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Next-generation sequencing, should I use anti-HER2 therapy for *HER2*-amplified tumors off-label? Illustrating an extrapolation framework

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Abstract

Background: Next-generation sequencing is used to increase targeted treatment opportunities, particularly for patients who have exhausted standard options. Where randomized controlled trial evidence for a targeted therapy is available for molecular alterations in one tumor type, the dilemma for the clinician is whether 'matching' targeted agents should be recommended off-label for the same molecular alterations detected in other tumor types, for which no trial data are available to guide practice. To judge the likely benefits, it may be possible to extrapolate evidence from cancers where treatment benefits have been established.

Methods: We present a framework for assessing the appropriateness of extrapolation using trastuzumab, an anti-HER2 antibody, for *HER2*-amplified tumors where trastuzumab use would be off-label as an illustrative example.

Results: The following should be considered for the tumor type where trastuzumab would be off-label: (a) reliability of the NGS assay for detecting *HER2* amplification; (b) criteria for defining HER2 positivity; (c) strength of evidence supporting the actionability of *HER2* amplification and trastuzumab; (d) whether better clinical outcomes with trastuzumab are due to a more favorable natural history rather than trastuzumab effect; (e) signals of trastuzumab activity and whether it translates to clinically meaningful benefit; (f) whether the safety profile of trastuzumab differs from established indications; and (g) discussion points for shared decision making (SDM) to facilitate informed consent.

Conclusion: We present a systematic approach for appraising evidence to support extrapolating trastuzumab benefits from established indications to off-label applications. Extrapolation criteria and areas of uncertainty to inform SDM are outlined. This framework is potentially generalizable to other tumor-agnostic biomarker-targeted therapy scenarios. It is a practical approach for clinicians to apply in routine practice and should be considered by molecular tumor boards who make off-label recommendations.

Keywords: gene expression profiling, HER2-targeted therapy, molecular testing, predictive biomarker, targeted therapy, tumor biology

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Introduction

Next-generation sequencing (NGS) is increasingly used for comprehensive molecular profiling to increase targeted treatment opportunities, particularly for advanced cancer patients who have exhausted standard options. Where randomized controlled trial (RCT) evidence for a targeted therapy is available for molecular alterations

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in one tumor type, the clinician's dilemma is whether 'matching' targeted agents should be recommended off-label for the same alterations detected in other tumor types, if RCT data are unavailable to guide practice. This is already a common recommendation from molecular tumor boards (MTBs) if appropriate clinical trials are unavailable,[1] with few presenting the strength of recommendations using standard level of evidence scales.[2,3]

To illustrate, human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase receptor encoded by the *ERBB2 (HER2)* gene (chromosome 17q12). Overexpression of HER2 protein occurs mainly from *HER2* gene amplification[4] and results in oncogenic signaling.[5] Clinical benefit of targeting *HER2* amplification by adding anti-HER2 therapy to chemotherapy has been established in RCTs in breast,[6–8] gastric and gastroesophageal (GE),[9] and uterine serous cancers.[10] Since *HER2* amplification is also detected in other cancer types, there is high interest in whether this clinical benefit also applies.[11]

To estimate the benefits of adding trastuzumab, an anti-HER2 antibody, to chemotherapy in *HER2*-amplified cancers where there is no RCT data, hereby referred to as 'off-label trastuzumab', it may be possible to extend data from cancers where clinical benefit of this treatment has been established in RCTs ('established indications'). However, extrapolation may not be appropriate in some settings because of biological differences between cancers. We present a framework for extrapolation and illustrate its application using off-label trastuzumab. The aim of this exercise is to help clinicians apply these principles which may be generalizable to other biomarker-targeted therapy scenarios.

Methods

We developed a framework to assess the appropriateness of extrapolating data from established indications to other cancers. This framework is articulated through a series of questions and addresses the distinct components required for extrapolation: analytical validity of the biomarker test, biomarker criteria to define the disease, strength of evidence supporting biomarker actionability, natural history of biomarker-defined cancers, signals of targeted therapy response, and similarity of safety profile. A prescriptive step-wise approach is not proposed as the evidence supporting each question for different biomarker-targeted therapy scenarios will likely be different. Alternative therapies available and costs will also be different for each scenario. Cost should be addressed upfront as further considerations will be futile if there is no reasonable way to cover the cost of off-label therapy.

Using the example of *HER2*-amplified cancers and the accompanying treatment trastuzumab, this article demonstrates the application of the framework. We limit the discussion to trastuzumab for illustration clarity although many other HER2-directed therapies exist. This work is not intended to provide a comprehensive review of the biology and management of *HER2*-amplified tumors.

Results

We outline seven questions to consider when estimating the benefit of off-label trastuzumab (Figure 1). The order of the questions is built around the Population, Intervention, Comparator, and Outcome (PICO) model to define the information needed to address our clinical question.[12,13] Questions 1 and 2 address defining the disease population according to *HER2* amplification status. Question 3 addresses the ability of *HER2* amplification status to predict trastuzumab effect. Question 4 addresses the treatment outcomes of the *HER2* amplified population on standard of care control treatment. Question 5 addresses signals of trastuzumab efficacy based on surrogate endpoints, and question 6 addresses the safety profile of off-label trastuzumab. Questions 1 to 6 should be considered individually, and judgment for the level of uncertainty for extrapolation should be made for each (Table 1).[14] Responses from other extrapolation questions either increase or decrease certainty of each question and the final treatment recommendation should be made based on the totality of the evidence. If there is probably no important uncertainty for most of the questions, then there is likely sufficient evidence to support off-label trastuzumab. However, if there is important uncertainty for many or most of the questions, there is insufficient evidence to support off-label trastuzumab. Question 7 addresses shared decision-making (SDM) and informed consent for recommendations made after considering questions 1–6. Recommendations should be individualized and consider the estimated benefit *versus*

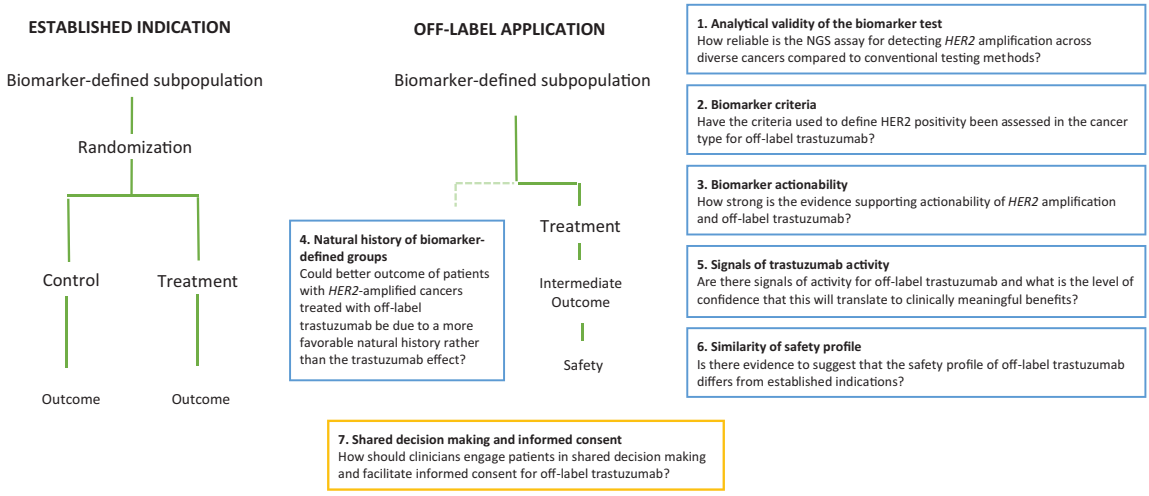

Figure 1. Assessing appropriateness of extrapolation.
Schema showing randomized trial evidence for the established indication and questions to consider when extrapolating this evidence for off-label application. Evidence for off-label use may be restricted to randomized or single-arm trials reporting on intermediate (surrogate) outcomes; non-randomized comparisons with the untreated population (natural history); and real-world evidence supplementing efficacy and safety data.

Table 1. Assessment of uncertainty when extrapolating evidence for off-label application.

Judgment*	Evidence Assessed for each question*	Treatment recommendation Assessed from evidence for all questions#
Important uncertainty	No research evidence identified or searched for	Insufficient evidence to support off-label therapy
Possibly important uncertainty	Judgment Responses from other extrapolation questions decrease certainty	Possibly sufficient evidence to support off-label therapy
Probably no important uncertainty	Judgment Responses from other extrapolation questions increase certainty	Likely sufficient evidence to support off-label therapy

Source: Adapted from 'Standardized wording to improve efficiency and clarity of GRADE EtD frameworks in health guidelines'. *J Clin Epidemiol* 2022; 146: 106–122.
*Judgment for the level of uncertainty for extrapolation should be made individually for each of the questions from 1 to 6. Responses from other extrapolation questions either increase or decrease certainty of each question.
#The final treatment recommendation should be made based on the totality of the evidence. If there is probably no important uncertainty for most of the questions, then there is likely sufficient evidence to support off-label therapy. However, if there is important uncertainty for many or most of the questions, there is insufficient evidence to support off-label therapy. Treatment recommendations should be individualized and consider estimated benefit *versus* risks of off-label therapy compared to alternative therapies if available.

risks of off-label trastuzumab compared to alternative therapies if available.

Analytical validity of the biomarker test

How reliable is the NGS assay for detecting HER2 *amplification across diverse cancers compared to conventional testing methods?*. In breast and gastric/GE junction cancers, the American Society of Clinical Oncology and the College of American Pathologists recommend testing for HER2 protein overexpression using immunohistochemistry (IHC) and *HER2* gene amplification using fluorescent or silver *in situ* hybridization (FISH or

Table 2. Measures of concordance and accuracy.

		Evidentiary standard – IHC and FISH	
		***HER2*-amplified**	***HER2* non-amplified**
Biomarker test – NGS	*HER2*-amplified	A	B
	HER2 non-amplified	C	D

Concordance is measured by cross-classifying the results of two tests. In this example, the overall concordance between the biomarker test (NGS) and the evidentiary standard (IHC and FISH) can be expressed as a percentage of A + D/(A + B + C + D).
Accuracy measures include test sensitivity, specificity, PPV, and NPV. The analytical sensitivity and specificity of the NGS assay can be assessed using reference samples, either patient samples or cell lines, which show varying degrees of *HER2* amplification.[14] PPV and NPV refer to the proportion of patients who test positive and negative, respectively, by the NGS assay, who also have (or do not have) *HER2* amplification when measured by evidentiary standard tests, a widely accepted orthogonal test, or subsequent established technologies. PPV = A/(A + B), NPV = D/(C + D). PPV and NPV depend on the prevalence of *HER2* amplification in the tested population. For an NGS assay with a given analytical sensitivity and specificity, PPV will be poorer if *HER2* amplification prevalence is lower and NPV will be poorer if *HER2* amplification prevalence is higher. Poorer PPV and NPV will result in a greater chance of incorrectly classifying a patient as having *HER2* amplification when they do not (false positive), or not having HER2 amplification when they do (false negative) and can result in incorrect trastuzumab recommendations, poorer clinical outcomes, and wasted resources.
FISH, fluorescent *in situ* hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NGS, next-generation sequencing; NPV, negative predictive value; PPV, positive predictive value.

SISH)[15,16] to select patients for trastuzumab. IHC and FISH/SISH are considered 'evidentiary standard' tests as they were used in pivotal RCTs to identify HER2-positive patients and demonstrated the survival benefit of adding trastuzumab to chemotherapy in these cancers ('clinical validity'). However, when using a different test, such as an NGS assay, concordance with these evidentiary standards should be assessed to determine reliability of results ('analytical validity', Table 2). When discordance exists, and the evidentiary standard is considered the best available indicator of the true biological state, accuracy measures are useful for assessing the performance of the different test. However, when technology has advanced following the pivotal treatment trial, the new test may be considered a more valid measure of the biological target, and accuracy measures are not clinically interpretable. However, assessment of discordance is important for transparency because treatment evidence for cancers defined by the evidentiary standard alone is being transported to a different cancer type defined by a different test, introducing some uncertainty about the size of clinical benefit for the NGS-defined patients.

Concordance of an NGS assay with IHC and/or FISH (IHC/FISH) can differ across cancers due to differences in biology, tumor sampling, and/or tissue processing techniques. The Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets assay is an NGS assay that has been analytically validated in breast and GE cancers,[17] and concordance was 97.1 and 78.8%, respectively, among cases amplified by IHC/FISH. For NGS assays, tumor content of sampled tissue and intratumoral heterogeneity (genetic diversity of tumor clones within a single patient) can affect test accuracy and may in part explain lower concordance in GE cancers. In GE cancers, samples obtained via endoscopic biopsy tend to be smaller and intratumoral heterogeneity more prevalent than in breast cancers (79%[18] *versus* 18% respectively[19]). Unlike NGS, IHC/FISH assays enable simultaneous tumor morphological assessment so that heterogeneity can be considered and invasive carcinoma (which should be assessed for *HER2* amplification) can be distinguished from *in situ* carcinoma and non-neoplastic tissue (which should not be included in *HER2* status assessment).

Concordance of different NGS assays with IHC/FISH developed by different laboratories may also differ. Performance characteristics such as the minimum tumor content required for an accurate test result and limits of detection, which refers to the lowest variant allele frequency that can be reliably detected can differ between NGS assays.

Prevalence of *HER2* amplification varies widely across different cancers, as outlined in Table 3. Differences in prevalence can also affect the usefulness of the same assay to identify the *HER2*-amplified population as illustrated in Table 4. For cancer types that have not yet been assessed in

Table 3. Overall cancer incidence and *ERBB2* amplification.

Cancer type	Estimated number of new cases in 2020	Crude Rate (per 100,000)	Frequency of *ERBB2* amplification (%)
Esophagogastric adenocarcinoma	604,100	7.8	15.8
Undifferentiated stomach adenocarcinoma	1,089,103	14.0	15.8
Cervical adenocarcinoma	604,127	15.6	13.0
Breast invasive carcinoma	2,261,419	58.5	11.5
Endometrial carcinoma	417,367	10.8	5.5
Bladder urothelial carcinoma	573,278	7.4	5.4
Pancreatic adenocarcinoma	495,773	6.4	4.9
Cervical squamous cell carcinoma			4.1
Colorectal adenocarcinoma	1,931,590	24.8	3.4
Esophageal squamous cell carcinoma			3.2
Ovarian epithelial tumor	313,959	8.1	2.3
Non-small cell lung cancer	2,206,771	28.3	2.1
Head and neck squamous cell carcinoma	1,116,546	14.4	2.1
Hepatocellular carcinoma	905,677	11.6	0.8
Prostate adenocarcinoma	1,414,259	36.0	0.4
Melanoma	324,635	4.2	0.3
Well-differentiated thyroid carcinoma	586,202	7.5	0.2
Renal clear cell carcinoma	431,288	5.5	0.2

All cancer incidences were obtained from 2020 data from the International Agency for Research on Cancer https://gco.iarc.fr/ and is based on organ of origin. Data for *ERBB2* amplification frequency were collected from cBioPortal from 10,953 patients/10,967 samples from 32 The Cancer Genome Atlas, Pan Cancer Atlas studies.

RCTs, studies assessing analytical validation of NGS may not even be performed.

Biomarker criteria

Have the criteria used to define HER2 positivity been assessed in the cancer type for off-label trastuzumab?. The criteria used to define *HER2* amplification on NGS may differ across different cancers. In uterine serous carcinoma (USC) and colorectal cancer (CRC), *HER2* amplification, defined as *HER2* gene copy number of six or more, was found to have perfect concordance with *HER2* amplification defined by standard criteria (2018 ASCO/CAP breast cancer criteria for USC and HERACLES Diagnostic Criteria for CRC).[20,21] However, studies in breast cancer showed the same cut-off did not have adequate sensitivity,[17] whereas a lower copy number cut-off of 3.2 or more was found to have 100% sensitivity and 98.5% specificity against standard criteria.[22] There are frequently no cancer-specific criteria to define HER2 positivity available for cancers outside established indications and decisions to use off-label trastuzumab for these cancers, based on criteria for other cancers involve further uncertainty of clinical benefit.

HER2 amplification should also be differentiated from *HER2* mutations. Somatic *HER2* mutations have been identified in all exons of the gene encoding various domains of the HER2 protein.[23] These mutations have been found in multiple cancers, with varying prevalence,[23,24] some

Table 4. Predictive values for an assay with 99% sensitivity and 95% specificity for *ERBB2* amplification across two tumor types with different prevalence rates.

	GE adenocarcinoma	Renal cell carcinoma
Prevalence of *ERBB2* amplification, %	15.8	0.2
Population, no.	1000	1000
Amplification, no.	158	2
No amplification, no.	842	998
TP, no.	156	2
FP, no.	42	50
TP plus FP, no.	198	52
PPV, %	79	4

FP, false positive; GE, gastroesophageal; PPV, positive predictive value; TP, true positive.

variants predicted as driver mutations while others passengers,[25] and in most cases have not been associated with concurrent gene amplification.[26–28] Unlike *HER2* amplification, which predicts trastuzumab sensitivity for established indications, *HER2* mutations are diverse, with some showing trastuzumab sensitivity, while others not, and some conferring trastuzumab resistance.[24,25] A single mutation may also confer differential sensitivity to trastuzumab and other anti-HER2 therapies.[29] Compared to *HER2* amplification, clinical studies testing anti-HER2 therapy for *HER2* mutations in various cancers are limited at present to a few small prospective studies and retrospective analyses and show wide-ranging results, raising uncertainty regarding targetability of *HER2* mutations for specific cancers.[23,30–32]

Biomarker actionability

How strong is the evidence supporting actionability of HER2 *amplification and off-label trastuzumab?* A biomarker is 'actionable' if treatment selection based on biomarker status improves clinical outcomes compared to decisions made without it. Actionability describes 'co-dependency' between biomarker and targeted treatment and is considered broadly across and between different cancers expressing the biomarker. The actionability of *HER2* amplification has been demonstrated in multiple prospective RCTs that showed adding trastuzumab to chemotherapy in breast,[6,7] advanced gastric/GE,[9] and advanced uterine serous cancers[10] resulted in a clinically meaningful survival improvement when compared with chemotherapy alone. However, in cancers where this evidence is not available, published frameworks, such as the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)[33] that rank biomarker-treatment matches into tiers according to strength of evidence, can be used to estimate the clinical value of *HER2* amplification to predict trastuzumab response and guide patient recommendations.[33–39] Applying ESCAT, evidence from the following sources may be adequate to support off-label trastuzumab: (a) retrospective biomarker analyses of clinical trials originally conducted in an unselected population show the *HER2*-amplified population have better clinical outcomes when trastuzumab is added to chemotherapy for the specific cancer type compared to the *HER2*-nonamplified population, or (b) non-randomized prospective clinical trials show increased tumor shrinkage with the addition of trastuzumab to chemotherapy in the *HER2*-amplified population, but it is not yet known whether this translates to increased survival. Where data are limited to preclinical models or computational ('*in silico*') studies predicting trastuzumab sensitivity, evidence is considered inadequate to recommend off-label trastuzumab as this may not translate to benefit in clinical studies.[40] Furthermore, relying solely on extrapolated evidence from established indications to infer universal actionability across all cancers is problematic. Actionability may differ between cancers due to differences in intratumoral heterogeneity, tumor microenvironment, and compensatory resistance mechanisms.

Natural history of biomarker-defined groups

Could better outcome of patients with HER2*-amplified cancers treated with off-label trastuzumab be due to a more favorable natural history rather than the trastuzumab effect?* Natural history, or prognosis, of a cancer population refers to the clinical outcomes experienced because of the biology of the cancer independent of treatment received. Although cancer-specific natural history is well-established, natural history of biomarker-defined subgroups may not yet be described. Pivotal trials showed median overall survival (OS) was longer in breast (20.3 months)[6] than in gastric/GE cancer (11.1 months)[9] in the control arms receiving cancer-specific chemotherapy and all patients with *HER2*-amplified tumors. *HER2* amplification can also affect natural history, but its prognostic effect

may differ across cancers. It is a poor prognostic factor in some cancers, such as breast cancer[41,42] and USC,[43] while studies are conflicting in others such as gastric/GE cancer.[44–46]

Understanding the natural history of the *HER2*-amplified subgroup within a specific cancer type is critical. It offers a default 'control' arm to estimate prognosis without trastuzumab when RCTs are not available and trastuzumab benefits are extrapolated from established indications, and for benchmarking clinical outcomes of off-label trastuzumab from single-arm studies. The critical question here is whether the better or worse outcome could be due to trastuzumab or prognosis associated with the *HER2*-amplified cancer type. Alternative sources of natural history data include retrospective biomarker analyses of RCTs, cohort studies, real-world studies, and disease registries. Limitations of these sources include confounding effects from other patient (e.g. age) and tumor (e.g. cancer stage) factors, differences in treatment assessment methods, and supportive treatments. In the absence of randomized comparisons, uncertainty regarding the magnitude of improvement from adding trastuzumab will remain.

Signals of trastuzumab activity

Are there signals of activity for off-label trastuzumab and what is the level of confidence that this will translate to clinically meaningful benefits? Even if scientific rationale exists that *HER2*-amplifed cancers are biologically similar across cancer types, evidence of off-label trastuzumab activity on surrogate endpoints in the cancer type of interest increases certainty to support extrapolation. Surrogate endpoints are endpoints used 'in lieu' of clinical endpoints because they are more easily measured on a scale to detect differences between treatment groups and/or can be measured earlier, thereby reducing sample size requirements and trial duration. Objective response rate and duration of response are widely used in targeted therapy trials, but these have been shown to correlate poorly with OS in most advanced cancer studies cautioning against overreliance on results based on these endpoints.[47–49] Surrogate endpoints used for extrapolation should ideally be validated in the cancer type considered for off-label trastuzumab to reliably predict clinical benefit of trastuzumab. As this may not be available, a surrogate validated in the established indication should be used. However, surrogates validated in one cancer may not be a valid surrogate in another and is a limitation of this approach. Thus, uncertainty regarding the validity of the surrogate used for off-label trastuzumab and confidence that results based on these endpoints will translate to clinical benefit will remain.

Similarity of safety profile

Is there evidence to suggest that the safety profile of off-label trastuzumab differs from established indications? It is frequently assumed that the safety profile of off-label trastuzumab is similar to the established indications. However, safety profile can differ across cancers. Trastuzumab used with anthracycline-containing chemotherapy in breast cancer showed greater cardiotoxicity in RCTs than chemotherapy alone (27% *versus* 8%), presumably due to additive cardiotoxic effects of anthracyclines.[6] Although trastuzumab added to anthracycline-free regimens in GE (6% *versus* 6%)[9] and USC trials (3% *versus* 0%),[50] showed no significant increase in cardiac toxicity compared to control therapy. In non-small cell lung cancer, greater cardiac toxicity (6% *versus* 0%) was observed when trastuzumab was added to chemotherapy *versus* chemotherapy alone, and it is hypothesized in this cancer, greater smoking history and/or cardiac risk factors may have contributed to this finding.[40]

The interaction between trastuzumab cardiotoxicity and other cardiac risk factors is likely to be important. Thus, other tumor-specific factors that can impact trastuzumab safety should be considered, such as environmental exposures (e.g. tobacco), organ-specific tumor burden, and residual toxicities from prior therapies. Combining trastuzumab with another cancer therapy adds another layer of complexity and uncertainty for safety.

Shared decision-making and informed consent

How should clinicians engage patients in shared decision making and facilitate informed consent for off-label trastuzumab? 'Off-label' therapy commonly refers to a drug used for an indication other than for which it was given market authorization based on judgments of adequate safety and efficacy by a relevant regulatory body.[51–53] The potential benefits and risks of off-label therapy are always best assessed in clinical trials. Generally, in the clinic, off-label therapy should only be considered when on-label therapies are exhausted, unavailable, or unsuitable for the patient.[52] Off-label therapy may be justified if

sufficient evidence exists to support a positive benefit-risk assessment. Assuming appropriateness of extrapolation has been assessed and the clinician has judged that sufficient evidence exists to support off-label trastuzumab, the clinician should engage the patient in SDM and facilitate adequate informed consent.

The legal doctrine of informed consent reflects the value placed on a patient's autonomy and a duty for clinicians to make 'disclosures which a reasonable medical practitioner would make under the same or similar circumstances' and what reasonable people would want to know about the prescribed treatment.[54–57] SDM refers to the presentation of this information by the clinician as options or choices for the patient and aims to arrive at a mutually acceptable decision based on shared knowledge and the patient's values and preferences.[56,58,59]

SDM and informed consent are particularly important for off-label treatment outside of a clinical trial because there are fewer safeguards and greater medical uncertainty. Potential uncertainties for off-label trastuzumab have been outlined under each extrapolation component.

Financial implications and out-of-pocket costs may be a barrier for access to off-label trastuzumab and should be discussed upfront.[52,60] The cost of off-label targeted therapies in general is very expensive (on average $120,000/year in the United States),[61] although loss of patent and use of generics can offset some of these costs.[53] Financial implications extend beyond the immediate out-of-pocket drug costs and include cost of tumor molecular profiling, supportive medications, toxicity management, costs to payers, such as insurers and/or hospitals who may bear a proportion of the costs, and eventually to taxpayers.[56,60] Costs can also have ethical implications and exacerbate access inequities to targeted therapies.[62] A more global approach involving health policymakers, payers, clinical trialists, practicing oncologists, and patients will be required to address the issue of cost for off-label therapy. Our framework will serve to provide the impetus for such discussions.

Clinicians should disclose that trastuzumab is being recommended off-label, discuss the rationale for off-label use, areas of uncertainty, and financial implications alongside existing evidence for any alternative therapies. This discussion and ultimate decision should be documented in a written informed consent.[52]

Conclusion

We have presented a systematic approach for appraising evidence to extrapolate trastuzumab benefits from established indications to off-label use. Criteria for extrapolation, potential reasons and an approach for judging uncertainty, and discussion points to facilitate SDM and informed consent are outlined. *HER2*-amplified cancers were chosen to illustrate framework application, as much work has been done to understand diagnostic tests, prognosis, and biomarker actionability across diverse cancers. This work is a practical approach for clinicians to guide discussions with multidisciplinary teams and potentially apply them in routine practice. It is potentially generalizable to other biomarker-targeted therapy matches and should be considered by MTBs who make off-label recommendations.

Declarations

Ethics approval and consent to participate

Ethics approval and informed consent was not required for this study as it did not involve human or animal participants. All data used in our study were obtained from publicly available published studies.

Consent for publication

Not applicable.

Author contribution(s)

Doah Cho: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Sarah J. Lord: Conceptualization; Investigation; Methodology; Supervision; Writing – review & editing.

John Simes: Conceptualization; Funding acquisition; Supervision; Writing – review & editing.

Wendy Cooper: Conceptualization; Methodology; Supervision; Writing – review & editing.

Michael Friedlander: Conceptualization; Writing – review & editing.

Susie Bae: Conceptualization; Writing – review & editing.

Chee Khoon Lee: Conceptualization; Investigation; Methodology; Supervision; Writing – review & editing.

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