tionship between anesthesia type and treatment effect have not yet been analyzed.

Khatri et al. question the generalizability of our trial results because we used the gray-area principle. This approach ensures that patients of all kinds are included in a trial, since nobody knows which patients will benefit most. However, most centers included all eligible patients, and in 2012, when the results of the Interventional Management of Stroke III trial became known, this became the official trial policy.[1] Our high median NIHSS score is not surprising, since it follows from the requirement that patients should have a confirmed occlusion before randomization. We agree that the generalizability of trial results does not follow only from its inclusion criteria but also from the analysis of subgroup effects, which need to be of similar direction and magnitude as the overall effect, and the absence of interaction between clinically meaningful subgroups and treatment. Our study findings meet these criteria.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1501204

Recent Trends in Euthanasia and Other End-of-Life Practices in Belgium

TO THE EDITOR: In Belgium, where euthanasia was legalized in 2002, large-scale repeat surveys have monitored the evolution of medical end-of-life practices since 1998, with subsequent surveys conducted in 2001 and 2007[1,2] and the latest in 2013.

As was done in previous surveys,[2] we sent questionnaires to 6188 physicians certifying death certificates from the first half of 2013 in Flanders, the Dutch-speaking half of Belgium, with approximately 6 million inhabitants and 58,000 deaths annually (see the Supplementary Appendix, available with the full text of this letter at NEJM.org). The response rate was 60.6%. The response sample was weighted to be representative of all the deaths that occurred in the first half of 2013.

After a large increase between 2001 and 2007, the total percentage of deaths preceded by one or more possibly life-shortening end-of-life practices remained stable at 47.8% in 2013 (Table 1). The intensified alleviation of pain and other symptoms with the use of drugs, with possible shortening of life taken into account (24.2% of deaths), and the withholding or withdrawing of life-prolonging treatment (17.2%) remained the most prevalent end-of-life practices.

The rate of euthanasia increased significantly between 2007 and 2013, from 1.9 to 4.6% of deaths. The overall increase relates to increases in both the number of requests (from 3.5 to 6.0% of deaths) and the proportion of requests granted (from 56.3 to 76.8% of requests made).

After a decrease from 3.2% in 1998 to 1.8% in 2007, the rate of hastening death without an explicit request from the patient remained stable at 1.7% in 2013. After an increase from 8.2% in 2001 to 14.5% in 2007, the rate of use of continuous deep sedation until death decreased to 12.0% in 2013.

As compared with practices in 2007, decision making in euthanasia and physician-assisted suicide in 2013 more often included an oral and written request from the patient and consultation with another physician, both of which are requirements of the euthanasia law[3] (Table S1 in the Supplementary Appendix). Palliative care services were involved in 73.7% of cases in 2013. These results suggest a stricter assessment of legal eligibility criteria in 2013 than in 2007. Decision making in other end-of-life practices also increasingly included patient and family input (data not shown).

We found an increased demand for euthana-

Table 1. Prevalence of Euthanasia and Other End-of-Life Practices in Flanders, Belgium, in 1998, 2001, 2007, and 2013.*

Variable	Survey Year				P Value†
	1998	2001	2007	2013	
Total deaths annually — no.	56,354	55,793	54,881	61,621‡	—
Deaths in survey sample — no.	3999	5005	6202	6188	—
Response rate — % of physicians surveyed	48.1	58.9	58.4	60.6	—
Studied cases — no.	1925	2950	3623	3751	—
Death preceded by at least one end-of-life practice — % (95% CI)	39.3 (37.0–41.6)	38.4 (36.5–40.3)	47.8 (45.9–49.8)	47.8 (46.1–49.5)	>0.99
Intensified alleviation of pain and other symptoms§	18.4 (16.6–20.4)	22.0 (20.5–23.6)	26.7 (25.1–28.4)	24.2 (22.9–25.7)	0.02
Withholding or withdrawing of life-prolonging treatment	16.4 (14.7–18.3)	14.6 (13.2–16.0)	17.4 (15.9–19.0)	17.2 (15.9–18.6)	0.85
Physician-assisted death¶	4.4 (3.5–5.5)	1.8 (1.4–2.4)	3.8 (3.2–4.5)	6.3 (5.6–7.1)	<0.001
Euthanasia	1.1 (0.7–1.7)	0.3 (0.2–0.5)	1.9 (1.6–2.3)	4.6 (4.0–5.2)	<0.001
Assisted suicide	0.12 (0.04–0.36)	0.01 (0.00–0.10)	0.07 (0.02–0.19)	0.05 (0.02–0.13)	0.97
% of deaths with request for euthanasia or assisted suicide	2.1 (1.6–2.9)	—‖	3.5 (3.0–4.1)	6.0 (5.3–6.7)	<0.001
% of requests for euthanasia or assisted suicide granted	57.4 (41.0–72.4)	NC	56.3 (48.2–64.0)	76.8 (71.2–81.6)	<0.001
Hastening of death without explicit request from patient	3.2 (2.4–4.1)	1.5 (1.1–2.0)	1.8 (1.3–2.4)	1.7 (1.3–2.2)	0.84
Continuous deep sedation until death — % (95% CI)	—‖	8.2 (7.1–9.4)	14.5 (13.1–15.9)	12.0 (10.9–13.2)	0.002
Patient decided to stop eating and drinking — % (95% CI)	—‖	—‖	—‖	0.5 (0.3–0.7)	NC

* Data regarding these practices are weighted percentages with 95% confidence intervals (CI). Analyses were performed with the use of the complex samples function of SPSS software, version 22.0 (IBM). NC denotes could not be calculated.
† Two-sided P values are for the comparison of 2007 data with 2013 data and were calculated with the use of Pearson's chi-square test.
‡ Data are preliminary and unconfirmed, as reported by Statistics Belgium.
§ Intensified alleviation of pain and other symptoms was performed with the use of drugs, with possible shortening of life taken into account.
¶ Physician-assisted death was defined as the administration of drugs with the explicit intention of shortening life. Euthanasia was defined as physician-assisted death at the explicit request of the patient.
‖ The survey question was not asked in the respective year.

sia in Belgium between 2007 and 2013, as well as growing willingness among physicians to meet those requests, mostly after the involvement of palliative care services. This finding indicates that, after 11 years of experience, euthanasia is increasingly considered as a valid option at the end of life in Belgium. For the first time, the rate of euthanasia in the Flanders area of Belgium is significantly higher than that in the Netherlands (2.8% in 2010).[4]

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Supported by a grant (100036) from Agentschap voor Innovatie door Wetenschap en Technologie, the Flemish government agency for Innovation by Science and Technology.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on March 17, 2015, at NEJM.org.

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DOI: 10.1056/NEJMc1414527

Detection of Drug-Resistant Tuberculosis by Xpert MTB/RIF in Swaziland

TO THE EDITOR: Tuberculosis is a major global health problem that has worsened with the increasing emergence of *Mycobacterium tuberculosis* (MTB) complex strains that are resistant to rifampin (RIF) and isoniazid. As recommended by the World Health Organization (WHO), the timely detection of drug resistance with the use of rapid molecular diagnostic tests, such as the Xpert MTB/RIF assay (Cepheid), is essential for appropriate treatment of patients with tuberculosis and for limiting the further spread of multidrug-resistant disease.[1,2]

We used 24-loci mycobacterial interspersed repetitive unit–variable number tandem repeat (MIRU-VNTR) analysis and spoligotyping to perform classic genotypic analysis of MTB complex strains from the most recent (2009) national survey of tuberculosis-drug resistance in Swaziland, a country with a high prevalence of tuberculosis (945 cases per 100,000 persons, or approximately 1%).[3] We found that 38 of 125 multidrug-resistant strains (30%) that were isolated during the survey carried the *rpoB* I491F mutation, which confers resistance to rifampin (Table 1; and the Supplementary Appendix, available with the full text of this letter at NEJM.org). This mutation, which was previously reported with low frequency in clinical isolates from Hong Kong and Australia,[4] is not detected by the Xpert MTB/RIF assay.

Xpert MTB/RIF, a cartridge-based point-of-care assay, is designed to identify rifampin resistance mutations in an 81-bp region of *rpoB* (codons 426 to 452). Its inability to detect the *rpoB* I491F outbreak strain raises new challenges, since Xpert MTB/RIF is used throughout most of Swaziland as the first-line diagnostic test for tuberculosis and for multidrug-resistant tuberculosis, as recommended by the WHO.[5] Thus, the circulation of strains with the *rpoB* I491F mutation substantially reduces the sensitivity of Xpert MTB/RIF–based diagnosis in Swaziland and presumably results in underdiagnosis and potentially inadequate treatment. This is problematic in a country where an estimated 26% of adults are infected with the human immunodeficiency virus (HIV) and 80% of patients with tuberculosis are coinfected with HIV. In addition, coinfected patients are more likely than

Table 1. Mutations in *rpoB* in 125 Multidrug-Resistant Strains from the 2009 Survey Regarding Tuberculosis-Drug Resistance in Swaziland.*

Mutation	Strains with Mutation	Mutation in *rpoB* Hot-Spot Region†
	no. (%)	
D435F	1 (0.8)	Yes
D435F, N437D	3 (2.4)	D435F, yes; N437D, yes
D435V	1 (0.8)	Yes
G442R,‡ I491F	1 (0.8)	G442R, yes; I491F, no
H445D	7 (5.6)	Yes
H445L	6 (4.8)	Yes
H445Y	6 (4.8)	Yes
I491F, R552C	1 (0.8)	I491F, no; R552C, no
I491F	38 (30.4)	No
QF432–433del	1 (0.8)	Yes
S450L	58 (46.4)	Yes
S450W	1 (0.8)	Yes
Unmutated	1 (0.8)	No

* Mutations are listed according to numbering for the *Mycobacterium tuberculosis* H37Rv genome. Some strains carry two mutations.
† The hot-spot region of *rpoB* ranges from codon 426 to codon 452.
‡ This is a heterozygous single-nucleotide polymorphism.