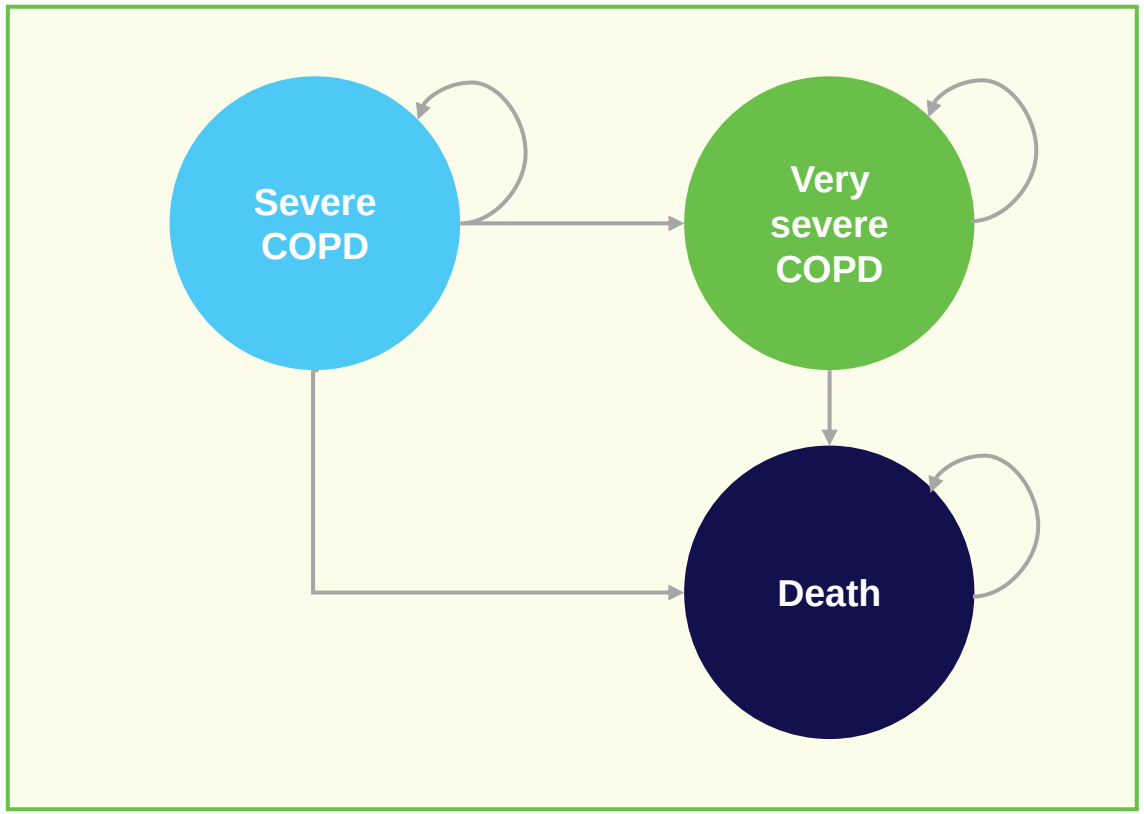
Baechle 2022 concluded[2]:

- *"Based on the results of more than 200 randomized trials, HbA1c is not a valid surrogate marker for all-cause mortality in people with type 2 diabetes."*

1. Daly MJ et al A Review of Economic Models Submitted to NICE's Technology Appraisal Programme, for treatments of T1DM & T2DM. Front Pharmacol. 2022 May 11;13:887298; 2.Baechle C et al Is HbA1c a valid surrogate for mortality in type 2 diabetes? Evidence from a meta-analysis of randomized trials. Acta Diabetol. 2022 Oct;59(10):1257-1263

3. Semi-Markov models linking early outcomes to late outcomes

- The trial of roflumilast in chronic obstructive pulmonary disease (COPD) showed a benefit in reducing moderate-to severe-exacerbations compared to placebo.
- In the economic model submitted to NICE, the rate of mortality due to severe exacerbations—the case fatality rate—was obtained from the 2014 UK National COPD Audit Report.[1]
- Similar to previous examples, survival benefits relied on a correlation with potentially the same caveats.



1. https://www.nice.org.uk/guidance/ta461/documents/committee-papers

Surrogacy analyses

- Several therapies (e.g., ezetimibe, evolocumab, and alirocumab) demonstrated a treatment effect on low-density lipoprotein cholesterol (LDL-C).
- In the corresponding economic models used for the HTA submissions:
  - Risk equations were used to model cardiovascular event risk over time for standard of care.
  - The treatment effect was modelled using surrogacy analyses published by the Cholesterol Treatment Trialists (CTT) Collaboration (shown at right).[2]
- Even with proven surrogacy, there were doubts on whether LDL-C was a true surrogate.[3]

CTT surrogacy analyses

Table 9 CTTC Rate Ratio (95% CI) per 1mmol/L reduction in LDL-c mapped from evolocumab and ezetimibe appraisals

	Rate Ratios in the base case for alirocumab	Rate Ratios mapped from ezetimibe	Rate Ratios mapped from evolocumab
Non-Fatal MI (ACS)	0.74 (0.71, 0.77)	0.74 (0.69, 0.78)	0.71 (0.58, 0.87)
Coronary Revascularisation	0.76 (0.73, 0.78)	0.76 (0.73, 0.80)	0.66 (0.60, 0.73)
Stroke*	0.79 (0.74, 0.85)	0.85 (0.80, 0.90)	0.69 (0.50, 0.95)
Any Vascular Death	0.88 (0.84, 0.91)	0.86 (0.82, 0.90)	0.86 (0.82, 0.90)

* Any stroke from the ezetimibe appraisal and Ischeaemic Stroke from the alirocumab/evolocumab appraisals

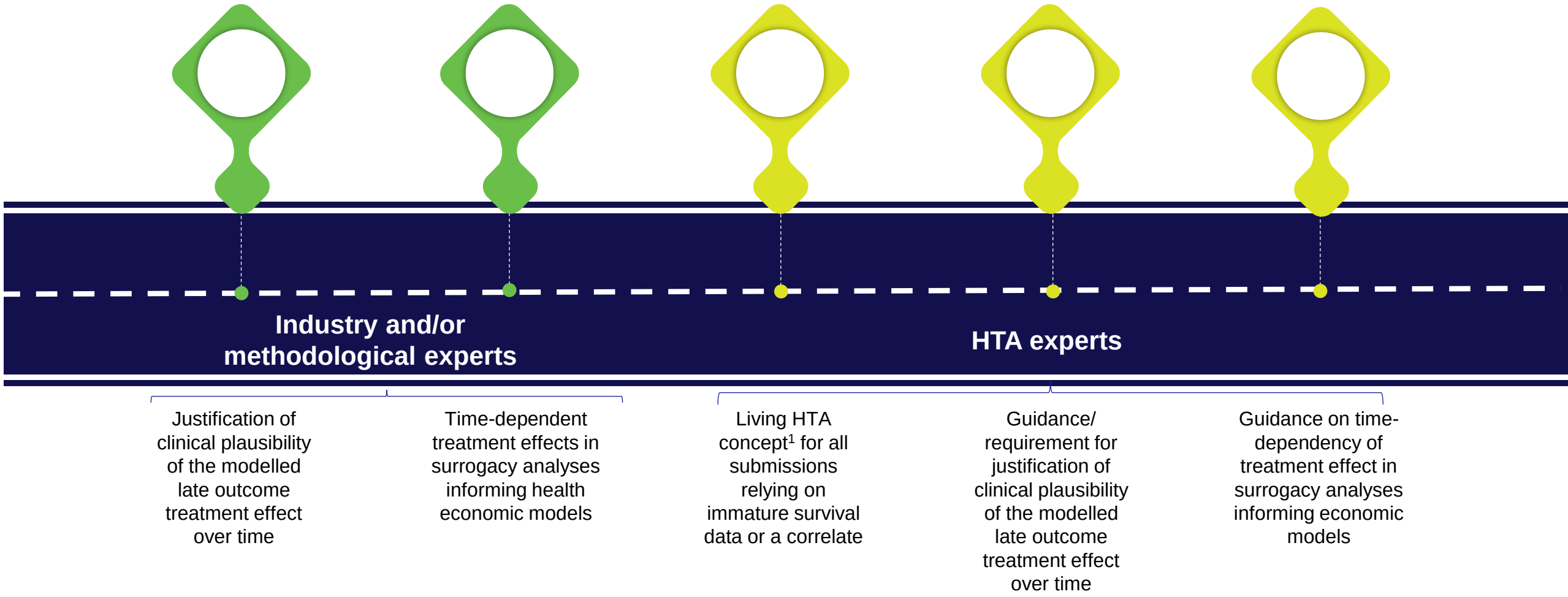
1. https://www.nice.org.uk/guidance/ta393/documents/committee-papers-2; 2. Cholesterol Treatment Trialists' (CTT) Collaboration Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet. 2015 Apr 11;385(9976):1397-405; 3. DuBroff R. Cholesterol paradox: a correlate does not a surrogate make. Evid Based Med. 2017 Mar;22(1):15-19

Conclusions

- It is well established that a correlate is not automatically a surrogate.[1,2]
- Health economic modeling relies on correlations often without formal proof of surrogacy.
- Proof of surrogacy at HTA is often challenging.
    - There is a lack of historical trials reporting short- and long-term outcomes (specialized therapies).
    - Effect modification exists in surrogacy association.
- Predicted treatment effect on OS over time is a crucial driver for decision-making and pricing.
- No specific guidance exists on modeling treatment effects on late outcomes over time if these late endpoints are not (sufficiently) captured in the trial.

1. Fleming, Thomas R. (1996). "Surrogate End Points in Clinical Trials: Are We Being Misled?". Annals of Internal Medicine. 125 (7): 605–613. doi:10.7326/0003-4819-125-7-199610010 00011. PMID 8815760. S2CID 12267404; 2.Prentice, Ross L. (1989). "Surrogate endpoints in clinical trials: Definition and operational criteria". Statistics in Medicine. 8 (4): 431–440.

Future considerations



1. Daly MJ et al A Review of Economic Models Submitted to NICE's Technology Appraisal Programme, for treatments of T1DM & T2DM. Front Pharmacol. 2022 May 11;13:887298