# ISPOR EU 2021 Methods Workshop:

## *Policy and Statistical Issues in HTA Review of Histology-Independent Technologies (HIT) in Oncology*

ISPOR
Improving healthcare decisions

**Jeremy Snider - Senior Quantitative Scientist, Flatiron Health**

**Dr Jacoline Bouvy - Technical Director, NICE Scientific Advice**

**Joshua Ray - Head Global Evidence, Global Access, Roche**

# Workshop Agenda

| Time (minutes) | Speaker | Goal |
|---|---|---|
| **0** | **Jeremy Snider** | • **Introduction of speakers / provide workshop overview** |
| 5 | Dr Jacoline Bouvy | • Provide background for previous HIT decisions<br>• Discuss evidence and analyses that can provide the best insight for future decisions |
| 15 | Joshua Ray | • Highlight implications of the current evidence and policy environment related to histology independent technologies<br>• Propose solutions to address evidentiary concerns with histology independent technologies inhibiting patients access |
| 25 | Jeremy Snider | • How can longitudinal RWD be leveraged in effectiveness analyses for histology independent technologies<br>• Discuss statistical methods that are appropriate for use in an HIT |
| 35 | Jeremy / Josh / Jacoline | • Interactive case study<br>• Discussion of methods and results with speakers |
| 50 | Jeremy / Josh / Jacoline | • Questions from participants<br>• Conclusory remarks |

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# Introduction to Histology-Independent Analyses Using Real-World Data


## Jeremy Snider, PhD MPH

Senior Quantitative Scientist
Flatiron Health
jsnider@flatiron.com


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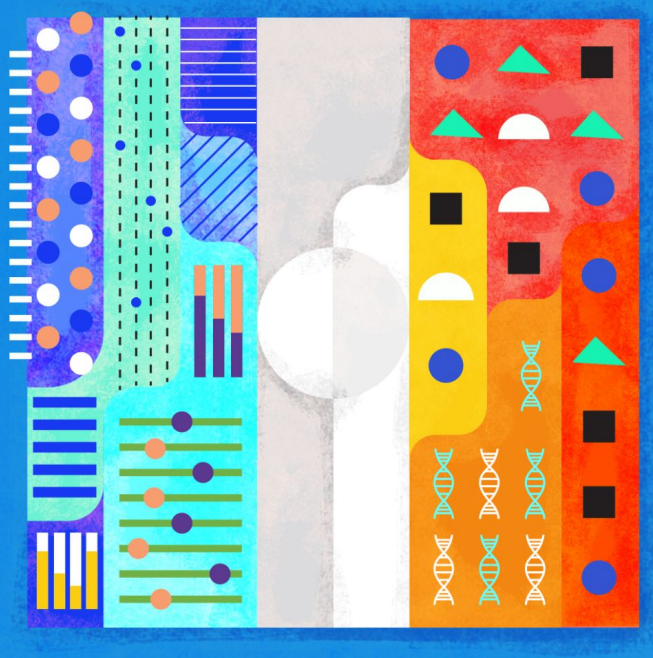
# Glossary of Terms

**Biomarker-defined cohort:** A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease (US NCI Dictionary of Cancer, 2021)

**Histology-Independent** *(aka **Tumor agnostic**)* **technology***:* A technology that targets a known biomarker, regardless of where in the body the tumor originates

**Real world data (RWD)**: Data relating to patient health status and/or the delivery of health care from routinely-collected information (EMA, 2021)



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# Workshop goals

- Describe the **current landscape** of Histology-Independent Technologies (HIT) in precision oncology
- Provide a **Health Technology Authority (HTA) and Pharmaceutical industry perspective** around research questions and evidence gaps in HIT decision-making
- Discuss the **value of longitudinal real-world data (RWD)** for improving decision-making
- Discuss **statistical issues and approaches that are introduced in HIT analyses**

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# Common challenges in biomarker-defined studies

- Drugs targeting biomarkers are of growing importance in oncology research, presenting challenges to researchers:
  - Uncertainty in natural history / standard of care in **newly-defined populations**

  - Biomarker-defined **trial data** tend to be:

    - **Immature:** capture **response** to trial drug, but often not longer-term survival outcomes

    - **Scarce: highly-specific**, (often) **rare** biomarkers where enrollment is not powered to assess longitudinal outcomes

    - **Heterogeneous:** basket trials may included parallel development in adult and pediatric populations, and inclusion of patients regardless of tumour type

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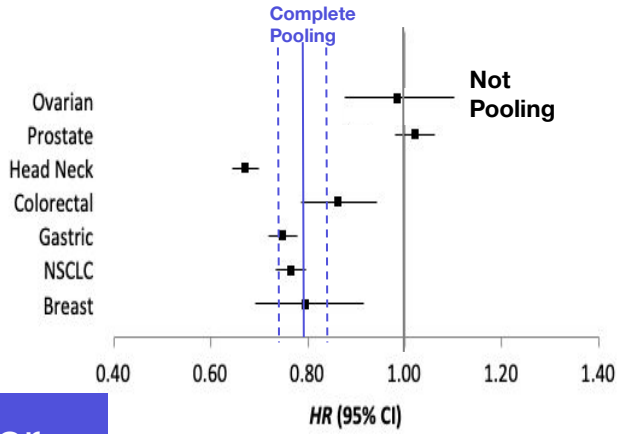
# Heterogeneity in histology-independent data adds complexity to analyses

- **Not pooling** is an inefficient use of data, often leading to inadequate sample size for precise stratum-level inference
- **Complete pooling** can inappropriately mask important differences in biomarker / drug effect across histologies




These traditional analytic methods (using complete or no pooling of data) may not address current HTA decision problems

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# Poll: What is your experience with HITs?

- No clue - hearing it about it for the first time

- Interested in the topic but limited experience

- Designing clinical trials

- Designing RWD studies

- Engagement in the HTA / Reimbursement process

# Poll: Please tell us about your background!

- Academic
- Industry (Pharma / Biotech Manufacturer)
- Consultancy
- Research institution
- Government Agency / HTA
- Other

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# Histology-independent cancer drugs

Dr Jacoline Bouvy

Technical Director, NICE Scientific Advice

NICE National Institute for Health and Care Excellence

# What is a histology-independent cancer drug?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 July 2019
EMA/CHMP/391684/2019
Media and Public Relations

**Press release**

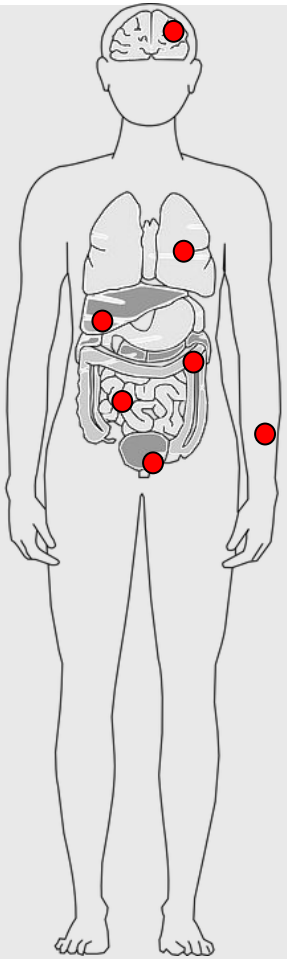
## First 'histology-independent' treatment for solid tumours with a specific gene mutation

EMA's human medicines committee (CHMP) has recommended granting a marketing authorisation in the European Union for Vitrakvi (larotrectinib) for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion. Treatment with Vitrakvi is recommended for patients whose disease has spread or cannot be surgically removed, and who have no other satisfactory treatment options.

Vitrakvi is the first so-called 'histology-independent' cancer treatment recommended for approval in the EU. This means that it can be used to treat non-haematological (i.e. that do not begin in the blood or bone marrow) tumours with this specific mutation, regardless of where in the body the tumour originated. Before patients can be started on the medicine, the presence of the mutation in the tumour should be confirmed by a validated test.

# Why are these drugs different?

| Traditional therapeutic indication | Histology-independent indication |
| --- | --- |
| First-line monotherapy of metastatic colorectal cancer (chemotherapy) | NTRK-positive solid tumours (larotrectinib, entrectinib) |
| RCT in patients with metastatic colorectal cancer | Basket trial of patients with biomarker-positive solid tumours |



NICE

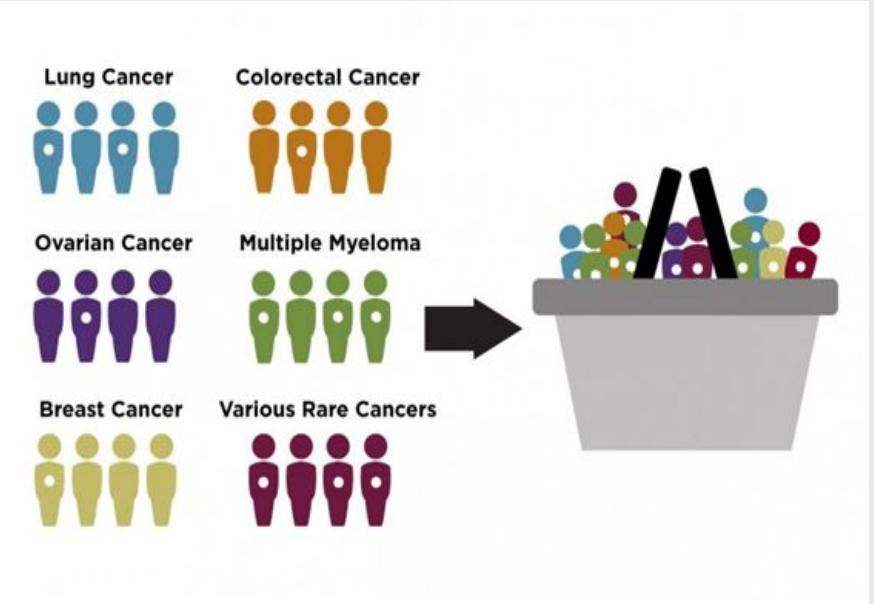
# What is a basket trial?

Includes patients with lots of different tumour types whose cancer shares a genomic mutation

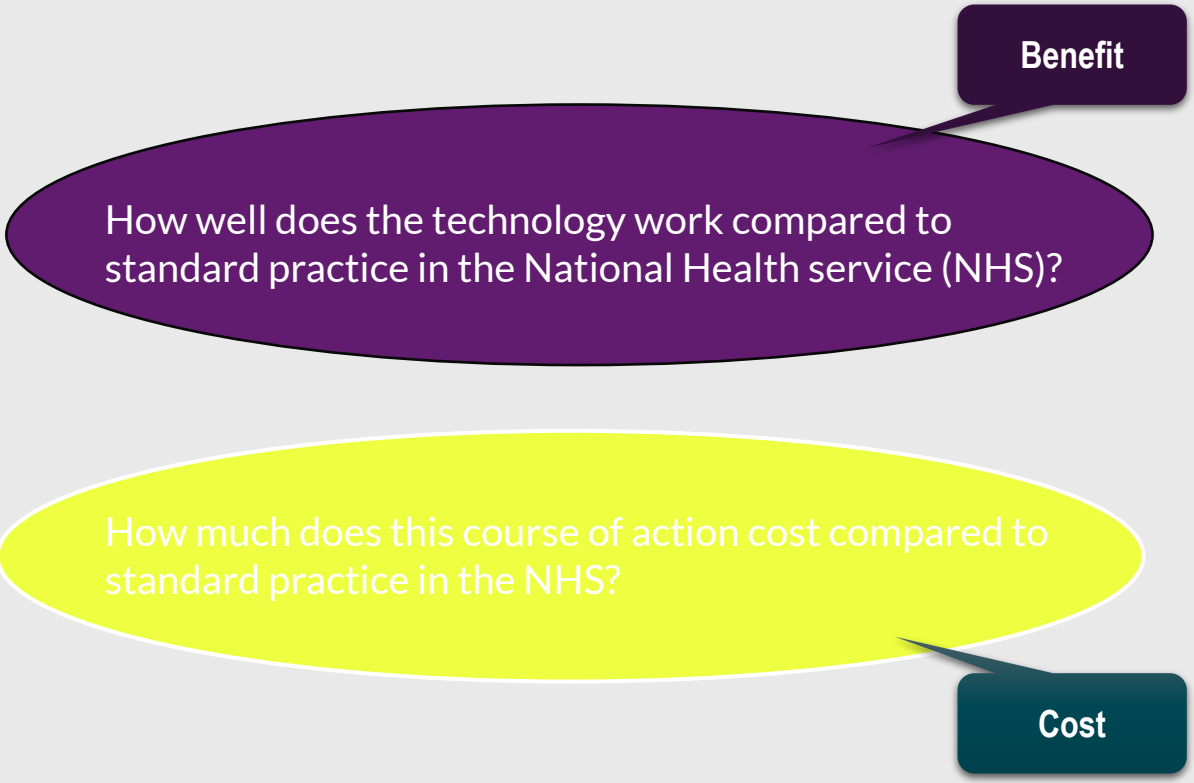
No comparator arm

Primary endpoints:

- Objective response rate
- Duration of response



# NICE asks 2 key questions about new drugs:

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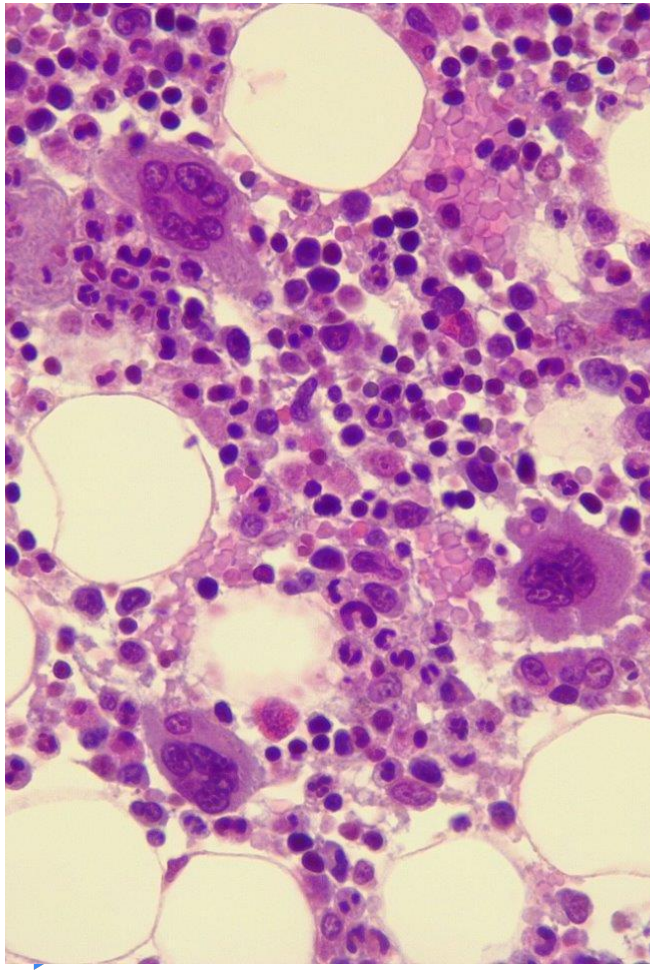

## Key challenges for HTA

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- Generalisability of trial evidence
- How to include testing costs
- To subgroup or not to subgroup?
- Developing the counterfactual
- Dealing with response-based endpoints

# Generalisability of trial evidence and testing costs

- Testing is required to identify patients eligible for treatment
- Point of testing in trial likely to differ from testing strategy in the NHS (no companion diagnostic)
- Extrapolation to histologies who were not included in the trial at all?

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# To subgroup or not to subgroup

**Calculating the cost effectiveness of a new drug:**

$$\frac{\text{Costs of new drug – costs standard of care}}{\text{Effects new drug – Effects standard of care}}$$

- Does a single ICER convey enough meaningful information on whether the drug provides value for money to the NHS across all indications?

NICE

# Developing the counterfactual

- What would have happened to these patients had they received the standard of care?
- No comparator arm in basket trial
- Usual approach for single-arm studies: indirect comparison to historical control data (data from a different trial)

**Trial population:**
NTRK positive tumours, treatment with histology independent drug

**Comparator:**
NTRK positive and NTRK negative tumours, treatment with standard of care

# Dealing with response-based endpoints

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## Traditional endpoints in cancer

Progression-free survival (PFS) and overall survival (OS)

## Partitioned survival models

Can use PFS and OS survival curves to extrapolate long-term outcomes

## Drug approved based on response

- Surrogate for PFS and OS or not?
- PFS and OS measured in trial, but data was immature at time of HTA

NICE National Institute for Health and Care Excellence

Thank you.

**Contact details:**


Jacoline.Bouvy@nice.org.uk


@jacolinebouvy

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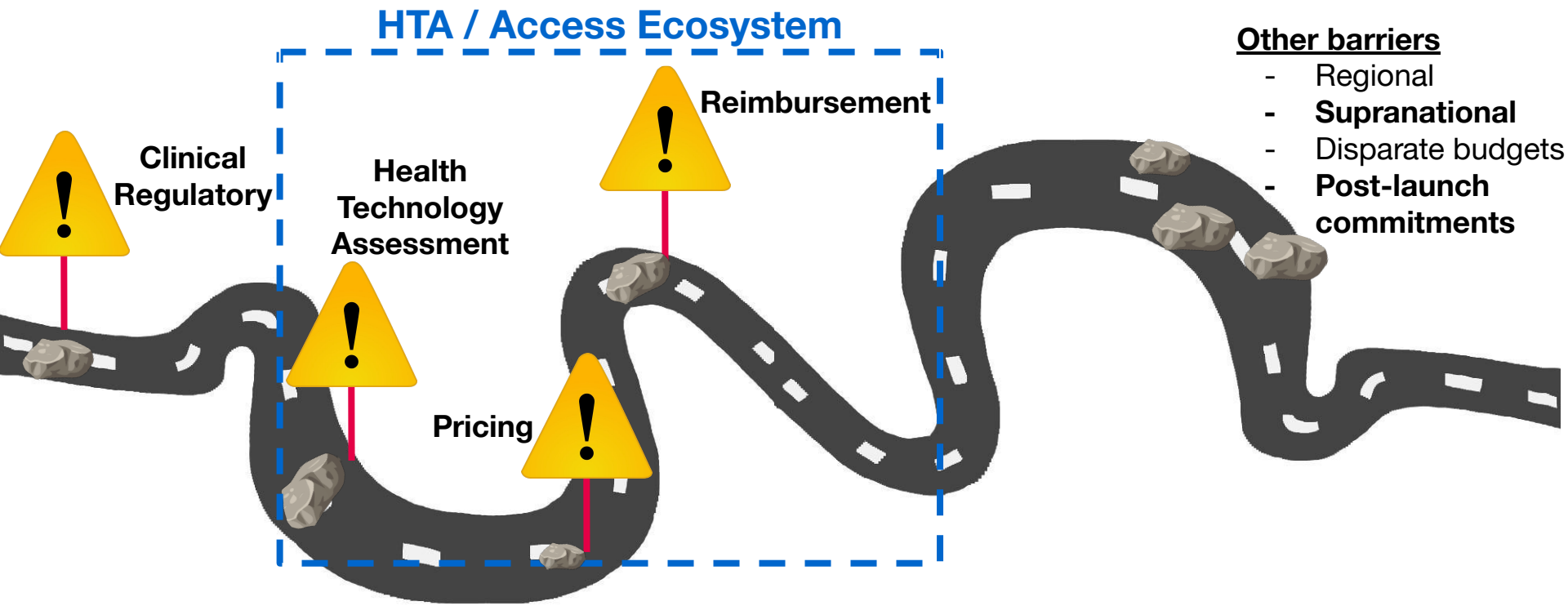
# Histology-independent cancer technologies

*Joshua Ray, Head Global Evidence, Global Access, Roche*

# Disclosure

*Joshua Ray is an employee of F. Hoffmann-La Roche Ltd.*
*The views expressed in this presentation & panel discussion are his personal opinions, and may not reflect those of his employer.*

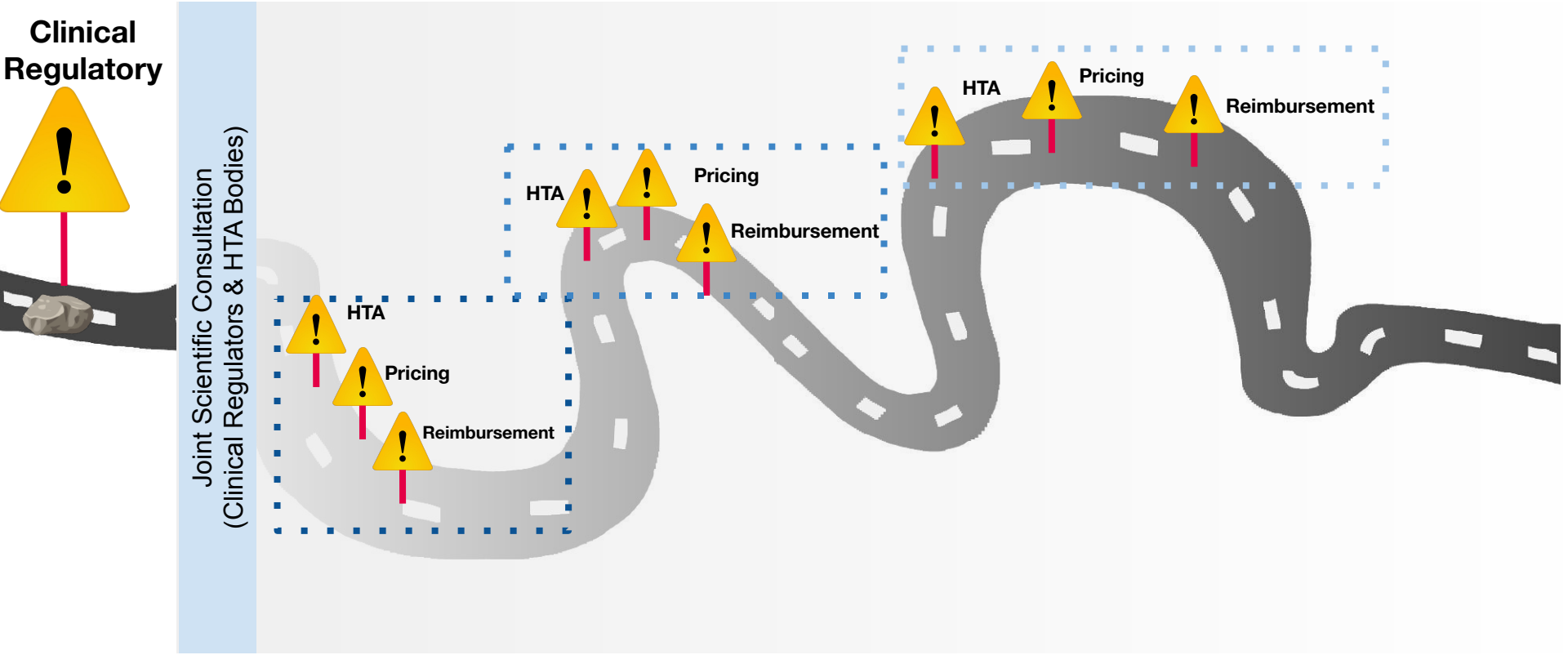
# Along the road to patient access




**Other barriers**

- Regional
- **Supranational**
- Disparate budgets
- **Post-launch commitments**

# The road to patient access is likely to change in the presence of histology independent technologies



# What's the situation?: Limited evidence base at the time of an initial access decision

**Technology's Evidence Package**

- Uncertainty around prevalence
- Partial understanding of natural history and prognostic impact of the genomic alteration
- Heterogeneity
  - Tumor origin
  - Line of therapy
- Lack of a clearly defined comparator (in trials & within the HTA evaluation)

**Environmental Concerns**

- Established reimbursement / HTA pathways
- Genomic testing
  - Clinical Guidance
  - Infrastructure
  - Reimbursement pathways

# Why does this matter?

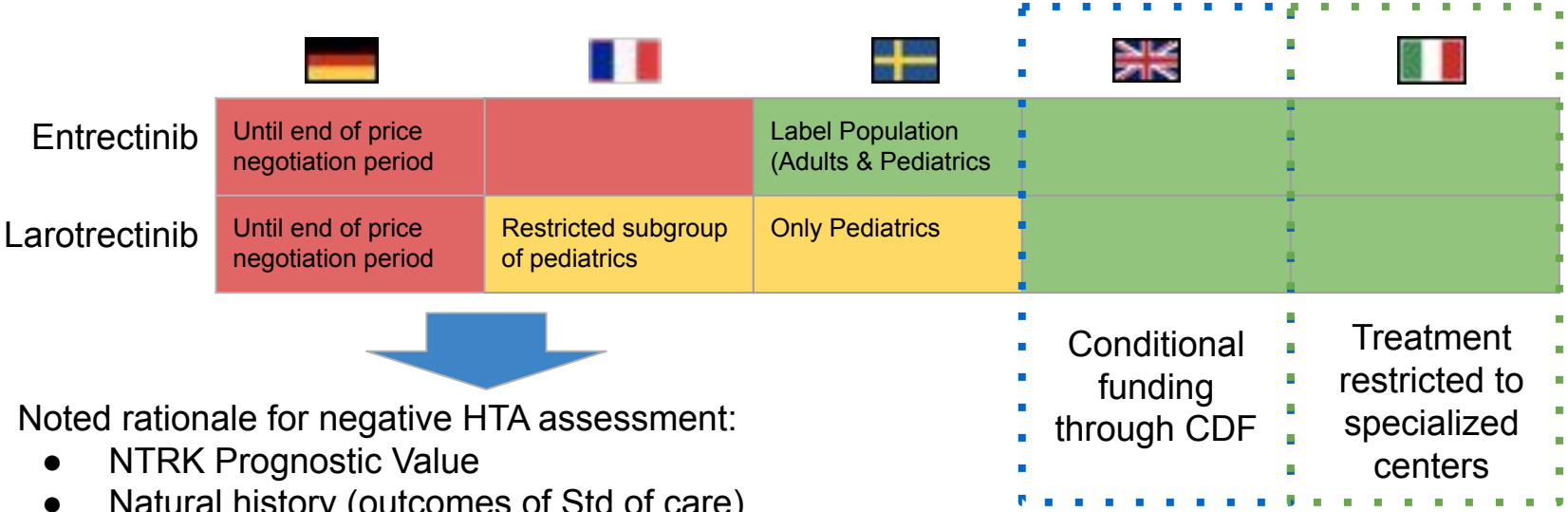
Sequential and separate processes for regulatory and reimbursement decisions creates challenges and uncertainty for HTA-bodies, Payers & Manufacturers

The environment...

- Select Clinical Regulatory (e.g. FDA, EMA, MHLW - Japan) bodies have evolved approval pathways
  - Expedite the development & assessment of technologies intended to treatment serious conditions with a high unmet need
  - Allows for the use of preliminary clinical evidence that demonstrates improvement over available therapy
- The paradigm for treating cancer continues to evolve [2]
  - As of 2019, 21 biomarker targeted therapies in development assessing a tumor agnostic label [2]
  - For NTRK fusions, previous estimates have estimated a tumor-specific RCT would take 17-105 years to complete [1]

1) Lozano-Ortega G. et al. Tumor-specific RCTs in rare oncogene-driven cancers: asking for the impossible? ISPOR 2019. 2) Mosele F. Recommendations for the use of NGS for patients with metastatic cancers. Annals of Oncology. 2020. 2) IQVIA Pipeline Intelligence; clinicaltrials.gov; trialtrove; Pharma Intelligence, Mar 2020

# What does this mean? A Snapshot at Europe



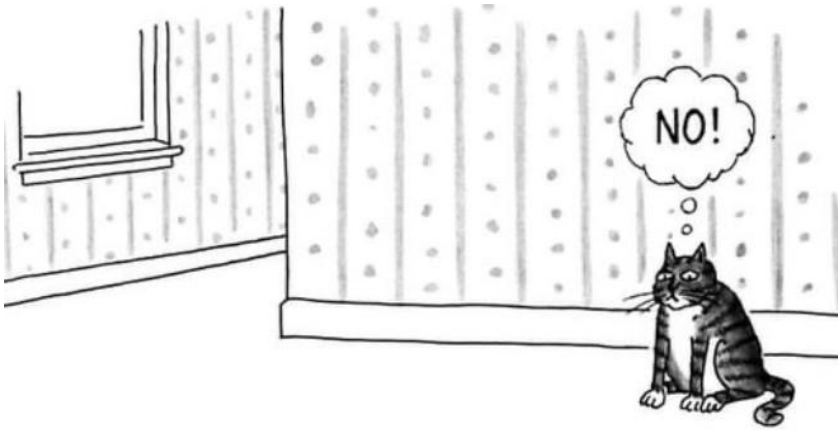

Noted rationale for negative HTA assessment:

- NTRK Prognostic Value
- Natural history (outcomes of Std of care)
- Surrogate endpoint validation
- Single arm trial / no comparative evidence (or randomization)
- Trial cohort size
- Limited acceptance of intra-patient comparison & RWD

# Where do we go from here?

- Utilize Joint Early Scientific Advice (Regulators & HTA) to align evidence generation plans

- Earlier evidence planning
  - Utilizing RWD
  - Intrapatient analyses




- Pivot towards continual evidence generation
  - Conditional approval & managed entry agreements

- Build upon evolving frameworks [1]:
  - Lessons from the existing histology independent technologies

1) Gaultney JG. Developing a Framework for the HTA of Histology-independent Oncology Therapies. Applied HE & HP 2021
2) Krebs MG, Intrapatient comparisons of efficacy in a single-arm trial of entrectinib in tumour agnostic indications. ESMO Open. 2021.

# Where RWD may help narrow the gap


**Biomarker Identification**

- Cost of identifying population with the biomarker
- Optimal testing scheme
- Availability / infrastructure for testing

**State of Unmet Need / SoC**

- Prevalence of biomarker
- SoC / External controls by tumor
- Prognostic effect (QoL/ Survival) of biomarker
- Prevalence of biomarker by tumor
- Co-occurrence / mutual exclusivity of biomarker w/ actionable alterations

**Assessing the Technology**

- Overall initial response
- AEs
- Refractory treatments
- Dosing levels / treatment cycles
- Overall durability of response (w/ survival QoL
- Treatment pathway (1L/2L)

# RWD can help address uncertainty in prevalence

Development → Launch

**Biomarker Identification**

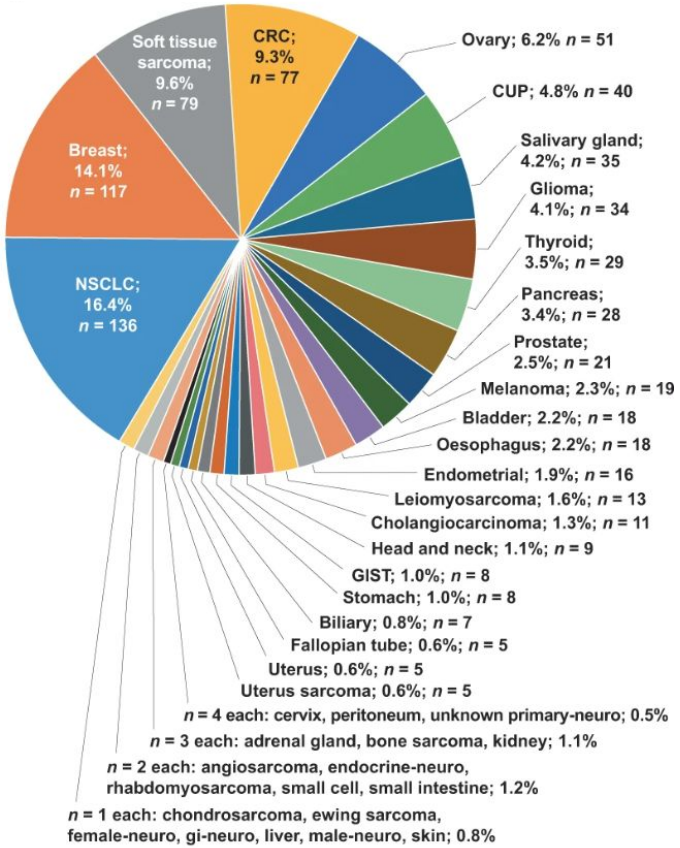
Cost of identifying population with the biomarker

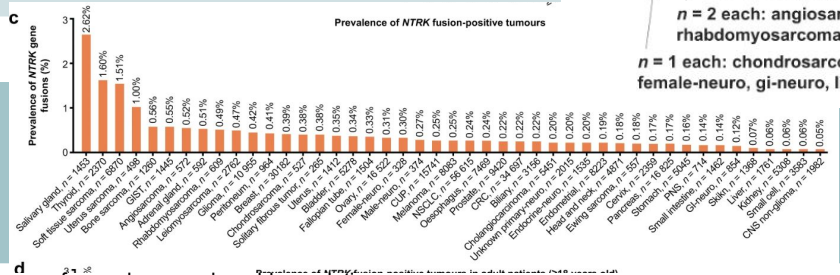
**State of Unmet Need / SoC**

Prevalence of biomarker

Prevalence of biomarker by tumor

**Assessing the Technology**




Westphalen et al.Genomic context of NTRK 1/2/3 fusion-positive tumors from a large real-world population.
npj Precision Oncology. 2021

# Example where RWD can address uncertainty in baseline prognosis

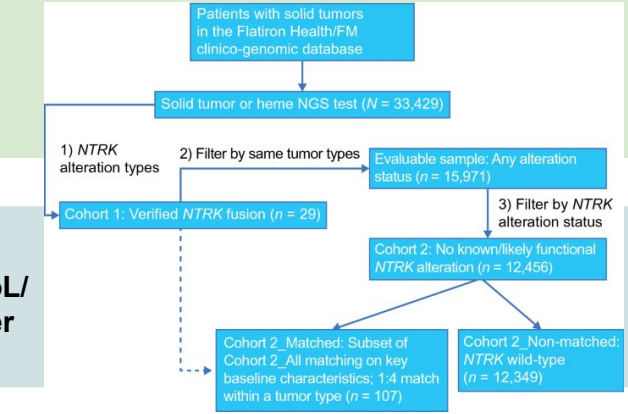
Development | Launch | Wider adoption

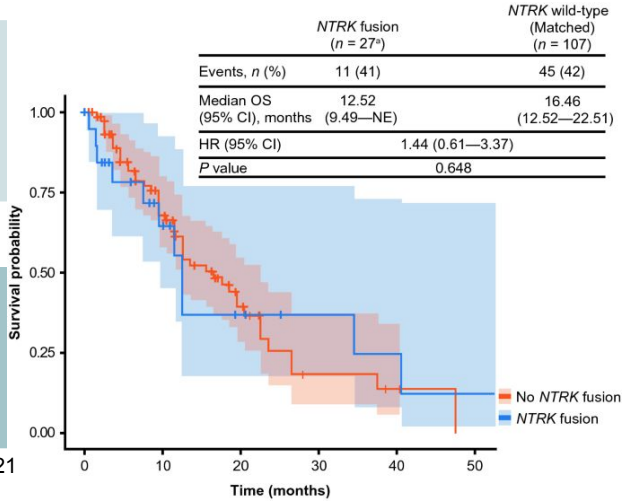
**Biomarker Identification**

**State of Unmet Need / SoC**

**Prognostic effect (QoL/ Survival) of biomarker**

**Assessing the Technology**




Bazhenova L. et al. TRK fusion cancer: Patient characteristics and survival analysis in the real-world setting. Targeted Oncology. 2021

# Summary

- Histology Independent Technologies present unique challenges and will become more commonplace

- Patient benefit may be foregone in the absence of early & multi-stakeholder dialog
  - This can be minimized by co-creating immediate and long-term solutions addressing patient-relevant outcomes and budgetary concerns
  - Focusing on both the implementation of acute treatments and their accompanying infrastructure requirements


*"I don't think reusable straws are going to be enough"*

*Doing now what patients need next*

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# Statistical Approaches for Histology-Independent Analyses Using Real-World Data

Jeremy Snider, PhD MPH
Senior Quantitative Scientist
Flatiron Health

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# Goals for this presentation:

- Motivate using **Real-World Data (RWD)** in a **biomarker-defined** and/or **histology-agnostic** study
- Understand **benefits and challenges of incorporating longitudinal data** into histology-independent studies
- Understand how to contend with **histology heterogeneity** in an HIT analysis

# RWD can enhance biomarker-defined HEOR studies

**Single-Arm Basket Trial Data**

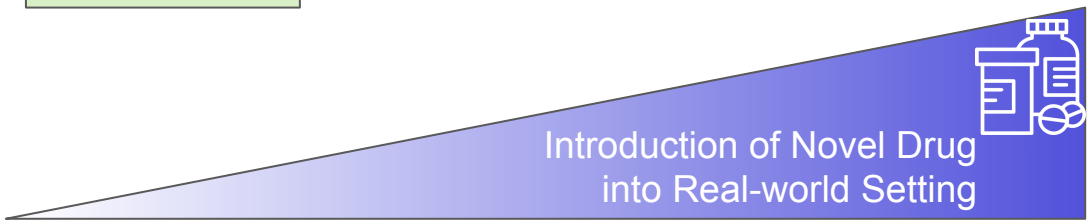
- Biomarker Prevalence
- Novel Technology Outcomes - Efficacy
- Novel Drug Adverse Events (AEs)

Green box: more straightforward, won't be addressed here

**Initial Real-World Data** → **Updated Real-World Data**

- Biomarker Prevalence
- SOC Practice Patterns
- SOC Outcomes - Effectiveness
- SOC Costs / AEs

- Novel Drug Uptake Patterns
- Novel Drug Outcomes - Effectiveness
- Novel Drug Costs / AEs

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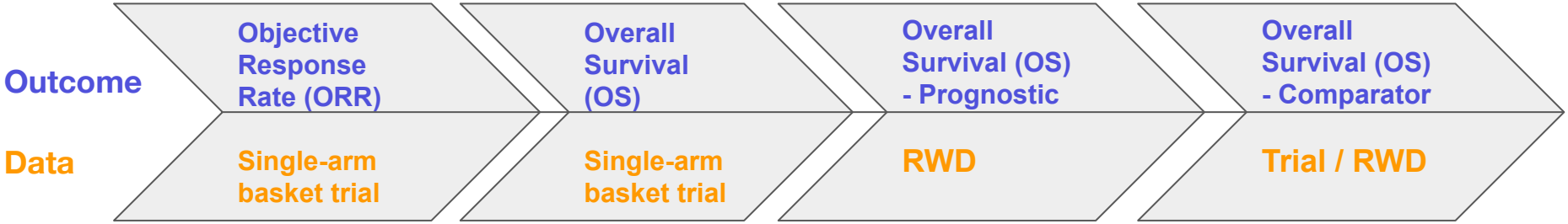
# Building evidence in histology-independent efficacy/effectiveness analyses




| | | | | |
|---|---|---|---|---|
| **Value of Study** | Understand **biological response** to drug | Understand a **long-term, meaningful** patient outcome and its relationship with objective response | Understanding **unmet need,** prognostic value of biomarker by comparing a untreated biomarker-defined vs. a wild-type patient population | Understanding **comparative effectiveness** of an untreated biomarker-defined population compared to a treated trial cohort |
| **Complexity Added** | Heterogeneity in **response** across histologies | Heterogeneity in **histology-specific baseline hazards** and **biomarker-driven prognoses** (unknown) | Defining **biomarker status**, **delayed entry** of RWD patients (based on biomarker testing) | Heterogenous trial and RWD **patient populations** |

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# The first step: Objective Response Rate (ORR) from Single-Arm Trial

**Table 2** Probabilities of response for all histologies

| Histology | Observed Response | Estimated Mean Response Based on BHM (%) | 95% CrI |
|---|---|---|---|
| Fixed effects | | | |
| Pooled | 41/55 = 74.5% | 74.20% | 62.0%−84.7% |
| Random effects | | | |
| Soft-tissue sarcoma | 10/11 = 90.9% | 88.10% | 66.0%−99.1% |
| Salivary gland | 10/12 = 83.3% | 81.80% | 58.0%−96.8% |
| IFS | 7/7 = 100% | 93.30% | 70.5%−100% |
| Thyroid | 5/5 = 100% | 91.60% | 63.0%−100% |
| Lung | 3/4 = 75.0% | 72.60% | 30.4%−97.8% |
| Melanoma | 2/4 = 50.0% | 52.50% | 12.4%−89.4% |
| Colon | 1/4 = 25.0% | 32.00% | 2.6%−75.5% |
| GIST | 3/3 = 100% | 88.30% | 49.3%−100% |
| Cholangiocarcinoma | 0/2 = 0% | 21.00% | 0.0%−75.7% |
| Appendix | 0/1 = 0% | 30.00% | 0.1%−89.7% |
| Breast | 0/1 = 0% | 30.00% | 0.1%−90.1% |
| Pancreas | 0/1 = 0% | 29.80% | 0.1%−89.7% |
| Unrepresented | — | 56.90% | 0.2%−99.9% |

Complete pooling suggests efficacious technology

However, histology-specific estimates are highly variable (11-93%)

Murphy et al. (2021) Exploring Heterogeneity in Histology-Independent Technologies and the Implications for Cost-Effectiveness, Medical Decision Making

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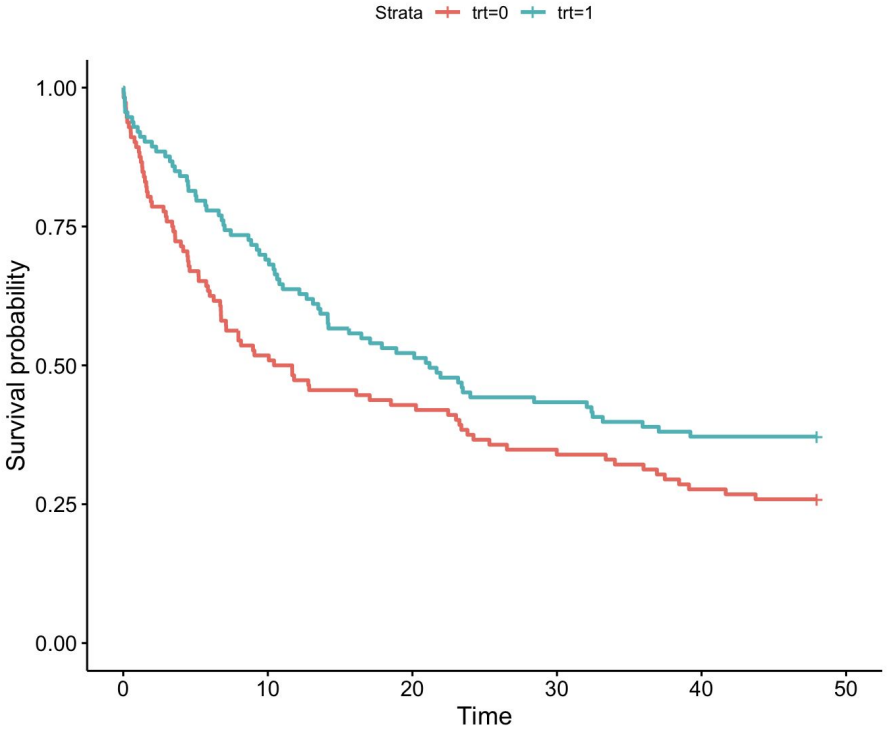
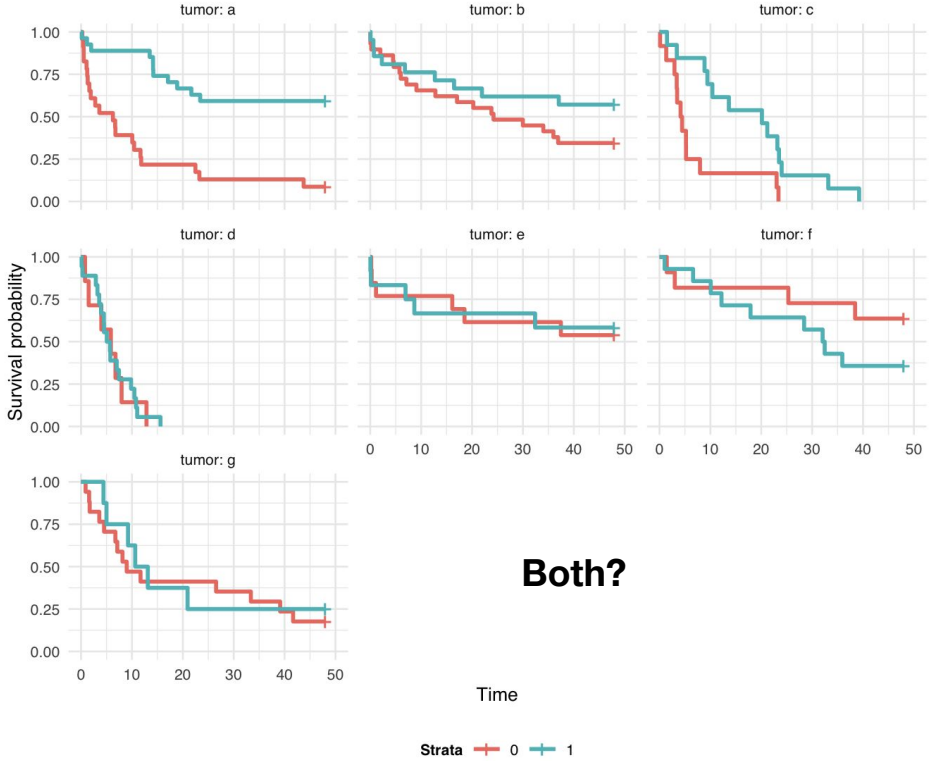
# How can do we contend with tumor heterogeneity in an Overall Survival (OS) analysis?

**Complete Pooling?**




**No Pooling** (Stratified by histology?)




**Both?**

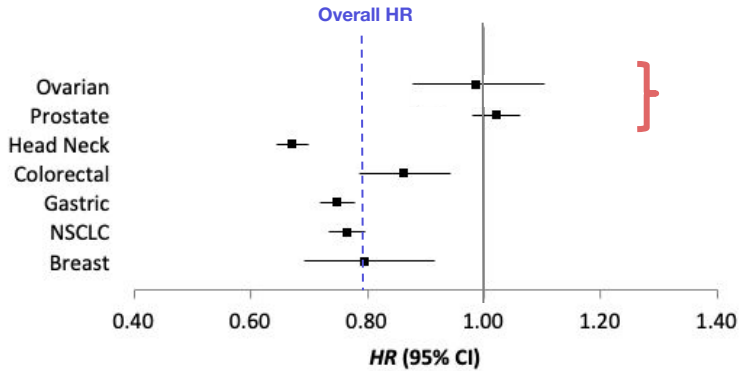
# Complete pooling: Can mask heterogeneity

**Model:** coxph(OS ~ received_drugX,
data = all_mutationY_patients)

| | Beta-coefficient | P-value |
|---|---|---|
| received_drugX | -0.23 | 0.002** |

*Should Drug X be approved for histology independent use?*

**HR = 0.79**
**Looks promising!**

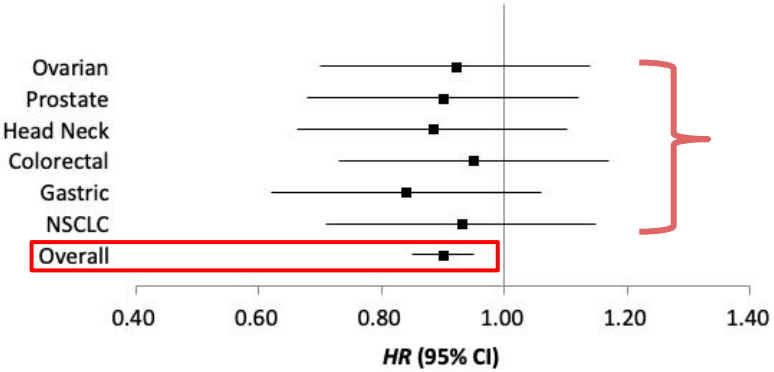



**Tumor-specific HRs raise indicate non-effectiveness**

**Tumor-level effects** are important!

# No Pooling: Stratum-level analyses do not make use of all available data

**Model:** coxph(OS ~ received_drugY,
data = all_mutationZ_patients_with_{cancer})



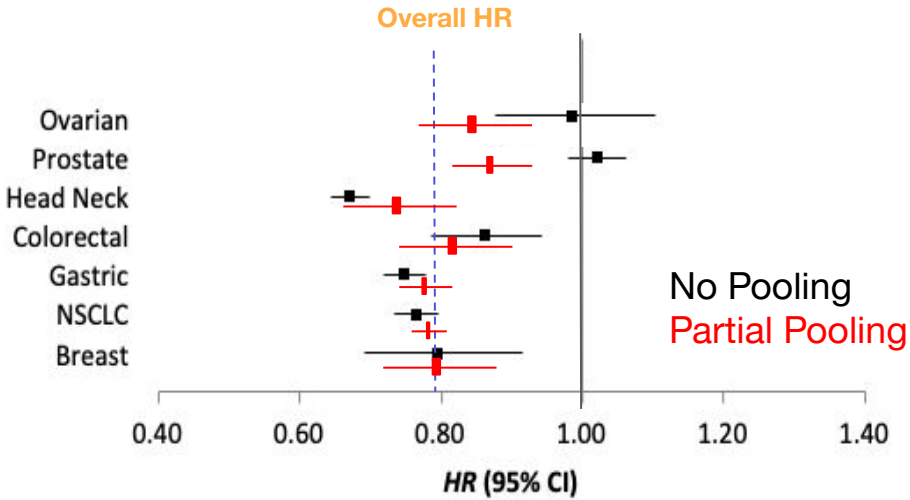

**Tumor-specific effects are inconclusive**

**Overall effect is promising!**

Both the **overall effect** and **tumor-level effects** are important!

# Partial Pooling: A happy medium?

- **Single source hierarchical models** are a common approach to partial pooling
- They assume that strata-level estimates come from a single parent **prior distribution**
- These prior distributions for can be **manually prespecified** (e.g. Bayesian analysis), or **calculated empirically** (e.g. random effects/empirical Bayes)
- Strata-level estimates are pulled towards the global mean based on strata size



# Balancing Clinical and Statistical Considerations when Interpreting Heterogeneity

Expert opinion on drug and tumor biology can inform a scientific rationale for pooling histologies. However, heterogeneity can also be interrogated in the data:

- **Analysis of Variance (ANOVA):** to test interaction effect between histology and biomarker/drug
- **Multi-source Exchangeability Models (MEM):** considers all possible pairwise exchangeability relationships, estimates the probability that subset of histologies should be considered statistically exchangeable (or poolable) - (Kane, 2019)

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# Quantifying Heterogeneity: ANOVA Interaction Test (in R)

- An unstructured interaction test can help identify if effect modification by tumor histology is present in the data
- However, it won't indicate which subgroups are the source of the interaction, nor characterize the magnitude of the subgroup treatment effect differences

```
 anova(coxph(Surv(eventtime, status)~ biomarker_status  + tumortype , data = dat) ,
       coxph(Surv(eventtime, status)~ biomarker_status * tumortype , data = dat))
Analysis of Deviance Table
 Cox model: response is  Surv(eventtime, status)
 Model 1: ~ biomarker_status + tumortype
 Model 2: ~ biomarker_status * tumortype
   loglik  Chisq Df P(>|Chi|)
1 -732.39
2 -723.57 17.643  6   0.00719 **
```

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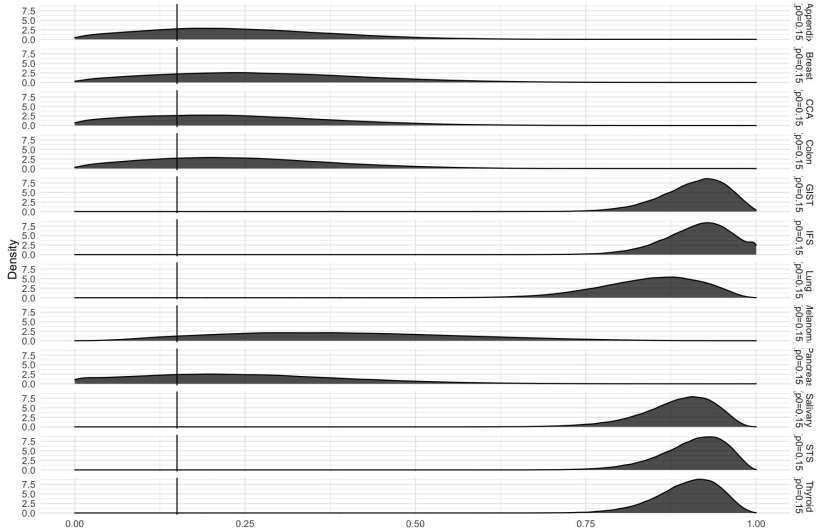
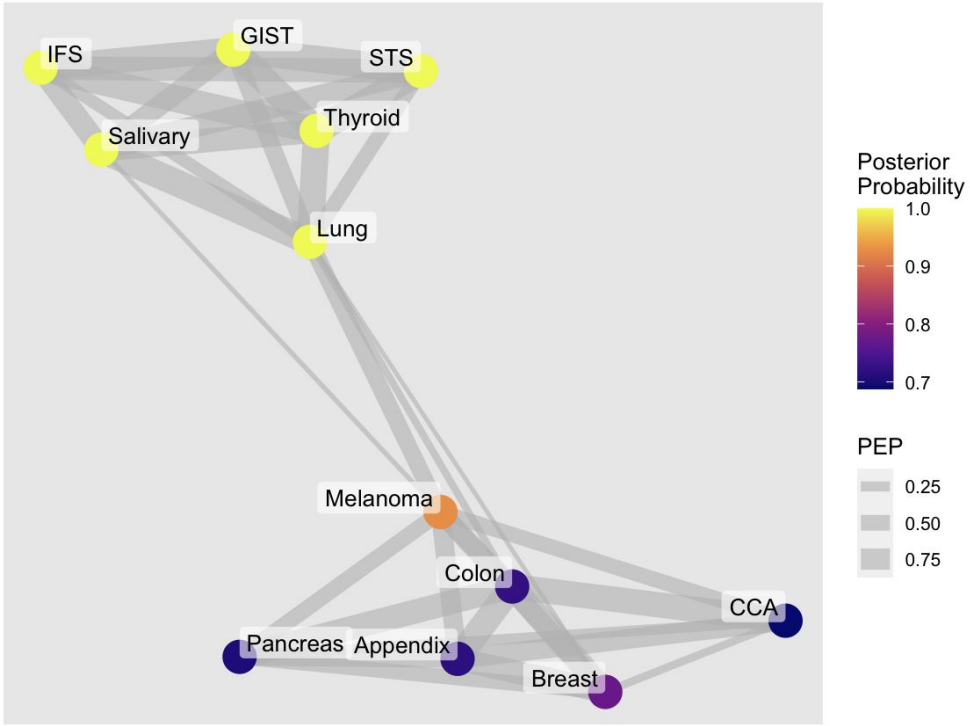
# Quantifying Heterogeneity: Multi-source Exchangeability Models (MEM)

Analyzing Basket Trials under Multisource Exchangeability Assumptions (Kane, 2019)

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# Conclusions

- RWD can enhance HEOR analyses that accompany HTA submissions:
  - Improving the **breadth and depth** of studied histologies
  - Providing **meaningful longitudinal** effectiveness data
- Longitudinal / survival data presents **unique challenges in HIT analyses**
- Multilevel modeling and measuring heterogeneity can improve analyses and guide methodological decisions

# Workshop Agenda

| Time (minutes) | Speaker | Goal |
|---|---|---|
| 0 | Jeremy Snider | • Introduction of speakers / provide workshop overview |
| 5 | Dr Jacoline Bouvy | • Provide background for previous HIT decisions<br>• Discuss evidence and analyses that can provide the best insight for future decisions |
| 15 | Joshua Ray | • Highlight implications of the current evidence and policy environment related to histology independent technologies<br>• Propose solutions to address evidentiary concerns with histology independent technologies inhibiting patients access |
| 25 | Jeremy Snider | • How can longitudinal RWD be leveraged in effectiveness analyses for histology independent technologies<br>• Discuss statistical methods that are appropriate for use in an HIT |
| **35** | **Jeremy / Josh / Jacoline** | • **Interactive case study**<br>• **Discussion of methods and results with speakers** |
| 50 | Jeremy / Josh / Jacoline | • Questions from participants<br>• Conclusory remarks |

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# Interactive case study

We'll go through one exercise together to understand how to answer a key question

**1: Using Longitudinal RWD to understand the prognostic value of a biomarker across histologies**

There are three additional exercises provided for your reference:

2: Using Longitudinal RWD to understand novel drug effectiveness across histologies

3: (Appendix): Combining Trial and RWD to improve precision and understand response heterogeneity in a histology-independent analysis

4 (Appendix 2): Prevalence across cohorts

Follow along at:
**http://bit.ly/ispor_hit**

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