Physician Perceptions of the FDA’s Breakthrough Therapy Designation: An Update

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Abstract
The US Food and Drug Administration developed the Breakthrough Therapy designation to expedite the development and review of drugs that show a clear advantage over available therapy for serious conditions. Prior research has shown that physicians tend to misunderstand that a drug may receive a Breakthrough Therapy designation based on preliminary clinical evidence (eg, effect on a surrogate endpoint or intermediate clinical endpoint that is likely to predict clinical benefit). The objective of this article is to examine whether physicians’ familiarity with and interpretation of the Breakthrough Therapy designation have changed since a survey on the topic was published in 2016. We replicated three of the questions in that study and explored beliefs that a Breakthrough Therapy designation automatically qualifies a drug for accelerated approval. We also draw comparisons by specialization (oncologists vs. primary care physicians). In general, physicians remain more likely than not to misunderstand the Breakthrough Therapy designation.

Key words: oncology; drug approval; breakthrough therapy; accelerated approval; regulatory science

Introduction
Drug companies can request a Breakthrough Therapy (BT) designation from the US Food and Drug Administration (FDA) for drugs intended to treat a serious medical condition if preliminary clinical evidence indicates substantial improvement on one or more clinically significant endpoints compared with available therapies.1,2 In 2016, Kesselheim et al3 published findings from a national survey of board-certified internists and specialists that revealed substantial deficits in knowledge concerning the BT designation. At that time, physicians tended to overestimate the efficacy required for drugs that are granted a BT designation—believing they were supported by stronger evidence than required by statute. We replicated three questions asked by Kesselheim et al1 to examine whether there have since been changes in physicians’ familiarity with and interpretation of the BT designation. In our study, we also drew comparisons by specialization (oncologists versus primary care physicians [PCPs]).

Subjects, Materials, and Methods
We conducted a self-administered anonymous online survey among PCPs and oncologists between October 2019 and April 2020. Data summarized in this article were collected as part of a larger study comprising three concurrent between-subjects experiments examining health care providers’ perceptions of, and attitudes toward, pharmaceutical promotional materials. Questions about FDA’s BT designation were unrelated to the experimental stimuli and included at the end of the survey instrument. The study was reviewed and approved by RTI International’s Institutional Review Board and granted an exemption from FDAs Research Involving Human Subjects Committee. All participants provided their informed consent to participate in the research.

Participants were recruited by a market research company that offers targeted access to proprietary panels of health care providers (HCPs). Eligible physicians had to spend at least 20% of their time on direct patient care and specialize in oncology, hematology, medical oncology, or pediatric oncology, or they had to be a primary care physician (PCP) who prescribed at least one oncology medication in the past month. We achieved our target distribution with an approximately 2:1 ratio of PCPs (n = 1418) to oncologists (n = 708). To reach the target sample size, the firm supplemented panel recruitment with an email campaign directed toward physicians identified through records from the American Medical Association (AMA). Nonresponding invitees were sent three to five reminder emails during data collection, which were spaced 2 to 3 days apart. Among panelists, a total of 45,893 panel invitations to participate were sent to oncologists and 26,731 invitations were sent to PCPs. An additional 13,586 invitations were sent off-panel to oncologists using the AMA email list. Within the firm’s core panel, 21% of HCPs clicked on the survey link in the invitation. The average click-through rate among partner panels was 10%, and the click-through rate from oncologists who were sent invitations using the AMA list was 2%. Furthermore, the number of completed surveys among
those who screened in as eligible was 82%. PCPs received an honorarium of $40 for completing the study and oncologists received $50. We weighted our data to population benchmarks by age and gender using the AMA Physician Masterfile (see Supplementary Table S1). 4

The study included four questions about the FDA’s BT designation, three of which were used in the study by Kesselheim et al 3 (see Supplementary Table S2). These asked about familiarity with the “breakthrough therapy” designation, the minimum level of evidence that the FDA requires manufacturers to gather for the FDA to label a drug as a breakthrough, and a hypothetical prescribing scenario where participants were asked to choose between two conceptually indistinct drugs—one described as an “FDA-designated breakthrough drug” and the other described using the definition of the BT designation. The fourth question asked whether FDA’s BT designation pathway automatically qualifies a drug to receive accelerated approval. 5 BT designated drugs are eligible for accelerated approval based on a surrogate or intermediate endpoint if certain criteria are met, but such approval is not automatically conferred. Some initial evidence suggests oncologists and other providers associate accelerated approval with the BT designation. 6 As such, the fourth question was designed to assess a nuanced aspect of physicians’ understanding of the BT designation. Contingency tables presented in the results section report weight-adjusted counts, percentages, and 95% confidence intervals (CIs). We conducted Pearson χ² tests of independence, converted to design-based F statistics, testing for differences in weighted responses by oncology specialization. When comparing our findings with those of Kesselheim et al, 1 nonoverlapping CIs are evidence of a statistically significant difference between populations (P < .05). 7

Results

Unweighted demographic characteristics are presented in Table 1. Weight-adjusted frequency data are reported in Table 2 along with comparable results reported by Kesselheim et al, 3 when applicable.

Familiarity with the BT designation was significantly associated with specialization, F 2.77,5876.57(.95) = 87.41, P < .001. Oncologists were more likely to report being familiar or very familiar with the BT designation than were PCPs and less likely to report being not at all familiar with it. Compared with Kesselheim et al, oncologists reported greater familiarity with the BT designation but there were no differences in familiarity for PCPs.

Physicians’ understanding and preferences for the BT designation did not significantly differ by specialization. Overall, 65% (95% CI [61%, 68%]) of physicians correctly identified the minimum level of evidence that the FDA requires for a drug to be labeled as a Breakthrough Therapy (ie, preliminary evidence). Compared with the results reported by Kesselheim et al, 3 there is evidence that a greater proportion of physicians now understand that the BT designation is based on preliminary clinical evidence.

Physicians preferred BT designated drugs described using the phrase, “an FDA-designated breakthrough drug,” but the magnitude of this preference was not as dramatic as was observed by Kesselheim et al. 3 Regardless, the lengthier descriptive phrase used in the other response option, “a drug

Table 1. Unweighted participant characteristics, no. (%).

| Characteristic                  | Oncologists (n = 708) | PCPs (n = 1418) | Total (N = 2126) |
|---------------------------------|-----------------------|-----------------|------------------|
| Age, years                      |                       |                 |                  |
| 49 and younger                  | 430 (60.7)            | 636 (44.9)      | 1066 (50.1)      |
| 50 to 80                        | 278 (39.3)            | 782 (55.1)      | 1060 (49.9)      |
| Gender                          |                       |                 |                  |
| Male                            | 530 (74.9)            | 1053 (74.3)     | 1583 (74.5)      |
| Female                          | 178 (25.1)            | 365 (25.7)      | 543 (25.5)       |
| Race/ethnicity                  |                       |                 |                  |
| White                           | 368 (52.0)            | 909 (64.1)      | 1277 (60.1)      |
| Black                           | 10 (1.4)              | 30 (2.1)        | 40 (1.9)         |
| Hispanic                        | 54 (7.6)              | 56 (4.0)        | 110 (5.2)        |
| Other                           | 211 (29.8)            | 361 (25.5)      | 572 (26.9)       |
| Did not answer                  | 65 (9.2)              | 62 (4.4)        | 127 (6.0)        |
| Regionb                         |                       |                 |                  |
| Northeast                       | 183 (25.9)            | 312 (22.0)      | 495 (23.3)       |
| Midwest                         | 131 (18.5)            | 325 (22.9)      | 456 (21.5)       |
| South                           | 229 (32.3)            | 458 (32.3)      | 687 (32.3)       |
| West                            | 159 (22.5)            | 317 (22.4)      | 476 (22.4)       |
| Pharmaceutical detailing policyc|                       |                 |                  |
| No restrictions in place        | 255 (36.0)            | 699 (49.3)      | 954 (44.9)       |
| Some restrictions (eg, appointments required) | 369 (52.1) | 483 (34.1) | 852 (40.1) |
| Representatives are not granted access | 83 (11.7) | 234 (16.5) | 317 (14.9) |

aPercentages may not sum to 100 due to rounding error.
bDenominators for calculating percentages by region include 6 oncologists (<1%) and 6 PCPs (<1%) with missing data.
cDenominators for calculating percentages by pharmaceutical detailing policy include 1 oncologist (<1%) and 2 PCPs (<1%) with missing data.
Table 2. Familiarity, understanding, perceptions, and beliefs about automatic qualification for accelerated approval of FDA’s BT designation by specialization in the present study and results from Kesselheim et al.3

| Present study, no. (% , 95% CI)a | Kesselheim et al % (95% CI) |
|--------------------------------|-----------------------------|
| Specialization | Oncologists | PCPs | Total | |
| Familiarity with BT designationb | | | | |
| Not at all familiarc | 283 (8, 5-11) | 77 936 (39, 37-42) | 78 219 (39, 36-41) | 42 (36-39) |
| A little familiar | 1409 (37, 33-43) | 87 334 (44, 41-47) | 88 743 (44, 41-47) | 37 (33-41) |
| Familiar | 1578 (42, 37-47) | 28 519 (14, 13-16) | 30 097 (15, 13-17) | 17 (14-20) |
| Very familiar | 488 (13, 10-17) | 4972 (3, 2-4) | 5450 (3, 2-4) | 3 (2-5) |
| Understanding of BT designationc,d,e | | | | |
| Strong evidence (eg, randomized trials evaluating clinical outcomes) | 981 (28, 24-33) | 40 838 (34, 31-37) | 41 819 (34, 30-37) | 52 (48-55) |
| Preliminary evidence (eg, uncontrolled studies or studies testing surrogate outcomes)f | 2434 (70, 65-75) | 77 774 (64, 61-68) | 80 209 (65, 61-68) | 45 (41-49) |
| Very preliminary evidence (eg, in vitro lab or animal studies) | 60 (2, 1-4) | 2213 (2, 1-3) | 2273 (2, 1-3) | 4 (2-5) |
| Preferences for BT designation—hypothetical prescribing scenariog | | | | |
| [Drug Name], an FDA-designated breakthrough drugh | 2380 (63, 58-68) | 117 591 (59, 56-62) | 119 971 (59, 57-62) | 94 (91-95) |
| [Drug Name], a drug with early promising study results showing that the drug may demonstrate substantial improvement over available therapiesi | 1378 (37, 32-42) | 81 170 (41, 38-44) | 82 548 (41, 38-43) | 6 (5-9) |
| Belief that BT designation automatically qualifies a drug for accelerated approvalj | | | | |
| True | 1862 (54, 48-59) | 72 257 (60, 56-63) | 74 118 (60, 56-63) | N/A |
| False | 1613 (46, 41-52) | 48 568 (40, 37-44) | 50 181 (40, 37-44) | N/A |

aWeighted counts and percentages are reported, which may not sum to column total sample sizes or 100%, respectively, due to rounding error.
bFamiliarity ratings between oncologists and PCPs are significantly different based on a Pearson χ² test of independence that is weight-corrected and converted to an F-test, F₁,₇₇₇₄₇₅₅₅ = 87.41, P = .001.
cThe percentage of oncologists and PCPs that selected this option is significantly different based on a pairwise test of proportions with a Bonferroni-adjusted significance threshold of P < .0125.
dParticipants who reported being “not at all familiar” with the BT designation were not asked this question.
eUnderstanding between oncologists and PCPs does not differ significantly.
fCorrect response option.
gPreferences between oncologists and PCPs hypothetical do not differ significantly.
h[Drug Name] is a placeholder for one of two fictitious drug names: Axabex or Zykanta. We randomized whether Axabex or Zykanta was described as an FDA-designated breakthrough drug.
i[Drug Name] is a drug with early promising study results showing that the drug may demonstrate substantial improvement over available therapies.
jBeliefs about automatic qualification for accelerated approval between oncologists and PCPs do not differ significantly, F₁,₂₁₁₂₅ = 2.03, P = .15.
kBeliefs about automatic qualification for accelerated approval between oncologists and PCPs do not differ significantly, F₁,₁₁₁₅₆₆ = 3.73, P = .05.

with early promising results...,” is the literal definition of a BT drug (Table 2); the preference for the first option persists even though the two response options are semantically and logically indistinct. By design, the question provides insufficient information about the two drug options for physicians to make a choice between them based solely on the text of the question. In the forced-choice scenario, we would expect physicians to have chosen more or less at random with about half selecting each option. Instead, physicians disproportionately chose the “FDA-designated breakthrough drug.”

Finally, regardless of specialization, 60% of physicians (95% CI, 56%-63%) incorrectly believed that the BT designation automatically qualifies a drug to receive accelerated approval.

Discussion

Physicians tend to misunderstand the BT designation; however, these misinterpretations are not as prevalent as those observed by Kesselheim et al3 over 4 years ago. Around a third of physicians in our sample misunderstood the meaning of the designation from an evidentiary perspective. This observation is particularly striking among oncologists, more than half of whom reported being familiar or very familiar with it, serving as a reminder that familiarity and comprehension are two different things. Knowledge gaps regarding the BT designation and accelerated approval pathways highlight opportunities for HCP outreach and education to improve understanding beyond a superficial familiarity with these regulatory terms. Future research could examine strategies to increase comprehension of these terms, such as including disclosures in physician-targeted materials.

Supplementary material

Supplementary material is available at The Oncologist online.

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Conflict of Interest
The authors indicated no financial relationships.

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Conception/design: V.B., A.C.O., K.J.A. Provision of study material or patients: V.B., A.C.O., K.J.A. Collection and/or assembly of data: R.S.P., V.B., A.C.O. Data analysis and interpretation: R.S.P. Manuscript writing: All authors. Final approval of manuscript: All authors.

Data Availability
The data underlying this article will be shared at reasonable request to the corresponding author.

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