Proportion of patients needing an implantable cardioverter defibrillator on the basis of current guidelines: impact on healthcare resources in Italy and the USA. Data from the ALPHA study registry

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Aims
Implantable cardioverter defibrillators (ICD) improve survival in selected patients with left ventricular dysfunction or heart failure (HF). The objective is to estimate the number of ICD candidates and to assess the potential impact on public health expenditure in Italy and the USA.

Methods and results
Data from 3513 consecutive patients (ALPHA study registry) were screened. A model based on international guidelines inclusion criteria and epidemiological data was used to estimate the number of eligible patients. A comparison with current ICD implant rate was done to estimate the necessary incremental rate to treat eligible patients within 5 years. Up to 54% of HF patients are estimated to be eligible for ICD implantation. An implantation policy based on guidelines would significantly increase the ICD number to 2671 implants per million inhabitants in Italy and to 4261 in the USA. An annual increment of prophylactic ICD implants of 20% in the USA and 68% in Italy would be necessary to treat all indicated patients in a 5-year timeframe.

Conclusion
Implantable cardioverter defibrillator implantation policy based on current evidence may have significant impact on public health expenditure. Effective risk stratification may be useful in order to maximize benefit of ICD therapy and its cost-effectiveness in primary prevention.

Keywords
Heart failure • Implantable cardioverter defibrillator • Public health expenses

Introduction
Several clinical trials have shown that implantable cardioverter defibrillators (ICD) improve survival in the primary prevention of sudden cardiac death (SCD).1–6 As Moss showed in a meta-analysis,7 the overall hazard ratio in seven ICD primary prevention trials was 0.72, a value indicating a 28% reduction in the risk of death in the ICD arm in comparison with conventionally
treated patients, with an overall absolute 2-year mortality reduction of 3.0 percentage points. Nevertheless, the survival benefit was quite different among the trials, ranging from a statistically significant 54% mortality reduction to a non-significant 8% increase. This different benefit has prompted debate as to who are the best candidates for ICD implantation among patients with heart disease and left ventricular dysfunction. Debate about ICD eligibility is common in published research and on hospital wards, particularly if only clinical data and left ventricular ejection fraction (LVEF) are used in the selection of ICD candidates, without additional non-invasive/invasive risk markers. The major trials focused on the issue of SCD prevention by means of ICD (MADIT-II, SCD-HeFT, COMPANION) demonstrated effectiveness, safety, and cost-effectiveness of ICDs in primary prevention and have driven the most recent updates of guidelines for ICD implantation. However, little information is available about the proportion of patients with left ventricular dysfunction who would be eligible for an ICD for the primary prevention of SCD in clinical practice, a particularly important point in policy making.

The aims of the present study, based on data coming from the Registry of the T-wave Alternans in Patients with Heart failure (ALPHA) study and available epidemiological information, were: (i) to assess the number of patients, in Italy and in the USA, with left ventricular dysfunction, both with and without heart failure (HF), potentially candidate for ICD implantation if eligibility is based on current international guidelines; (ii) to compare the clinical characteristics of patients potentially eligible for device implantation in the registry with clinical profiles of the MADIT-II, SCD-HeFT, and COMPANION trial participants; (iii) to estimate in a 5-year timeframe the annual incremental rate of ICD implantation procedures necessary to treat all eligible patients, according to international guidelines, in Italy and the USA, and the budget implications from the perspective of each country’s government.

### Methods

#### Patients eligible for implantable cardioverter defibrillators implantation

The sample considered in the present analysis comes from the registry of the (ALPHA) study. Design and the main results of the study have been published elsewhere. Patients screened from April 2001 to July 2004 at the HF clinics of nine Italian hospitals (n = 3513) were entered in the ALPHA registry. The screening procedure considered all consecutive patients who were visited at the HF clinics during routine follow-up for HF treatment. A screening log was used to collect basic information on the registry population; no criteria were defined to exclude patients from being entered in the screening log. The variables collected in the registry were: gender, age, QRS complex and PR interval duration, New York Heart Association (NYHA) functional class, LVEF, and aetiology of cardiomyopathy.

Given the selection criteria of international guidelines and of MADIT-II, SCD-HeFT, and COMPANION trials, we classified patients as eligible for an ICD according to the inclusion criteria listed in Table 1. Clinical and demographic variables of patients in the registry who fitted the inclusion criteria reported in Table 1 were compared with those of the populations enrolled in the ICD arm of MADIT-II, SCD-HeFT, and COMPANION trials.

### Table 1 Inclusion and exclusion criteria available and applied to the ALPHA study registry

<table>
<thead>
<tr>
<th>Trial</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT-II (2002)</td>
<td>Age &gt; 21 years</td>
</tr>
<tr>
<td></td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td></td>
<td>NYHA class I–III</td>
</tr>
<tr>
<td></td>
<td>LVEF ≤ 30%</td>
</tr>
<tr>
<td>COMPANION (2004)</td>
<td>NYHA class III or IV</td>
</tr>
<tr>
<td></td>
<td>Ischaemic or non-ischaemic aetiology</td>
</tr>
<tr>
<td></td>
<td>LVEF ≤ 35%</td>
</tr>
<tr>
<td></td>
<td>QRS ≥ 120 ms</td>
</tr>
<tr>
<td></td>
<td>PR interval &gt; 150 ms</td>
</tr>
<tr>
<td></td>
<td>Sinus rhythm</td>
</tr>
<tr>
<td></td>
<td>No clinical indication for PM or ICD</td>
</tr>
<tr>
<td>SCD-HeFT (2005)</td>
<td>Age ≥ 18 years</td>
</tr>
<tr>
<td></td>
<td>LVEF ≤ 35%</td>
</tr>
<tr>
<td></td>
<td>NYHA class II–III</td>
</tr>
<tr>
<td></td>
<td>Ischaemic or non-ischaemic aetiology</td>
</tr>
<tr>
<td>CURRENT GUIDELINES (2007)</td>
<td>NYHA class ≥I</td>
</tr>
<tr>
<td></td>
<td>Ischaemic or non-ischaemic aetiology</td>
</tr>
<tr>
<td></td>
<td>LVEF ≤ 30–35%</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Age &gt; 80 years</td>
</tr>
<tr>
<td></td>
<td>Low life expectancy (&lt;1 year)</td>
</tr>
</tbody>
</table>

ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PM, pacemaker.

The total number of potential candidates to ICD in Italy and the USA was estimated by calculating the proportions of patients in the ALPHA registry who fitted the inclusion criteria of current guidelines (NYHA class ≥I, LVEF < 30–35%). and excluding those who also fitted selected exclusion criteria (Table 1); the resulting proportion was applied to the number of HF prevalent and incident cases retrieved from literature (Table 2). National data on prevalence and incidence were used to estimate the total number of HF cases in the USA among the adult population, whereas European epidemiological data were used for Italian estimates, in the absence of national data. We assumed that the sample data entered in the ALPHA registry well represent characteristics of patients affected by HF. A list of exclusion criteria have been applied to better represent patients needing an ICD: proportion of older patients (>80 years) and of those with a life-expectancy inferior to 1 year because of non-cardiac co-morbidities were estimated among the HF population who met the inclusion criteria and applied to prevalent and incident cases as specific exclusion criteria (Table 2). Additionally, an estimate of the total number of patients who already underwent ICD implantation for primary prevention in the previous years and were still alive, representing the proportion of patients already treated, were excluded. Alive patients with an ICD were estimated considering data on first ICD implantations for primary prevention available in the national registries from years 2000 to 2007 in Italy and the USA and assuming from literature and a recent systematic review a mean mortality rate per year. The budget impact analysis

Given the total number of estimated patients to be potentially treated, a measure of total costs affordable from the National Health Systems has been calculated. Italian and US National Health System data (Italy: DM 30.06.1997, DRG 105; USA: ICD US DRG— grouper version 24.0, and average cost of Medicare in 2005, DRG 515) were used to estimate an ICD national implantation...
reimbursement rate in Italy (€15 493.71) and the USA ($36 593 for ICD without cardiac catheters). In order to be adherent to a real-life environment, we considered that all patients who need to be treated according to this estimate cannot be implanted with an ICD within a year. Consequently, we assumed that the potential growth of ICD implants per year for primary prevention in a 5-year time frame could increase according to the mean incremental rate of prophylactic ICD implants observed in the last 2 years in Italy and the USA.

The number of eligible patients per each year in the selected 5-year time frame was calculated by adding the new eligible incident cases to prevalent cases, subtracting already treated patients in the previous year and adjusting the result by an annual estimate of all-cause mortality in ICD recipients.

Sensitivity analyses were conducted to test how several factors would affect basal results. Each factor was analysed independently from the other. Variability of epidemiological data (prevalence, incidence, exclusion criteria, and mortality) was estimated on the basis of literature data. Variability of inclusion criteria was assessed by varying the LVEF cutoff from 30 to 35%, according to the international guidelines.

Results

Clinical and demographic data: comparison of the ALPHA registry with MADIT-II, SCD-HeFT, and COMPANION trial population

The main clinical and demographic characteristics of the population in the ALPHA registry are reported in Table 3. Of 3513 patients included in the present analysis, 636 (18%) met the MADIT-II, 1686 (48%) the SCD-HeFT, and 308 (9%) the national registries was used to estimate future growth of implants; (iii) demographic data, HF epidemiology as well as ICD guidelines are supposed to remain unchanged in the near future. Sensitivity analyses were conducted to test how several factors would affect basal results. Each factor was analysed independently from the other (Table 2). Variability of epidemiological data (prevalence, incidence, exclusion criteria, and mortality) was estimated on the basis of literature data. Variability of inclusion criteria was assessed by varying the LVEF cutoff from 30 to 35%, according to the international guidelines.

### Table 2 Patients potentially candidates to implantable cardioverter defibrillators for primary prevention

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal estimate</th>
<th>Superior estimate</th>
<th>Inferior estimate</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria rate (NYHA &gt; 1; LVEF ≤ 30–35%)</td>
<td>44.4%</td>
<td>52.2%</td>
<td>40.3%</td>
<td>ALPHA Registry</td>
</tr>
<tr>
<td>Age &gt; 80 among HF patients with LVEF ≤ 30–35%</td>
<td>13.5%</td>
<td>15%</td>
<td>12%</td>
<td>16,20,21</td>
</tr>
<tr>
<td>Low life expectancy—non-cardiovascular causes</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>21</td>
</tr>
<tr>
<td>Mortality rate in HF (&lt;80 years, LVEF ≤ 30–35%, NYHA &gt; 1)</td>
<td>17.5%</td>
<td>15%</td>
<td>20%</td>
<td>16,17,20,29,33</td>
</tr>
<tr>
<td>Mean annual rate mortality in ICD recipients</td>
<td>12%</td>
<td>10%</td>
<td>14%</td>
<td>29–32</td>
</tr>
</tbody>
</table>

Estimates for Italy and the USA. Abbreviations as in Table 1.
COMPANION6 inclusion criteria. Inclusion criteria of at least one trial were met by 1786 (51%) patients. Table 3 shows the main clinical and demographic characteristics of patients eligible for an ICD in the registry tabulated alongside those of the patients enrolled in the ICD arm of each clinical trial. Patients in the registry were older than those included in all three clinical trials and had higher NYHA functional class than both the MADIT-II3 and SCD-HeFT6 trial populations. A trend toward a higher LVEF was found in comparison with the clinical trials. In comparison with the MADIT-II3 and SCD-HeFT6 trials, a higher proportion of patients in the registry showed an QRS complex duration ≥120 ms or had permanent atrial fibrillation.

Patients with implantable cardioverter defibrillators indication

According to the inclusion criteria (NYHA class > I, LVEF ≤ 30–35%), a proportion of HF patients varying from 40.3% (LVEF cutoff ≤ 30%) to 54.2% (LVEF cutoff ≤ 35%) meet current guidelines for ICD implantation in the ALPHA registry population.

Table 2 summarizes, both for Italy and the USA, the epidemiological data on HF prevalence and incidence as well as all the other variables and ranges assumed in the model. The table also reports the estimate of patients already implanted with an ICD to date. National registries on ICD report 9853 first implantations in Italy in year 200722,23 and around 191 900 in the USA in year 2007.29 In the last considered year, patients treated for primary prevention represent 60 and 79% of total ICD implants in Italy and the USA, respectively, leading to 5912 and 151 585 implants and representing 91.6 and 530 implants per million inhabitants, respectively. Assuming an annual mortality from 10 to 14% among ICD patients and considering all primary prevention implants done since year 2000, it is estimated that 11 231 and 422 449 patients are alive and implanted with ICD for primary prevention in Italy and the USA. Finally, after applying all the model assumptions, emerged that a total number of 154 148 patients in

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**Table 3** Clinical and demographic characteristics of patients eligible for an implantable cardioverter defibrillators in the ALPHA registry and in implantable cardioverter defibrillators arms of MADIT-II, SCD-HeFT, and COMPANION and in the subgroups of the ALPHA registry selected on basis of the trial’s inclusion criteria

<table>
<thead>
<tr>
<th></th>
<th>ALPHA registry (all patients)</th>
<th>MADIT-II registry</th>
<th>MADIT-II ICD arm</th>
<th>SCD-HeFT registry</th>
<th>SCD-HeFT ICD arm</th>
<th>COMPANION registry</th>
<th>COMPANION ICD arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers</td>
<td>3513</td>
<td>636</td>
<td>742</td>
<td>1686</td>
<td>829</td>
<td>308</td>
<td>595</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>71</td>
<td>82</td>
<td>84</td>
<td>67</td>
<td>77</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 ± 13</td>
<td>69 ± 10</td>
<td>64 ± 10</td>
<td>68 (59–76)*</td>
<td>60 (52–70)*</td>
<td>70</td>
<td>66</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>35 ± 13</td>
<td>25 ± 5</td>
<td>23 ± 5</td>
<td>29 (25–31)*</td>
<td>24 (19–30)*</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>QRS ≥ 120 ms (%)</td>
<td>47</td>
<td>58</td>
<td>50</td>
<td>57</td>
<td>42</td>
<td>150</td>
<td>160</td>
</tr>
<tr>
<td>NYHA class I (%)</td>
<td>9</td>
<td>5</td>
<td>35</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NYHA class II (%)</td>
<td>56</td>
<td>48</td>
<td>35</td>
<td>59</td>
<td>70</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NYHA class III (%)</td>
<td>29</td>
<td>47</td>
<td>25</td>
<td>41</td>
<td>30</td>
<td>83</td>
<td>86</td>
</tr>
<tr>
<td>NYHA IV (%)</td>
<td>6</td>
<td>—</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>22</td>
<td>16</td>
<td>9</td>
<td>20</td>
<td>17</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy (%)</td>
<td>46</td>
<td>100</td>
<td>100</td>
<td>50</td>
<td>52</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>Pts potentially implantable with ICD in the Alpha cohort, n (%)</td>
<td>1786 (50.8%)</td>
<td>636 (18%)</td>
<td>1686 (48%)</td>
<td>308 (9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

*Median and quartiles.
Italy and 1,218,664 in the USA should be eligible for ICD implantation. These estimates would lead to 2,671 and 4261 patients to be treated per million inhabitant in Italy and the USA, which correspond to a ratio of actual ICD implants/potential patients equal to 0.04 and 0.12, respectively.

Budget impact analysis

Data from national ICD registries showed an increment of prophylactic ICDs in the last 2 years ranging from 7 to 14%22–28 both in Italy and the USA. According to our model, projections of implantations in a 5-year timeframe would lead to a trend of the number of patients who need to be treated as shown in Figure 1. Accordingly, the present growth rate of primary prevention implants in the USA would allow to treat a relevant part of patients who meet these indications within these 5 years. On the contrary, the same model applied to Italian data would be totally insufficient to implant all patients. In particular, a 20 and 68% increment per year in ICD implants would be necessary in the USA and Italy, respectively, to treat all patients in the same timeframe. According to projections for the USA, considering the necessary 20% annual increment of ICD implants, 1375 patients per million inhabitants would be treated with ICD in year 2013: on the basis of the DRG rate, this should account for a total cost of €6274 million dollars representing 3.1% of total US public health expenditure in 2006. On the other side, in Italy, a 68% annual increment of ICD implants should be necessary, 1367 patients per million inhabitants would be treated with ICD in year 2013, accounting for a cost of €1255 million euros, equal to 1.2% of total Italian public health expenditure in 2005.

Discussion

In our study, we included and analysed data from patients referred to a selected number of HF clinics. Data analysis revealed that more than half of our patients would qualify for ICD implantation, on the basis of the criteria used in the major ICD studies. Moreover, they had a worse clinical profile that the respective patients in these trials. Our study also demonstrated that an ICD implantation strategy based on current guidelines would increase the ICD implantation rate in Italy and the USA, thereby having a significant impact on the activity of electrophysiological facilities and public health system expenditure.

Despite several trials demonstrated efficacy of prophylactic implantation of ICD in reducing sudden and total mortality,1–7 and international guidelines have been updated accordingly,10 ICDs are still underused, with implantation rates varying from country to country.22,23 These differences may account for epidemiological differences, acceptance rate of guidelines, as well as economic background and healthcare policies.

Few information is available about the proportion of patients who should actually undergo ICD implantation for the primary prevention of SCD. In a paper published just after MADIT-II trial results,9 a generalization of ICD indication in patients matching criteria of primary prevention trials led to evidence of a heavy economic burden to be added to the healthcare system. More recently, in 263 consecutive patients seen in a specialized HF clinic, Toma et al.11 found that the application of the SCD-HeFT criteria increases the proportion of patients eligible for an ICD by nearly 60% in comparison with the proportion deemed eligible on the basis of the MADIT-II criteria.1 These authors also found that more than half of all patients in their HF clinic would qualify for ICDs on the basis of trial eligibility criteria.

A registry of over 3500 consecutive patients screened for enrolment in the ALPHA study was used for the present analysis. The data showed that more than half of all patients included in the registry, and 66% of those with systolic left ventricular dysfunction, would qualify for ICDs if selection is based on current international guidelines. Moreover, results showed that a large proportion of them (48%) met the SCD-HeFT criteria, a proportion 2.6-fold higher than that yielded by the MADIT-II criteria, and that 9% of them would be considered eligible not only for an ICD but also for resynchronization therapy. A particularly relevant result of the present analysis was that patients in the registry had a worse clinical profile than SCD-HeFT, MADIT-II, and COMPANION trial participants, in that they were older, fell into higher NYHA functional classes and more frequently had atrial fibrillation and intra-ventricular conduction delay. These findings, similar to those of Toma et al.,11 raise questions about the impact of ICD use in more compromised populations than those included in clinical trials. The impact of ICDs should therefore be assessed beyond the selected cases of the trials, in populations seen in everyday clinical practice and who receive routine clinical care, in whom peri-implantation risks and the likelihood of death from co-morbidities may be greater. Indeed, by preventing SCD, the impact of other causes of death such as progressive HF or other concomitant diseases may be greater, making the cost-effectiveness of ICD therapy less favourable outside the randomized trial setting.34 Finally, we found that an implantation policy based on current guidelines could strongly increase the ICD implantation rate particularly in Italy: an annual percent increase of prophylactic implants of 20% in the USA and 68% in Italy should be necessary to treat all eligible patients in a 5-year timeframe, with a strong impact on budget.

The use of ICDs in Italy and the USA is increasing and more implanting centres are being established; however ICDs are still underused for patients with accepted indications according to evidence-based medicine. How a further likely increase in ICD use will impact on the provision of services within the National Health System in terms of cost and service capacity is unknown. On the basis of the assumptions made in the present estimate, this analysis demonstrated that the implantation rate of ICDs according to the Guidelines would be significantly higher than the present rate, even if the implantations are diluted over a 5-year time frame. Therefore, application of ICD indications in patients with HF and cardiac dysfunction may have a heavy and presently unbearable impact on the activity of electrophysiological facilities. This conclusion is more evident in Italy than the USA, despite lower prevalence and incidence of HF, because of the lower rate of adoption of guidelines for primary prevention: to date in Italy 60% of ICDs are implanted with a primary prevention indication, if compared with a 79% proportion of prophylactic implants in the USA.22

As decisions based on evidence from randomized trials may have a significant impact on healthcare resources, further analyses
are needed in this field. On the basis of these data, further risk stratification may be useful in patients with LVEF ≤ 30–35% in order to identify those who have a good prognosis and do not need an ICD despite the presence of cardiac dysfunction. Presently, there are no validated criteria for selecting or excluding patients with reduced LVEF for prophylactic ICD therapy. Among the several available risk stratifiers, T-wave alternans seems to be the most promising technique in the prediction of arrhythmic risk in patients with left ventricular systolic dysfunction. In several studies performed in patients non-treated with an ICD, a negative T-wave alternans test identified a group at very low risk when negative and a group at elevated risk when positive or indeterminate. Since there is no evidence showing that ICD provides a mortality benefit for primary prevention in patients with a negative T-wave alternans result, T-wave alternans may serve as a means of guiding ICD therapy to appropriate patients. Also a clinical risk score such as that suggested by Goldenberg et al. may be useful in evaluating prognosis in patients eligible to receive an ICD on the basis of a low LVEF. A simple clinical risk score that includes age, HF functional class, blood urea nitrogen levels, QRS duration, and the presence of atrial fibrillation can delineate lower- and higher-risk subsets in the low LVEF population that correlate with ICD efficacy.

Limitations
The present analysis has some limitations. As it provides empirical data on eligibility for ICDs in the setting of specialized HF clinics, owing to referral biases our estimates cannot be extended to the broader HF population. Moreover, estimates of the epidemiology of HF were taken from the literature in Europe and the USA and may not necessarily be representative of the real situation in Italy and the USA. Additionally, a discordant trend was found between some clinical variables in the ALPHA registry population in comparison to patients enrolled in clinical trials. An estimate based on prevalent cases of the proportion of patients eligible for ICD could not be applicable to incident cases, which are less sick, due to the progressive condition related to CHF. Additionally, a constant incremental rate in ICD implants for the next 5 years may not reflect the real environment and does not take into account a possible saturation of healthcare resources. Finally, caution must be deserved when using present estimates to make future predictions: the projections for future years did not take into account background changes, such as demographic and epidemiological alterations and/or guideline updates.

Conclusions
The present analysis found that an implantation policy based on current guidelines would strongly increase the ICD implantation rate in Italy and the USA, significantly impacting on the activity of electrophysiological facilities and public health system expenditure. Moreover, data showed that patients who are eligible for an ICD in everyday clinical practice may have a worse clinical profile than clinical trial participants since they are older, have a worse NYHA functional class and more frequently develop atrial fibrillation and intra-ventricular conduction disturbances. These data, applied to two different environments, Italy and USA, suggest that the decision to implant ICDs based on evidence from randomized trials may have a significant impact on different healthcare resources showing the need for further analyses in this field.

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Appendix: ALPHA Study Group
Steering Committee: Chairman: J.A.S.-U.; Members: G.M.F., C.K., R.F.E.P., M.T., L.S.

List of centres and physicians


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