# From evidence-based medicine to clinical practice: not always straightforward

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## Introduction

When selecting among options for management of a patient with malignant disease, the oncologist will usually recommend a treatment that has undergone prior investigation in one or more clinical trials. If well-performed clinical trials have been undertaken on patients with similar characteristics to the one in his or her consulting room, then that recommendation should be for a treatment that has been shown to lead to therapeutic benefit compared with possible alternatives. Especially for common scenarios such as choice of adjuvant post-operative treatment for a woman with breast cancer, that treatment decision may be supported by evidence-based guidelines, in which the available evidence has been reviewed critically by a group of fellow oncologists. Or it may be facilitated by an overview analysis where several trials have been combined to give estimates of benefit and risk that are based on large number of participants in clinical trials.

Quite often, however, recommendations for management of a patient have to be made on the basis of imperfect evidence. Either clinical trials have provided relatively low-level evidence (see Table 1) for or against a particular strategy of management, or the available clinical trials have not been performed to rigorous standards. Alternatively, clinical trials that address the situation confronted by the oncologist may not have been done. Even if trials have been undertaken there may be questions about their relevance to a less selected group of patients. To enter a clinical trial a patient may be required to have a certain level of performance status, or of kidney or liver function, leading commonly to exclusion of a substantial percentage of patients with the disease and stage for which the trial was designed. How then to manage the patient with biochemical abnormalities, or with different characteristics from patients included in a clinical trial? Interpreting the available evidence to make appropriate clinical decisions is not always straightforward. In this paper, I will try to suggest some guidelines for interpreting the results of clinical trials using examples from common clinical situations.

Table 1
Levels of clinical evidence [a]

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|---|---|
| Level I | Adequately powered, high quality randomised trial, or meta-analysis of randomised trials showing statistically consistent results |
| Level II | Randomised trials inadequately powered, possibly biased, or showing statistically inconsistent results |
| Level III | Non-randomised studies with concurrent controls |
| Level IV | Non-randomised studies with historical controls (i.e. typical single arm phase II studies) |
| Level V | Expert committee review, case reports, retrospective studies |

[a] Adapted from others, following discussion between Buyse, Bentzen, Tannock and Therasse (May 2003).

## Should I change treatment in the face of a positive trial?

The following question arises frequently in the minds of oncologists: "A clinical trial is published (or presented at a meeting) that suggests that a new treatment is better than the standard one that I am currently recommending to my patients. Should I change my practice and recommend the new treatment?" In considering this question, the oncologist might consider the following checklist.

(1) What is the level of evidence provided by the trial?

Levels of clinical evidence have been discussed above both by Bentzen [1] and Therasse [2], and are summarised in Table 1. For common diseases only large randomised controlled trials (RCTs) should be considered a basis for changing practice, and the ele-

ments of a good phase III trial design have been reviewed above by Buyse [3]. However, there are many situations in oncology — for example management of patients with rare tumours, unusual presentations of those with common tumours, or patients with comorbidity — where level I evidence is not available, and clinical decisions have to be made on imperfect evidence.

There is an increasing trend for the development of evidence-based guidelines, which can assist in selecting from among various options for therapy in relatively common situations. Guidelines have been produced in Ontario, Canada, in France, by the American Society of Clinical Oncology (ASCO) and by other organisations; they involve a careful review of the evidence followed by feedback from practitioners [4–6]. Evidence-based guidelines should not be confused with consensus statements. Consensus that is not based on a comprehensive review of evidence has little value. There was, for example, reasonable consensus in the United States that high-dose chemotherapy with stem cell transplantation was the preferred treatment for some patients with breast cancer, but this was shown subsequently to lead to similar survival to conventional therapy with increased toxicity. A cynical opinion is that *"The agreement of experts is responsible for all the medical errors of history"*.

(2) Does the trial have internal validity? (Is the trial of high quality?)

Several publications have addressed the requirements for interpreting the quality and rigour of clinical trials, including the preceding chapters of this section [1–3,7–9]. Some of the more important considerations are the following.

*(i) Did the trial address a clinically important question?* Randomised clinical trials should, in general, compare an experimental with a standard treatment. Sometimes there may be difficulty in establishing the standard of care, and hence in defining which questions to address in clinical trials [10]. A more common problem, particularly for trials that may be sponsored by pharmaceutical companies, is a comparison of two non-standard treatments. An example of the latter was the trial that led to the registration of granulocyte colony-stimulating factor (G-CSF) in the US. In this trial, chemotherapy for small cell lung cancer using an aggressive schedule of cyclophosphamide, doxorubicin and etoposide was compared with the same chemotherapy plus G-CSF. The trial showed that the rate of septic neutropenia was reduced by G-CSF from 57% to 28%, with a corresponding reduction in hospitalisation that offset the added cost of the drug [11]. However, the trial was flawed because there is no evidence that this aggressive chemotherapy was superior to standard treatment with cisplatin and etoposide, which gives a lower rate of infectious complications than in either of the arms of the above study.

*(ii) Was a primary and relevant endpoint defined and was the main analysis applied to the primary endpoint?* It is surprising how often-published clinical trials have failed to indicate the primary endpoint even if published in high impact journals [12]. Most trials have a sample size that is at most sufficient (in statistical terms *"powered"*) to address a single primary endpoint, and analysis of secondary endpoints should be regarded as exploratory and hypothesis generating (also discussed above by Buyse [3]). In phase III trials, the primary endpoint should be an index of benefit to patients (see below). Oncologists must be particularly wary of trials that emphasise secondary endpoints or subgroup analyses that can appear positive simply because of chance. An illustration of how subgroups can be misleading can be found in the two original trials that established 5-fluorouracil-based chemotherapy as adjuvant treatment for Dukes' C colon cancer [13,14]. Although their overall results were concordant in demonstrating a survival benefit for adjuvant therapy, in one of them the effect was greater in older patients and men, and in the other in younger patients and women.

It is also important that all endpoints, including the primary and pre-established secondary endpoints, be evaluated stringently and with low probability of measurement error. This is not usually a problem with survival, provided that an intention-to-treat analysis is used and all patients are accounted for. It is a frequent problem for less well-defined endpoints such as response rate or time to progression. These endpoints can be manipulated to inflate the apparent value of a new treatment by excluding patients who do not receive a certain number of courses and/or by the presence of measurement error from using non-stringent criteria to define tumour response or progression [7,15]. It is particularly disturbing to witness the re-introduction of endpoints such as *"minimal response"* and *"stable disease"* in trials of biological therapies, when it was shown two decades ago that these were so subject to measurement error as to be almost worthless [16,17].

*(iii) What is the probability that the results of the trial are falsely positive?* False positive trials are common, especially if sample size is relatively small, multiple endpoints are used, the result is unexpected, and the level of significance is borderline. Factors that contribute to false-positive trials include statistical artefacts from multiple comparisons (including subgroup analyses); publication bias (the bias to pub-

lish, or to present at a meeting, results with apparently positive results); and the low prior expectation of a positive result [12]. The problems of multiple analyses and of publication bias are understood by most oncologists; we have shown recently that there is evidence of non- or delayed publication for even large randomised trials in oncology, if their results appear negative [18]. Fewer oncologists are aware that if the expectation of a positive result for a particular trial is rather low, then a single positive trial has a high chance of being false-positive [19]. For this reason, trials showing benefit of a new treatment should generally be repeated before that treatment becomes accepted as a standard of care. Repetition of the trial showing benefit of 5-FU and levamisole as adjuvant treatment for Dukes' Stage C colon cancer (an unexpected result for most oncologists at the time) is a good example of verification of an important result [13,14].

*(iv) Does the report reflect the results of the trial?* It is still relatively common to find a concluding statement in the abstract of the paper that does not apply to the primary endpoint, or does not reflect the results that were obtained. The oncologist should be particularly wary of such statements in papers describing trials purporting to show advantage to a product marketed by the sponsor.

(3) Does the trial have external validity?

The oncologist should ask whether the results of the trial are biologically plausible, and whether they are consistent with clinical experience and with the results of related trials? If so, the trial has external validity. If not, the trial is likely to be falsely positive, and may achieve prominence as a result of publication bias. Some trials may give unexpected results, which are shown ultimately to be valid. However, as stated above, such results need verification in a second independent trial.

(4) Does the trial really show therapeutic benefit? Benefit to patients implies that:

*(i) The primary endpoint is a measure of patient benefit.* Measures of patient benefit include overall survival or a well-defined measure of symptoms or quality of life. Response rate, time to progression, and disease-free survival are not measures of patient benefit, although they may correlate with benefit if the treatment is well-tolerated. However toxic treatments that lead to improvements in any of these three endpoints may not produce clinical benefit for patients.

*(ii) There is improvement in therapeutic index.* All clinical trials of cancer therapy should report toxicity in a critical and objective fashion; they should recognise that unusual types of toxicity (e.g. myocardial infarction, severe fatigue) may result from the treatment. Ideally, all phase III trials should include a validated measure of quality of life. A small improvement in survival may not be judged beneficial if there is high toxicity and a decrease in quality of life.

*(iii) The demonstrated effect is clinically important.* Clinically important has a different meaning to statistically significant. Very small but statistically significant gains in endpoints that do not represent patient benefit have been used, for example, to promote expensive and toxic drugs.

There is confusion among oncologists about the magnitude of effects that are described in clinical trials, which result from alternative methods for presenting the data. For example, adjuvant chemotherapy given to pre-menopausal women with breast cancer may reduce the hazard ratio for death by 25% (an impressive number). However, when applied to women with node negative disease this hazard ratio may lead to an absolute gain in survival at 10 years of only about 4%, and a need to treat a large number of women in order to save one life [20]. Questionnaires sent to doctors have indicated that they would change treatment based on the results of a clinical trial if presented with an (impressive) hazard ratio, but would be successively less likely to do so when the *same results* are presented as a (small) gain in absolute survival, or a (very large) number of patients who need to be treated to save a life [21]. In a previous study, we asked oncologists how large a difference in relapse-free or overall survival they would require to offer adjuvant therapy to patients with breast cancer. The median requirement was greater than shown in the overview analysis, although almost all of the respondents were offering such treatment [22]. Most patients who are prescribed relatively toxic treatment state that they are willing to accept it for very small gains in survival [23]. However, those who are not offered such treatment would require much larger gains in survival to accept treatment, suggesting that this is more reconciliation to a treatment decision rather than an objective assessment of risk and benefit [24].

(5) Are the results relevant to my practice?

Clinical trials are often undertaken in major cancer centres. In such centres, there may be a bias to refer patients with certain characteristics, and there may be resources (house-staff on call, multi-disciplinary care) that allow aggressive and complex treatments to be given with relative safety. It is therefore important to ask whether patients included in the trial are representative of those seen by the oncologist who is posing the question about benefit to his or her patients? Also important is whether they (or their hospital) have the expertise to apply the therapeu-

tic intervention? There is substantial evidence, especially for surgical procedures, that outcome relates directly, and toxicity indirectly, to the experience of the doctor and the hospital [25].

Many trials have quite restrictive eligibility criteria, such as a requirement for good performance status. There is a tendency to offer treatments that are shown to be superior in such trials to patients with the same disease, who would not have fitted the eligibility criteria. For example, the trials showing survival benefit of undertaking nephrectomy in patients with metastatic renal cancer recruited only patients with ECOG (Eastern Cooperative Oncology Group) Performance Status 0 or 1 [26,27]. There is no evidence that such surgery would benefit patients with lower performance status.

One indication that results might be biased towards a subset of patients is where trials for patients with common diseases take a long time to meet their accrual goals. One should be cautious about applying the results of such trials because there may be strong selection bias that limits the relevance of their results.

## Should I change treatment in the face of an equivalence trial?

An alternative question posed in the minds of oncologists, albeit less frequently than that described above, is the following: *"A clinical trial compares treatment that I currently recommend for my patients with treatment that appears to be less toxic and/or cheaper. Should I adopt the alternative treatment?"*

Many of the same questions apply to this trial as to the one discussed in the previous section. The level of evidence, internal and external validity and relevance are all equally important. However, here one needs to ask if the trial really shows equivalence, or if it could be a false negative trial. False-negative trials occur commonly because the sample size is inadequate to demonstrate a clinically important difference in outcome between the treatment arms — in statistical terms the study is *under-powered.* As described above by Bentzen [1] and by Buyse [3], failing to detect a difference in outcome is not the same as proving that a difference does not exist. Showing that two treatments differ by a minimal amount requires very large trials.

## Making clinical decisions with imperfect evidence

Unfortunately, the majority of decisions in clinical medicine are made on the basis of rather low levels of evidence. A frequent question that arises in oncology, especially in the treatment of rarer tumours, or rarer presentations of less common tumours is the following: *"There is a new treatment that appears superior to the treatment that I am recommending in trials that provide lower levels of evidence (small randomised or non-randomised trials). In the absence of large randomised trials how should I treat my patients?"*

There is no simple answer to this question. It will depend on the weight of evidence (multiple small or non-randomised trials showing consistent results should carry more weight than an isolated result from a single trial), on biological and clinical plausibility and on the apparent ratio of benefit to toxicity of the new treatment. Perhaps the best advice to colleagues is to be open-minded and flexible — discuss the available evidence with patients, admit to them that there is uncertainty and involve them in the clinical decision making. Be prepared to change your practice if new and better evidence emerges.

## Published trials versus those presented at meetings

Many trials are first presented at meetings such as ASCO or ECCO (European Cancer Conference), and some of the problems from using such information in clinical practice have been reviewed above by Bentzen [1]. The available information consists most often of a 200-word abstract, often written hurriedly to meet a deadline and therefore subject to rather minimal verification of the data. The presentation may provide more details but has not undergone the rigorous peer-review process that is provided by most journals. There is bias to select abstracts describing positive trials for presentation (especially oral presentation), although some negative trials with delayed or non-publication are presented at meetings [18,28]. Sometimes there are substantial differences in the report of the abstract and the subsequent full publication of the trial [29].

For all of the above reasons, oncologists should avoid basing clinical decisions on early reports of trials presented at meetings, or on the abstracts that describe them. If the results of a clinical trial are of such importance that they should lead to change in clinical practice, most high impact journals now have mechanisms for accelerated publication. Advances in oncology are rarely of sufficient magnitude that delaying the institution of a new treatment is of serious concern. Loss of benefit to a few patients is almost certainly counterbalanced by gains to others from not applying premature results in their treatment.

## Examples of the application of evidence to clinical practice

The wisdom of hindsight is great and in this section I will provide initially a few examples where therapies were introduced that were shown subsequently to be inappropriate. It is important to gain insight into the reasons for these faulty decisions, and to try to prevent them from recurring. I will then review some current trials and present arguments for and against making changes in treatment policy.

### *Learning from history — why did we make wrong decisions?*

Several examples of the adoption of new therapies on the basis of inadequate evidence have been reviewed by Therasse [2]; these include the widespread use of high-dose chemotherapy with stem-cell transplantation for breast cancer and intensive chemotherapy (compared with the standard CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen) for non-Hodgkin's lymphoma (NHL). Both of these examples were supported by several phase II trials, which made the subsequent conduct of randomised phase III studies rather difficult. A substantial number of oncologists expressed the opinion that the benefits of more aggressive chemotherapy were so obvious that it would be unethical to subject patients to the control arms of randomised trials. In the above examples, the phase III trials were undertaken, they showed no difference, and the body of opinion was shown to be wrong. It is now widely accepted that future variants of these strategies should only be investigated in well-designed clinical trials and that reproducible results in phase III trials will be required to change practice.

It is easy to adopt the superior attitude of the rigorous investigator in the above scenarios *"How could you have been so misled by results for selected patients in single arm trials?"* However, it is equally important to point out the example of cisplatin-based chemotherapy for patients with metastatic testicular cancer where changes in practice were made on the basis of phase II data, and where phase III trials would have been unethical because of denial of effective treatment to patients on the control arm. What are the differences between this scenario and those described in the preceding paragraphs? One difference is the magnitude of effects in the phase II trials of cisplatin-based chemotherapy for testicular cancer — these were really results akin to the discovery of penicillin. Such advances occur rarely in oncology. Secondly, testicular cancer is a relatively rare disease that affects mostly young and otherwise healthy individuals. Thus, although the therapy has substantial morbidity, the patients in the phase II trials were minimally selected — quite different to patients with breast cancer selected for high-dose chemotherapy and stem-cell transplantation or those with NHL selected for trials of aggressive chemotherapy.

Helpful studies that led to a more appropriate perspective on the (lack of) benefit of stem cell transplantation for breast cancer were those that described the stringent selection for the clinical trials, and the stage migration that occurred [30–32]. It was demonstrated that if subgroups of patients who receive standard therapy were selected by the same rigorous criteria as those receiving high-dose therapy and stem-cell transplantation, they had comparable survival (equally enhanced compared to unselected historical controls). Thus studies of selection bias may be helpful in the rare situation that a new treatment emerges that appears to give a quantum advance in outcome. A new treatment that might fall into this category is imatinib mesylate (Gleevec, STI571, Glivec) for chronic myelogenous leukaemia (CML) and gastrointestinal stromal tumours (GISTs). Here a randomised trial comparing imatinib mesylate with standard therapy for CML was completed quickly (it accrued 1106 patients in 7 months [33]) and probably succeeded because for many patients the drug was only available if they participated in the trial. A 50% chance of receiving imatinib mesylate was better than none (although this raises major ethical questions). Ongoing randomised trials for patients with GISTs may be threatened by refusal to accept the control arm. Despite the level of evidence currently available, this may be appropriate given the marked improvement in responsiveness of patients with this rare disease compared with treatment with any previous agents [34]. How many oncologists would accept alternative therapy in a randomised trial for themselves or their families?

An ethical requirement for undertaking a randomised trial is that there be equipoise for the options presented, that is either arm should be equally likely to be better. The high proportion of negative trials suggests that equipoise may apply to many situations in oncology [35], but in the above situations (such as high-dose chemotherapy and stem-cell transplantation for breast cancer), equipoise does not or did not exist. As indicated previously, the consensus of experts is often proven wrong by subsequent evidence; the studies of selection bias helped to restore a measure of equipoise to the trials of stem cell transplantation for breast cancer. There will be only very rare situations where phase II data should be used to change practice.

*Small randomised trials and high-impact journals*

Two small randomised control trials (each randomised 60 patients), published in the *New England Journal of Medicine* and the *Journal of the National Cancer Institute*, suggested marked improvement in survival when patients with operable non-small cell lung cancer were treated with pre- or peri-operative chemotherapy [36,37]. These journals are respectively those with the highest impact factor in clinical medicine and in oncology. The trials did not introduce new drugs, and there are multiple other larger trials, and a patient-based meta-analysis [38] that failed to show significant benefit of chemotherapy added to surgery. Both of the above trials therefore had poor external validity. They also had poor internal validity because of their small sample size (and some other problems in design and analysis). Despite this, they had a huge impact in their field, leading many oncologists to prescribe chemotherapy prior to surgery for lung cancer.

These trials represent an extreme example of publication bias: because of their publication in prominent journals they had a much greater impact on oncological practice than was appropriate. This fault lies less with the authors (most of us will submit to high impact journals if there is a reasonable chance of publication) than with reviewers and editors. It is important that all evidence be reviewed objectively as described in this paper and others in the session, and not be influenced by site of publication. Chemotherapy as an adjunct to surgery for non-small cell lung cancer remains experimental.

*Weighing the evidence from some current trials*

*(Neo)adjuvant chemotherapy for muscle-invasive bladder cancer*

Two recent randomised trials of adding chemotherapy prior to local therapy for bladder cancer show somewhat conflicting results, one showing significant benefit compared with local therapy alone and the other not. The MRC/EORTC-led international trial randomised 976 patients to 3 courses of cisplatin, methotrexate and vinblastine (CMV) prior to local therapy (surgery, radiation or both) and reported a trend to improved survival that did not reach predetermined levels of benefit required to adopt the therapy [39,40]. The absolute difference in survival at 5 years is 6%. An American trial took many years to randomise 317 patients to 3 courses of MVAC (same drugs as CMV + doxorubicin) and has reported at the ASCO meeting a significant difference in survival, but used one-sided statistics [41]. A recent patient-based meta-analysis that includes 2688 patients indicates about 5% improvement in absolute survival with neoadjuvant chemotherapy [42]. Case series of patients with node-positive disease or other very aggressive features have also indicated outcomes that are "considerably better than prior experience" with added chemotherapy. Important questions for oncologists are:

1. Should neoadjuvant chemotherapy be the standard of care for patients without contraindications to receiving it?
2. Is it appropriate to enter patients in the ongoing large international trial (led by EORTC) that compares adjuvant chemotherapy after cystectomy with cystectomy alone?

There is no simple answer to either of these questions. The American trial undoubtedly has selection bias, but the common trends in the two large randomised trials (and in the patient-based meta-analysis) provide convincing evidence that there is at least a small benefit from adding modern chemotherapy to local treatment. Moreover, the result is biologically plausible since bladder cancer is quite sensitive to chemotherapy (more so than breast cancer; there are rare patients who achieve cure even when treated for metastatic disease). Also the combination of gemcitabine and cisplatin now provides considerably less toxic chemotherapy that appears equally effective, at least for treatment of advanced disease [43]. Thus the question relates less to whether there is benefit, and more to whether the level of benefit outweighs the toxicity of chemotherapy.

A reasonable but not unique approach (the one that we have adopted) is the following:

1. All patients fit to receive chemotherapy are informed about the available evidence, and have the right to receive it or not if they so choose.
2. Patients with more aggressive disease (positive nodes, lymphovascular invasion) are encouraged to undergo chemotherapy.
3. Patients who are ambivalent (the majority) are informed about the ongoing trial and encouraged to participate.

*Adjuvant hormonal therapy for postmenopausal patients with breast cancer*

A substantial number of large randomised trials, and the overview analysis based on many thousands of patients has established 5 years of adjuvant tamoxifen as standard treatment for almost all postmenopausal women with hormone-responsive breast cancers. The (substantial) benefits and (relatively minor) toxicities of this treatment are probably known with greater precision than for almost any

other therapy in the field of medicine. The large three arm ATAC trial (more than 9000 patients were randomised), introduced above by Buyse [3], now presents data which indicates that the aromatase-inhibitor anastrazole gives superior relapse-free survival compared with tamoxifen (or to the combination of the two drugs) for such patients [44]. Should this now be the new standard of care?

Relevant considerations here are that:

(i) ATAC is a single trial, albeit a very large one
(ii) Follow-up is relatively early and there is as yet no difference in survival
(iii) Anastrazole appears even better tolerated than tamoxifen, with less side effects in most areas, but there is greater bone-loss
(iv) The poor result in the combined arm was unexpected (although biological arguments have been advanced, *post-hoc*, to explain it)
(iv) Anastrazole is considerably more expensive than tamoxifen.

Based on the above considerations, a committee convened by ASCO weighed the evidence and produced a guideline that tamoxifen should remain the standard of care pending further follow-up and the results of other ongoing trials. However, patients with particular risks from tamoxifen (such as a history of thromboembolic disease or predisposing factors such as hypertension or diabetes) should be offered anastrazole. This guideline seems reasonable, and we use it; however, we do not refuse anastrazole to patients who wish to take it after being informed of the above data.

*Adjuvant chemotherapy for patients at high risk of recurrence of breast cancer*

The first results of a large (2005 patients) randomised trial from the CALGB (Cancer and Leukemia Group B) were reported recently to show improved disease-free and overall survival for patients with breast cancer who received accelerated chemotherapy (cycles at 2 week intervals with growth factors [45]). The trial also reported that such treatment could be given without added toxicity. Should this be the new standard of treatment?

The issues here are rather different. Follow-up is short, and although differences appear to be statistically significant they are small. The result is biologically plausible — if you can give chemotherapy with shorter intervals between courses there is likely to be less repopulation of surviving tumour cells and greater net cell kill [46]. However, external validity is lacking since trials of more aggressive chemotherapy above the normal range have not, in general, had a major effect on outcome. There is also the precedent of a former CALGB trial which compared four courses of doxorubicin/cyclophosphamide with or without subsequent paclitaxel that showed very promising results initially, but which have become less impressive with longer follow-up, and which may not be reproduced in other trials [47,48]. The above considerations would argue against early adoption of this accelerated treatment as standard therapy.

## Concluding remarks

This paper and the ones that preceded it in this session have tried to give indications as to how to review the available evidence from existing and new clinical trials to arrive at optimal strategies for treating patients. The above examples may be used to illustrate the process of weighing evidence from clinical trials, but there are few right or wrong answers. What is important is that the evidence is weighed carefully and logically, that uncertainty is recognised, that patients are informed and take part in the decision process, and that flexibility is maintained.

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