Sex Bias: Is it Pervasive in Otolaryngology Clinical Research?

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**Objectives/Hypothesis:** Recent initiatives highlight substantial sex bias in biomedical research. The objective was to determine whether sex bias is present in otolaryngology and whether sex is appropriately analyzed as an independent variable in otolaryngology clinical research.

**Study Design:** Literature review.

**Methods:** We systematically reviewed all 2016 articles in three major otolaryngology journals: *The Laryngoscope, JAMA Otolaryngology–Head and Neck Surgery,* and *Otolaryngology–Head and Neck Surgery.* Extracted data included study origin, location, subspecialty, number/sex of subjects, ≥50% sex matching (SM ≥50), and sex-based statistical analysis.

**Results:** Six hundred of 1,209 articles comprising original clinical research were reviewed including 8,997,345,495 subjects (males: 3,898,559,264 [43.3%]; females: 5,095,592,583 [56.6%]; and unknown: 3,193,648 [0.04%]). There were 533/600 (88.8%) studies that included both sexes, eight (1.3%) included females only, five (0.8%) included males only, and 56 (9.3%) did not document participant sex. Only 280 studies (46.7%) analyzed data by sex, and 330 studies (60.7%) had SM ≥50. Sex-based statistical analysis and SM ≥50 were similar in domestic and international studies (48.7% vs. 42.8% and 60.9% vs. 62%, respectively). Database studies performed sex-based statistical analysis more frequently than single and multi-institutional studies (79.1% vs. 40.4% and 43.4%, P < .00001). Analysis by sex was more frequently performed in head and neck surgery (53.6%) and pediatric otolaryngology (51.3%), whereas SM ≥50 was highest in pediatric otolaryngology (86.8%) and otology (82.4%).

**Conclusions:** Sex bias exists in the clinical otolaryngology literature, with less than half the studies analyzing sex. Acknowledging the intertwinement of sex with disease pathophysiology and outcomes is important. Eliminating sex bias in research and clinical care should become a major focus for otolaryngologists.

**Key Words:** Sex bias, otolaryngology, research.

**Level of Evidence:** NA

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**INTRODUCTION**

In the last 4 decades, scrutiny of research methods created an uproar in the academic biomedical community revealing that most treatment recommendations and guidelines are based on research conducted on primarily male subjects. Several rationales were provided for the exclusion of women or female animals from research in the late 1900s. One argument suggested that the cyclic nature of estrogen hormonal variation was a confounder with biologic variability throughout the cycle; however, many studies confirmed that female animals do not have significant cyclic biochemical variation when compared to male animals. Other reasons included less availability of female animals for research compared to males or simply oversight of animal or cell sex. Additionally, sex reporting of study subjects in publications was frequently neglected, even though well-known sex-based differences in physiology and disease propagation exist.

In the 1970s, women were excluded from clinical trials due to concern of unknown hazards from any tested treatments that may impact their childbearing potential. An analysis by the US Public Health Service Task Force on Women’s Health Issues concluded that this well-intentioned exclusion was resulting in a lack of scientific knowledge about female biology and pathophysiology, inadvertently having a negative impact on women’s health. As a result, the National Institutes of Health (NIH) changed its policy to include women of childbearing age in research in 1986. Subsequently, the NIH Office of Research on Women’s Health was created in 1990 to ensure that sex and gender are accounted for in clinical research. In 1993, the NIH Revitalization Act was passed to advance the inclusion of women and minority subjects in clinical research. However, enrollment of women in many clinical trials remained unrepresentative of the higher disease prevalence in females, and reporting of

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Additional supporting information may be found in the online version of this article.

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sex-specific results remained infrequent. An analysis of 300 new Food and Drug Administration (FDA) drug applications between 1995 and 2000 highlighted a lack of sex-specific dosages for drugs that had significantly different metabolism in men and women. Similarly, a 2001 report by the US Government Accountability Office demonstrated that eight of 12 drugs removed from the market by the FDA had adverse drug reactions in women. After much pressure from the scientific community, the NIH finally released a memorandum in 2016 requiring all future funding proposals to account for sex as a biological variable in all preclinical research involving humans and animals. Similar mandates were enacted internationally prior to the NIH statement in the United States.

The interaction between sex and disease processes is unique, and research methods in otolaryngology should account for this complex interaction by employing sex-specific results reporting whenever possible. For instance, women have a greater incidence of benign thyroid nodules; similarly, differentiated and anaplastic thyroid cancers are thrice and twice more likely to develop in women compared to men, respectively. Furthermore, the histologic prevalence of otsclerosis is similar for men and women, although the clinical diagnosis is more common amongst females at a 2:1 ratio. Due to immunologic differences, autoimmune diseases with many otolaryngic manifestations are more common in women compared to men as well. Alternatively, certain conditions such as obstructive sleep apnea (OSA) are more prevalent in men, but women with OSA are at a significantly greater risk for cardiovascular diseases. Sex differences in otolaryngic diseases are prevalent, and otolaryngology research should accord with good-science practices and report sex-specific results.

In this age of personalized medicine, analyzing sex as an independent variable is crucial. For decades, both sexes have been unequally represented in clinical studies, and many current treatment recommendations are based on this research. Although an assessment of sex bias has been undertaken in other surgical disciplines including general and orthopedic surgery, no prior studies have reviewed whether sex bias is present or sex underreporting occurs in the overall clinical otolaryngology literature. The purpose of this study was to determine whether sex bias exists in the otolaryngology literature and whether sex is appropriately analyzed as an independent variable in otolaryngology clinical research.

MATERIALS AND METHODS

We systematically reviewed all articles in 2016 in the three highest-impact factor general otolaryngology journals: The Laryngoscope, JAMA Otolaryngology—Head and Neck Surgery (JAMA Oto-HNS), and Otolaryngology—Head and Neck Surgery (Oto-HNS). Highest-impact factor journals were selected because studies published in the journals should reflect the highest standards of current otolaryngology research. Because this research was undertaken in late 2017, monthly issues for the year 2016 were analyzed for the last complete year. Each journal was accessed through institutional subscriptions, and each issue was reviewed chronologically starting with January by one of two reviewers. Accuracy and reliability of consistent data entry by both reviewers was verified by comparison of data collection for the first month of each journal. Studies in supplemental issues were also included in the total research article count. All basic science and cellular studies were excluded. Additional exclusion criteria applied were editorials, opinion pieces/commentary/How I Do It reports, best practices, non-patient-related studies (cost or practice analyses and education-based studies analyzing trainees), cadaver studies, meta-analyses or systematic reviews, methods, and development/feasibility articles. Additionally, case reports or cases series with 10 or fewer patients were also excluded from the overall cohort because they are not classified as original clinical research, and have the potential to bias the results for sex-based statistical analysis due to fewer research participants. However, because case reports and small case series are prevalent in the otolaryngology literature, these studies were reviewed separately for sex reporting and included in a supporting table.

Abstracts for each article were reviewed first. If studies met the criteria for original clinical research based on the abstract, the manuscript text, figures, tables, and if present, supplements were reviewed for data collection. Randomized controlled trials (RCTs) were identified and marked for subset analysis. Extracted data included study origin (single institution, multi-institutional, or national/international database study), location (international or domestic), subspecialty, number/sex of subjects, >50% sex matching (SM≥50), and sex-based statistical analysis. Participant numbers were calculated for studies that only reported percentages of male and female participants. To analyze whether studies met a minimum standard for sex matching, we utilized SM≥50 criteria described and previously used by Mansukhani et al., which is representative of whether there were at least half as many participants of the less-represented sex as there were participants of the majority sex in the study. For example, a study met criteria for SM≥50 if a study with 100 male subjects also included at least 50 females. Data were stored in Microsoft Excel 2016 (Microsoft Corp., Redwood, WA).

Sex reporting, SM≥50, and sex-based statistical analysis were analyzed for all original clinical studies, and subset analyses were performed by journal, study origin, location, and subspecialty. Sex-based subset analysis was similarly performed for RCTs. Statistical analysis was performed with Stata 15 software (StataCorp, College Station, TX), and the χ² test was utilized as appropriate. A P value of <.05 was considered statistically significant.

RESULTS

A total of 1,209 articles were present in the three journals. Following exclusion of studies meeting exclusion criteria and basic science/ translational studies, 600 articles were included comprising original, patient-centered clinical research (Fig. 1). The studies included 8,997,345,495 subjects (males: 3,898,563,542 [43.3%]; females: 5,098,597,117 [56.7%]; and unknown: 3,184,836 [0.04%]). The majority of the studies were domestic (N = 392, 65.3%) and originated from single institutions (N = 425, 70.8%) (Table I). The most common represented otolaryngology subspecialties included head and neck (N = 196, 70.8%) and otology (N = 110, 18.3%).

A total of 22 case series with fewer than 10 patients and 84 case reports were excluded as part of exclusion criteria. For completion, sex reporting data for these manuscripts are available in Supporting Table 1 in the online
version of this article, with 12.6% of small case series and 3.6% of case reports not reporting subject sex.

**Overall Sex Reporting, Sex-Based Statistical Analysis, and Sex Matching**

A total of 544/600 studies (90.7%) reported participant sex, whereas 56 studies (9.3%) did not (Table I). Sex reporting rates ranged from 86.9% in Oto-HNS to 95.1% in JAMA Oto-HNS, and were not significantly different among the three journals \((P = .050)\) (Table II). Thirteen studies (2.1%) had single-sex participants, of which eight (1.3%) analyzed females and five (0.8%) analyzed males only. Sex-based statistical analysis was performed in 280/600 studies (46.7%), and the difference in sex-based outcomes reporting among the journals was not statistically significant \((P = .116)\) (Table II). Less than two-thirds of studies \((N = 330, 60.7\%)\) met \(\text{SM}_{\geq 50}\); amongst journals, there was no statistically significant difference in \(\text{SM}_{\geq 50}\) \((P = .782)\) (Table II).

**Subset Analysis: Study Location and Origin**

Nearly 90% of both domestic and international studies reported participant sex \((P = .565)\) (Fig. 2). Domestic studies more frequently performed sex-based statistical analysis (48.7% vs. 42.8%), whereas more international studies met \(\text{SM}_{\geq 50}\) (62% vs. 60.9%), although the differences were not statistically significant \((P = .165 \text{ and } P = .747, \text{ respectively})\). Comparing study origins, single institution, multi-institution, and database studies had similar sex reporting rates ranging from 90.4% to 92.3% \((P = .867)\) (Fig. 3). However, database studies performed sex-based statistical analysis significantly more frequently compared to single- and multi-institutional studies \((P < .00001)\) (Fig. 3). \(\text{SM}_{\geq 50}\) was highest in database studies (63.1%) but overall similar among the three study origins \((P = .894)\).

**Subset Analysis: Subspecialty**

Among otolaryngology subspecialties, head and neck surgery literature most frequently performed sex-based statistical analysis (53.6%) followed by pediatric otolaryngology (51.3%) (Fig. 4). The disciplines least frequently performing statistical analysis by sex included sleep medicine, laryngology, and facial plastics (33.3% each) (Fig. 4). \(\text{SM}_{\geq 50}\) was highest in pediatric otolaryngology (86.8%) and otology (82.4%), and the lowest in head and neck surgery (41.3%) and sleep medicine (30%) (Fig. 5).

**Subset Analysis: RCTs**

Thirty RCTs were published in the three journals in 2016. The most represented subspecialties included otology (36.7%) and rhinology (26.7%) (Table III). The majority of RCTs were international (63.3%) and single institution (70%) (Table III). Two studies (6.7%) did not state participant sex. Among the 28/30 (93.3%) studies reporting sex, a slight male participant predominance (51.2% vs. 46.1%) was evident. Twelve (40%) RCTs performed sex-based statistical analysis, whereas 19 (67.9%) met \(\text{SM}_{\geq 50}\) (Table III).
DISCUSSION

This work demonstrates a deficiency in sex reporting and sex-based statistical analysis in the high-impact clinical otolaryngology literature. Specifically, we have shown that the otolaryngology sex reporting rate was less than 100%, whereas less than half of the studies analyzed outcomes by sex, and nearly two-thirds of studies had over 50% or greater participant sex matching. Sex-based differences in genetics, metabolism, and disease pathophysiology have been demonstrated across medicine and surgery. However, additional subtler but clinically significant sex-based variability may be present in biological processes that has not yet been recognized due to lack of analysis by sex. Awareness of this deficit is the first necessary step toward improving research practices pertaining to basic demographics, which may play a significant role in patient outcomes. This is the first analysis of sex bias and reporting in the clinical otolaryngology literature. Only one prior study has assessed sex bias and reporting in basic science/translational otolaryngology research.23 A review of 210 basic science/translational studies conducted from 2010 to 2015 on noise-induced hearing loss highlighted lack of sex reporting in animal subjects; among studies reporting sex, the majority used male animals in experiments.23

In recent years, similar disparities in sex reporting and analysis have been demonstrated among other medical disciplines.5,21,22,24 An extensive review of literature analyzing changes in brain structure via imaging in the course of substance abuse disorders noted significantly less female participation as late as 2016, with nearly three-fourths of studies without sex-based analysis.24 A review of neuroscience animal research highlighted an uptrend in use of male animals only, with a persistent lack of sex-based statistical analysis in studies utilizing both animals.25 Among surgical disciplines, general and orthopedic surgery have demonstrated substantial sex bias and underreporting. A review of clinical research in five major general surgery journals from 2011 to 2012

TABLE II.

<table>
<thead>
<tr>
<th></th>
<th>Otolaryngology–Head and Neck Surgery</th>
<th>The Laryngoscope</th>
<th>JAMA Otolaryngology–Head and Neck Surgery</th>
<th>Total</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of total</td>
<td>7,195,495,177</td>
<td>1,749,745,961</td>
<td>52,104,357</td>
<td>8,997,345,495</td>
<td>N/A</td>
</tr>
<tr>
<td>No. of males</td>
<td>2,987,717,196 (41.5%)</td>
<td>884,053,468 (50.6%)</td>
<td>26,792,878 (51.4%)</td>
<td>3,898,563,542 (43.3%)</td>
<td></td>
</tr>
<tr>
<td>No. of females</td>
<td>4,207,024,158 (58.4%)</td>
<td>863,362,194 (49.3%)</td>
<td>25,210,765 (48.4%)</td>
<td>5,095,597,117 (56.7%)</td>
<td></td>
</tr>
<tr>
<td>No. unknown</td>
<td>753,823 (0.1%)</td>
<td>2,330,299 (0.1%)</td>
<td>100,714 (0.2%)</td>
<td>3,184,836 (0.04%)</td>
<td></td>
</tr>
<tr>
<td>Manuscripts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex reported</td>
<td>173/199 (86.9%)</td>
<td>273/298 (91.6%)</td>
<td>98/103 (95.1%)</td>
<td>544/600 (90.7%)</td>
<td>.050</td>
</tr>
<tr>
<td>Unknown sex</td>
<td>26</td>
<td>25</td>
<td>5</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Single sex</td>
<td>1</td>
<td>10</td>
<td>2</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Male only</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Female only</td>
<td>0</td>
<td>6</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Sex-based analysis</td>
<td>96/199 (54.3%)</td>
<td>128/298 (43.0%)</td>
<td>56/103 (48.2%)</td>
<td>280/600 (46.7%)</td>
<td>.116</td>
</tr>
<tr>
<td>SM≥50</td>
<td>102/173 (59.0%)</td>
<td>166/273 (60.8%)</td>
<td>62/98 (63.3%)</td>
<td>330/544 (60.7%)</td>
<td>.782</td>
</tr>
</tbody>
</table>

*The number of studies reporting sex was used as the denominator to calculate the percentage of ≥50% sex matching (SM≥50).

Fig. 2. Sex analysis of domestic versus international studies. SM≥50 = ≥50% sex matching.

Fig. 3. Sex analysis by study origin. SM≥50 = ≥50% sex matching.
revealed that nearly 17% of studies did not specify participant sex, whereas approximately one-third of studies reported and analyzed data by sex. A similar analysis of basic science/translational general research demonstrated that over one-fifth of animal studies omitted animal sex; among studies reporting sex, 80% utilized male animals. Lastly, a longitudinal review of high-impact clinical orthopedic surgery literature discovered only a slight improvement in sex-based statistical analysis from 19% in 2000 to 30% in 2010. The lack of sex reporting and sex-based analysis in the overall medical literature is a cause for concern. Although sex reporting and analysis rates are higher in otolaryngology, they remain suboptimal.

Subset analysis yielded key insights into various facets of the clinical otolaryngology literature. Importantly, the research originating in domestic and international institutions had similar deficiencies in sex reporting and analysis, highlighting that sex bias and underreporting are global problems. Database studies are understandably and significantly better at performing sex-based statistical analysis, likely due to the employment of high-speed statistical software to review large datasets. Unfortunately, overall sex-reporting rates in database studies parallel that of single and multi-institution studies, which typically include fewer subjects.

Sex-based statistical analysis across subspecialties was generally low, in the range of 30% to 55% of studies, thus highlighting a need for improvement in all subspecialties. Sex-matching rates were higher in certain disciplines including pediatric otolaryngology, rhinology, and otology. However, we acknowledge that some discrepancy in SM≥50 in certain disciplines may be appropriate. For example, head and neck diseases have sex predispositions, with the higher prevalence of oral cavity and oro-pharyngeal cancers in men and thyroid disorders/cancer in women. Additionally, many outcome analyses in otolaryngology are typically retrospective in nature, reporting on all patients within a certain timeframe, so sex matching may be overlooked. Historically, less knowledge exists of disease processes and interactions in the sex with a lower prevalence of disease. To mend this gap in prospective studies, we recommend the inclusion of sex-matched participants to better analyze outcomes by sex.

**TABLE III.** Randomized Controlled Trial Analysis.

<table>
<thead>
<tr>
<th>Randomized Controlled Trials, N = 30</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study location: Domestic 11 (36.7%)</td>
<td></td>
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<tr>
<td>International 19 (63.3%)</td>
<td></td>
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<tr>
<td>Study institution(s): Single institution 21 (70%)</td>
<td></td>
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<tr>
<td>Multi-institutional 10 (30%)</td>
<td></td>
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<tr>
<td>Studies by participant sex: Both sexes 28 (93.3%)</td>
<td></td>
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<tr>
<td>Male only 0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Female only 0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Sex not reported 2 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Participants, N = 3,990: Males 2,026 (50.8%)</td>
<td></td>
</tr>
<tr>
<td>Females 1,856 (46.5%)</td>
<td></td>
</tr>
<tr>
<td>Sex not reported 108 (2.7%)</td>
<td></td>
</tr>
<tr>
<td>Statistical analysis by sex: SM≥50* 19 (67.9%)</td>
<td></td>
</tr>
<tr>
<td>Discipline: Head and neck 5 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Laryngology 1 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Otology 11 (36.7%)</td>
<td></td>
</tr>
<tr>
<td>Pediatrics 3 (10%)</td>
<td></td>
</tr>
<tr>
<td>Rhinology 8 (26.7%)</td>
<td></td>
</tr>
<tr>
<td>General 1 (3.3%)</td>
<td></td>
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<tr>
<td>Sleep 1 (3.3%)</td>
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</table>

*The number of studies reporting sex was used as the denominator to calculate the percentage of ≥50% sex matching (SM≥50).

**Fig. 4.** Sex-based statistical analysis by subspecialty. HN = head and neck surgery; Laryng = laryngology; Oto = otology; Peds = pediatric otolaryngology; Rhino = rhinology.

**Fig. 5.** Analysis of ≥50% sex matching (SM≥50) by subspecialty. HN = head and neck surgery; Laryng = laryngology; Oto = otology; Peds = pediatric otolaryngology; Rhino = rhinology.
female participants were almost equal in the otolaryngology RCTs, \( \text{SM}_{\leq 50} \) was only 67.9%. Furthermore, statistical analysis by sex was surprisingly performed in only 40% of RCTs, which is less frequent than in the overall clinical otolaryngology literature. Because RCTs are the basis for new treatment recommendations or significant changes in treatment algorithms, otolaryngology researchers must ascribe to a higher standard of sex inclusion, reporting, and analysis in RCTs.

This work is a call to action to otolaryngology researchers for the implementation of better research practices. Participant sex reporting is among the most elementary characteristics of research that allows healthcare providers to understand the applicability of the evidence to their patient population. Researchers must assess sex critically by performing statistical analysis of outcomes by sex, particularly in RCTs. We understand that many otolaryngology conditions are uncommon, and as a result, many clinical studies often include few participants; when sufficient participants are included, statistical analysis should be performed. Lastly, studies should strive for sex matching, particularly in prospective studies including RCTs.

Journal editors play a significant role in the establishment and improvement of research standards and can have substantial impact in changing the current landscape of sex reporting and analysis in otolaryngology. Previously, the International Committee of Medical Journal Editors proposed requirements on reporting and analyzing data by sex or gender in human studies, and sex in all animal and cell studies.\(^{26}\) Many journals have adopted these requirements. Similarly, the JAMA Network recently implemented specific guidelines for reporting participant demographic information including sex and gender. The instructions require authors to describe sex or gender distribution and report outcome data by sex in all human, animal, and cell/tissue studies. Single-sex studies must also provide a rationale for excluding the other sex. Adoption of similar journal guidelines in the instructions for authors across otolaryngology journals would diminish sex bias in otolaryngology.

This study is not without limitations. Firstly, we analyzed only three of the highest-impact general otolaryngology journals. Therefore, the data presented are not applicable to lower-impact general otolaryngology journals or otolaryngology subspecialty journals. However, these journals were chosen as a representation of the current highest standard of sex reporting and analysis in otolaryngology, providing an upper limit. Thus, other lower-impact otolaryngology journals may be susceptible to a greater degree of sex bias. Furthermore, we analyzed the most recent, complete full year of research articles only at the time this work was conducted. There may be variability in sex reporting and analysis between years, but the intended goal of this study was to review the status of sex bias in recent literature, which this work fulfills. The data presented will serve as a baseline for future comparisons, and should engage researchers, editors, and reviewers alike to address the issue of sex bias. Lastly, otolaryngology literature rarely differentiates sex from gender. Although sex is binary (male vs. female) and is typically based on an individual’s biology, gender is based on personal identification. Although many studies may mislabel sex as gender and dichotomize gender into a male versus female category, demographics reported in otolaryngology research primarily include sex. Therefore, only sex as an independent variable was analyzed.

**CONCLUSION**

Although it may be less prevalent in otolaryngology compared to other surgical disciplines, sex bias exists in high-impact clinical otolaryngology research. All otolaryngology studies do not report participant sex, and less than half the studies analyze outcomes by sex. Researchers must ascribe to higher sex reporting/analysis standards. Similarly, journals should establish more stringent criteria for sex reporting and sex-based statistical analysis. The elimination of sex bias is necessary for the development of evidence-based management/treatment guidelines that take patients’ biologic differences into account.

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**BIBLIOGRAPHY**


