Passport for Travel: Proposed Framework for the Transportability of Oncology Real-World Evidence

Brennan Beal PharmD, MS[1], Ivy Altomare MD[1], Joshua Ray MD[2], Danielle Bargo[1], Blythe Adamson PhD, MPH[1,3]

[1] Flatiron Health, New York, NY [2] Roche, Basal, Switzerland [3] University of Washington, Seattle, WA

Background

- There is an increased demand for oncology real-world data (RWD) to support decision-making by health-technology assessment (HTA) bodies
- The extent to which insights generated from US RWD could be used to address uncertainty in ex-US markets is commonly questioned
- These questions are usually referred to as ones of *transportability* (Figure 1) and are often challenged by criteria for causal inference such as the condition of consistency, among other things[1]
- This study aimed to identify challenges in assessing the transportability of evidence derived from real-world US electronic health records (EHR) and proposes a framework for mitigating risks to HTA decision-makers

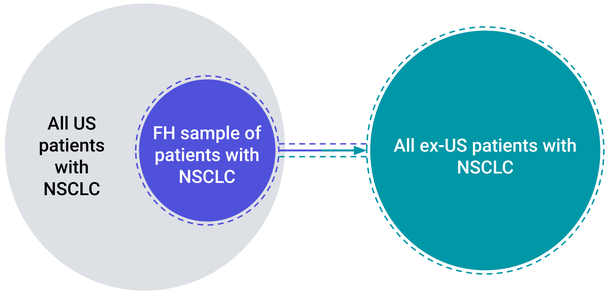

Figure 1. Transportability refers to how well inferences generated from a sampled population may extend to a target population from which the original sample was not derived

Methods

- Identified literature published with German oncology data between the years of 2015 and 2020 in four tumor types: multiple myeloma, non-small cell lung cancer, breast cancer, and bladder cancer[2,3,4,5]
- The identified published inferences were compared to those able to be generated from the longitudinal de-identified US EHR-derived Flatiron Health (FH) database, which is comprised of de-identified patient-level structured and unstructured data curated via technology-enabled abstraction originating from approximately 280 cancer clinics and ~800 sites of care in the US.[6,7]
- Created a qualitative enumeration of challenges when replicating results between countries
- Categorized observable and non-observable data elements which could lead to dissimilarities between the inferences from the German and US data studies and thus scenarios that would prove difficult to assume transportability from country-to-country
- Factors that affect the representativeness of the core themes (and thus the transportability of the RWD) were then identified

Results

- Three core themes were identified with four to five factors within those themes affecting the representativeness, and hence transportability, of RWD with the identified themes being: patient-characteristic differences, setting-of-care differences, and treatment pattern differences (Table 1)
- Accounting for the identified themes in the pre-specification process allowed for a clearer understanding of whether inferences generated from the Flatiron Health EHR-derived data source may be transportable to other countries of interest for the purposes of HTA

Conclusions

- Differences in a target population from the sampled population may impact the transportability of causal inferences generated from RWD
- Some differences may be accounted for, such as baseline demographics or prevalence, with methodological adjustments while other things, such as unknown confounders, may not be
- Clearly characterising these differences in a consistent framework promotes a more systematic approach during the pre-specification process, allowing for increased representativeness in the sample population and more transparency during a given HTA submission

Results (cont.)

Table 1. Considerations for the Representativeness of US EHR Data for HTA Use Cases

Note:
This table is intended to be a dynamic, living tool that will change over time. As Flatiron Health develops more learnings from experience with HTA use cases, and transportability nuances that arise, this tool will continue to be updated.

	TRANSPORTABILITY ELEMENT	RATIONALE
	Patient characteristic differences	
✔	Baseline demographics	Demographics may encompass a set of effect-modifying variables – differences in the prevalent and incident population should be considered.
✔	Prevalence of disease	The baseline prevalence of a given disease may affect the transportability of some elements based on the mathematical association with relevant endpoints.
✔	Preference for modifiable risk-factors	Preferences, and thus the prevalence, for modifiable risk factors (smoking, obesity, etc.) within a given population may modify the transportability of outcomes between countries if these risk-factors are known effect modifiers.
✔	Biomarker prevalence	For cancers with a diverse genetic etiology, there may exist significant treatment effect heterogeneity. Therapies indicated for those cancers may lack transportability in populations with a widely different biomarker makeup. Further, because biomarker testing rates may differ between populations, those selected into the cohort may also differ and affect the transportability of outcomes.
	Setting differences	
✔	Treatment site variation	The distribution of academic and research institutions as well as high- and low-volume sites, may vary between countries, or jurisdictions, and influence the transportability of a given insight.
✔	Differences in time-to-treatment initiation within a disease's natural history	Time-to-treatment initiation may vary dramatically between countries (driven by locality's procedures to confirm diagnosis and/or healthcare system capacity) and therefore change a particular risk set and influence outcomes
✔	Disease assessment frequency	Disease assessment frequency can provide erroneous conclusions about metrics such as progression free survival or other outcomes that rely on monitoring schedules, and thus the time at which observations can be made.
✔	Preference for end of life care	In later lines of therapy, the risk-set a country chooses to treat may be different from that of another country based on differences in preferences for hospice. So, countries that tend to treat more aggressively may treat a sicker risk-set than that of a country that is more likely to choose for alternative end-of-life remedies.
	Treatment Differences	
✔	Access to a given treatment	A prevalent population may not be represented in the EHR data given restriction in access based on socio-economic status or variability in payer preferences for a given product. Thus, patients selecting into a given cohort could vary and impact observed outcomes. For example, cost-prohibitive therapies may naturally select healthier populations, and reveal better outcomes, in countries with worse access arrangements.
✔	Access to supportive care	Supportive care is known to improve outcomes for patients in many settings; however, access to supportive care varies within and between countries.
✔	Market share of the pharmaceutical(s) of interest and competitors	Environments with a large diversity of available technologies for a specific indication require contextualization for who selects into a cohort treated with a specific technology.
✔	Market share of backbone therapies used concomitantly with a therapy of interest	Even in situations where the market share for a technology of interest is the same, concomitant therapies of interest (eg. high- versus low- dose dexamethasone) may differ. If these therapies are effect-modifying, the distribution of them in the given data will affect transportability of the outcomes.
✔	Guideline differences between jurisdictions / localities	Because the approved label/reimbursement criteria for a given therapy may vary, the way a product is used between countries may also sometimes differ, which may present itself in what is known as the compound treatment problem. Further, labels may also influence the preceding drugs that patients have been exposed to, complicating the question of transportability.

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