Quality of Histopathological Reporting in Breast Cancer: Results From Four South African Breast Units

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PURPOSE High-quality histopathology reporting forms the basis for treatment decisions. The quality indicator for pathology reports from the European Society of Breast Cancer Specialists was applied to a cohort from four South African breast units.

METHODS The study included 1,850 patients with invasive breast cancer and evaluated 1,850 core biopsies and 1,158 surgical specimen reports with cross-center comparisons. A core biopsy report required histologic type; tumor grade; and estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) status, with a confirmatory test for equivocal HER2 results. Ki-67 was regarded as optional. Pathologic stage, tumor size, lymphovascular invasion, and distance to nearest invasive margin were mandatory for surgical specimens. Specimen turnaround time (TAT) was added as a locally relevant indicator.

RESULTS Seventy-five percent of core biopsy and 74.3% of surgical specimen reports were complete but showed large variability across study sites. The most common reason for an incomplete core biopsy report was missing tumor grade (17.9%). Half of the equivocal HER2 results lacked confirmatory testing (50.6%). Ki-67 was reported in 89.3%. For surgical specimens, the closest surgical margin was reported in 78.1% and lymphovascular invasion in 84.8% of patients. Mean TAT was 11.9 days (standard deviation [SD], 10.8 days) for core biopsies and 16.1 days (SD, 11.3) for surgical specimens.

CONCLUSION Histopathology reporting is at a high level but can be improved, especially for tumor grade, HER2, and Ki-67, as is reporting of margins and lymphovascular invasion. A South African pathology consensus will reduce variability among laboratories. Routine use of standardized data sheets with synoptic reports and ongoing audits will improve completeness of reports over time.

INTRODUCTION Breast cancer incidence has significantly increased, and it has become the most common malignancy among women in South Africa.1 Delayed presentation linked to late stage at diagnosis, inconsistent access, and poorer overall quality of care has resulted in women from low- and middle-income countries (LMICs) having higher mortality rates than women in high-income countries (HICs).2,3

High-quality histopathology reporting with clear communication of predictive and prognostic markers is critical for clinical decision making. South Africa is an upper- and middle-income country with more advanced breast pathology resources than most sub-Saharan African countries.4 Not all diagnostic tests are feasible in lower-resourced areas, and the Breast Cancer Initiative 2.5 (BCI 2.5) stratifies diagnostic services according to available resources into basic, limited, enhanced, and maximum levels. In South Africa, there is a dual health care system that fulfills criteria of an enhanced level in the public sector and maximum level in the private sector.5 Although many HICs have adopted multigene assays to determine recurrence risk and guide therapies, these are not available in the public sector in South Africa, and breast units rely on grade, receptor status, lymphovascular invasion (LVI), and Ki-67 for treatment decisions.

For many years, efforts have been made to standardize high-quality breast cancer care in HICs, and various guidelines have been established to improve the quality of breast cancer pathology reporting.6-10 To date, there is a paucity of data from South Africa and other LMICs on the adequacy of breast histopathology reporting, and there are no national guidelines for breast histopathology reporting.
One of the widely applied sets of quality indicators (QIs) was published by the European Society of Breast Cancer Specialists (EUSOMA). This study aimed to apply the EUSOMA histopathology QIs to a South African cohort to evaluate local breast cancer histopathology reports and compare reporting quality across participating centers.

**METHODS**

**Patients and Data Collection**

This is a retrospective review of patients enrolled in the South African Breast and HIV Outcomes (SABCHO) study, which evaluates the impact of HIV on the care and outcomes of women with breast cancer. The period of review was July 2015 to September 2017 and included 1,850 consecutive patients from Chris Hani Baragwanath Academic Hospital (CHBAH), Charlotte Maxeke Johannesberg Academic Hospital (CMJAH), Inkosi Albert Luthuli Central Hospital (IALCH), and Grey’s Hospital (GH). CHBAH and CMJAH are both located in Johannesburg in the Gauteng province, and IALCH and GH are both in the KwaZulu-Natal (KZN) province. All four are public sector academic breast cancer units and serve socioeconomically disadvantaged patients.

The pathology reports of 3,008 specimens, including 1,850 core biopsies and 1,158 surgical specimens, were evaluated. Reports for specimens from Gauteng sites were generated by the hospital’s respective pathology departments from the National Health Laboratory Services (NHLS), which serves the public health sector in South Africa. The majority of samples from KZN units had been outsourced to private laboratories.

This study was approved by the human research ethics committee of the University of the Witwatersrand. All patients signed written informed consent at the time of enrollment into the SABCHO study.

**QIs**

Reports were considered complete if they included the following parameters for core biopsy: histologic type, tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor 2 (HER2) status with a confirmatory in situ hybridization test for equivocal results (usually fluorescence in situ hybridization [FISH] in our setting). During the study period, HER2 2+ (equivocal) status was generally defined as circumferential membrane staining that is weak to moderate in > 10% of cells or complete and circumferential membrane staining that is intense within < 10% of tumor cells. HER2 3+ status was considered positive and did not require confirmatory testing. A Ki-67 score is recommended but not required in the EUSOMA guidelines. Because Ki-67 is routinely considered for clinical decisions in our units, it was added as an optional parameter with a cutoff of 20% to define immunohistochemical (IHC) surrogates for molecular subtypes. In addition to these parameters, the following were required for surgical specimens: pathologic stage, size in millimeters for the invasive component, peritumoral LVI, and distance to nearest invasive margin; receptors did not require repeat because we expected them routinely on core biopsy. The EUSOMA guidelines set a minimum standard of ≥ 95% complete reports with an ideal target of ≥ 98%. Report turnaround time (TAT) was measured as a locally relevant parameter, defined as the number of days between the laboratory receiving the specimen to final report release, and included IHC where performed.

**Statistical Analysis**

The proportion of complete reports in each center was recorded as frequency with percentage and compared among centers by Pearson’s χ² test or Fisher’s exact test for sparse data. Analysis was carried out using Stata 14 statistical software (StataCorp, College Station, TX).

**RESULTS**

Demographic characteristics of the cohort, tumor grade, and IHC subtype distributions are listed in Table 1. Unknown IHC receptor subtyping was 8.4% overall, ranging from 5.2%, 5.4%, and 5.7% at the CMJAH, IALCH, and
CHBAH sites, respectively, to 20.8% at the GH site. The majority of patients had hormone receptor–positive disease (76.1%), and 16.8% had luminal B HER2-positive disease; only 8.0% were HER2 enriched, and 15.8% had triple-negative breast cancer. Luminal B HER2 negative was the most common subtype for the cohort (38.3%), except at IALCH where luminal A was more common at 35.9%.

The proportion of complete core biopsy reports, when not considering Ki-67, was 75% overall, with rates of 90.2%, 91.6%, 43.0%, and 63.5% at CHBAH, CMJAH, IALCH, and GH, respectively (Table 2). With inclusion of Ki-67, this dropped to 69.7% overall, with rates of 89.0%, 90.5%, 34.5%, and 49.4% at CHBAH, CMJAH, IALCH, and GH, respectively. Completeness of IHC reporting was high overall throughout all sites (ER, 98%; PR, 97.9%; HER2, 97.8%). The most common reasons for incomplete core biopsy reports were missing tumor grade; no FISH testing for equivocal HER2 results; and, when included, missing Ki-67 (Table 2). Ki-67 was reported in absolute percentage values at all sites except for IALCH, where it was reported as ≤ 14% or > 14%. Significant cross-center differences were found for overall report completeness, grade, confirmatory HER2 testing, and Ki-67 (all $P \leq .001$).

The completeness of surgical specimen reporting was 74.3% overall (CHBAH, 89.66%; CMJAH, 86.78%; IALCH, 37.96%; GH, 70.76%; Table 3). Failure to report on closest invasive margin, LVI, and tumor grade were the most commonly missing parameters. Closest invasive margin reporting was 78.1% overall, ranging from 88.5%, 86.0%, and 81.8% at CHBAH, CMJAH, and GH, respectively to 48.2% at IALCH ($P \leq .001$). LVI was included in 84.8% of cases overall, with 92.4%, 89.7%, 72.2%, and 78.8% reporting at CHBAH, CMJAH, IALCH, and GH, respectively ($P \leq .001$). Tumor grade was reported in 92.1%, ranging from 97.5% at CHBAH to 90.7% at GH ($P \leq .001$). Histopathological type and pathologic staging were reported in 98.8% and 94.7%, respectively, and showed significant cross-center differences ($P \leq .001$). Average overall TAT was 11.9 ± 10.8 days for core biopsies and 16.1 ± 11.3 days for surgical specimens, again with significant cross-center differences (Table 4).

**DISCUSSION**

None of the sites fulfilled the EUSOMA minimum requirement of 95% complete histopathology reports. Among the overall cohort, there was complete reporting for

| Characteristic                  | Total | CHBAH | CMJAH | IALCH | GH          | $P$        |
|--------------------------------|-------|-------|-------|-------|-------------|-----------|
| No. of patients                | 1,850 | 643   | 442   | 409   | 356         |           |
| Mean age ± SD                  | 56.0 ± 14.4 | 54.8 ± 14.3 | 55.3 ± 14.1 | 57.5 ± 14.3 | 57.4 ± 14.9 | .004      |
| Ethnicity                      |       |       |       |       |             |           |
| Black                          | 1,417 (76.6) | 590 (91.8) | 322 (72.9) | 225 (55) | 280 (78.7) |           |
| Colored                        | 91 (4.9)   | 38 (5.9) | 25 (5.7) | 12 (2.9) | 16 (4.5)   |           |
| Indian                         | 203 (11.0) | 5 (0.8) | 15 (3.4) | 136 (33.3) | 47 (13.2) | < .001    |
| White                          | 139 (7.5)  | 10 (1.6) | 80 (18.1) | 36 (8.8) | 13 (3.7)   |           |
| Tumor grade                    |       |       |       |       |             |           |
| Missing                        | 332 (17.9) | 27 (4.2) | 23 (5.2) | 222 (54.3) | 60 (16.9) |           |
| No. reported                   | 1,518 | 616   | 419   | 187   | 296         | < .001    |
| 1                              | 114 (7.5)  | 41 (6.7) | 24 (5.7) | 10 (5.3) | 39 (13.2)  |           |
| 2                              | 817 (53.8) | 323 (52.4) | 189 (45.1) | 135 (72.2) | 170 (57.4) |           |
| 3                              | 587 (38.7) | 252 (40.9) | 206 (49.2) | 42 (22.5) | 87 (29.4)  |           |
| IHC-based subtype              |       |       |       |       |             |           |
| Missing                        | 156 (8.4)  | 37 (5.7) | 23 (5.2) | 22 (5.4) | 74 (20.8)  |           |
| No. reported                   | 1,694 | 606   | 419   | 387   | 282         | < .001    |
| Luminal A                      | 356 (21.0) | 79 (13.0) | 96 (22.9) | 139 (35.9) | 42 (14.9)  |           |
| Luminal B (HER2 negative)      | 649 (38.3) | 257 (42.4) | 101 (38.7) | 101 (26.1) | 129 (45.7) |           |
| Luminal B (HER2 positive)      | 285 (16.8) | 144 (23.8) | 62 (14.8) | 47 (12.1) | 32 (11.4)  |           |
| HER2 enriched                  | 136 (8.0)  | 34 (5.6) | 34 (8.1) | 41 (10.6) | 27 (9.6)   |           |
| Triple negative                | 268 (15.8) | 92 (15.2) | 65 (15.5) | 59 (15.2) | 52 (18.4)  |           |

Abbreviations: CHBAH, Chris Hani Baragwanath Academic Hospital; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; GH, Grey’s Hospital; HER2 human epidermal growth factor receptor 2; IALCH, Inkosi Albert Luthuli Central Hospital; IHC, immunohistochemistry; SD, standard deviation.
75.0% of core biopsies and 74.3% of definitive surgical specimens. There were striking differences among the study sites, with significantly higher completeness rates for both core and surgical specimens among Gauteng sites compared with KZN sites.

The audit of core biopsy specimens showed serious under-reporting of grade and HER2 equivocal FISH reporting. For surgical specimen reporting, the Gauteng sites approached EUSOMA reporting standards, whereas the KZN sites were deficient in reporting of LVI and closest invasive margin, which compromises the assessment of adequacy of surgery as well as the need for reoperations or adjuvant therapies.

Tumor grade is an established prognostic marker, and reliability in core specimens is relatively high. The propensity toward grade 2 reporting at IALCH is particularly noteworthy: At 72.2%, this is much higher than reported in the literature. While grading may not be possible in very few cases on core biopsy, IALCH did not report grade in 54.3% of core biopsies and 17.6% of surgical specimens, and the overall reliability of grade reporting therefore seems questionable. The extremely high number of missing grade was the main contributor to the overall very low complete core biopsy reporting of 43% at IALCH.

HER2-targeted treatment was not accessible in the public sector during most of the study period but has now become...
available for selected patients. Nevertheless, even in the absence of targeted treatment, HER2 should always be tested because it is a predictive marker for the utility of chemotherapy. The BCI 2.5 classification suggests HER2 status as the process metric for quality control for settings of an enhanced level, such as the South African public sector.5 HER2 IHC was tested in the majority of biopsy specimens across all study sites (97.8%). Two hundred thirty-five specimens were HER2 2+ and regarded as equivocal. However, 50.6% of these equivocal HER2 results lacked further FISH testing (75.6%, 68.4%, 43.3%, and 15.6% at CHBAH, CMJAH, IALCH, and GH, respectively). Differences in complex laboratory processes and outsourcing of FISH testing may explain site differences, and silver in situ hybridization testing within the laboratories may assist to overcome logistical hurdles.

EUSOMA does not classify Ki-67 reporting as mandatory but has recommended its routine use.12 In South African public sector units, where multigene assays are not affordable, Ki-67 status is routinely used for decisions about chemotherapy, especially in hormone receptor–positive breast cancers. Routine reporting of Ki-67 at the Gauteng NHLS laboratories was 96.3% and 95.5% at CHBAH and CMJAH. In contrast, only 85.3% of core biopsies reported Ki-67 at IALCH and 74.6% at GH. The inclusion of Ki-67 decreased overall complete reports from 75% to 69.7%.

# TABLE 3 Surgical Specimen Reporting

| Reporting Parameter | Total | CHBAH | CMJAH | IALCH | GH | P |
|---------------------|-------|-------|-------|-------|----|---|
| No. of specimens    | 1,158 | 435   | 242   | 245   | 2236 |   |
| Complete surgical specimen |       |       |       |       |     | < .001 |
| Complete            | 860 (74.3) | 390 (89.7) | 210 (86.8) | 93 (37.9) | 167 (70.8) |   |
| Incomplete          | 298 (25.7) | 45 (10.3) | 32 (13.2) | 152 (62.1) | 69 (29.2) |   |
| Total               | 1,158 (100.0) | 435 (100.0) | 242 (100.0) | 245 (100.0) | 236 (100.0) |   |
| Histologic type     |       |       |       |       |     | < .001 |
| Reported            | 1,144 (98.8) | 434 (99.8) | 242 (100.0) | 241 (98.4) | 227 (96.2) |   |
| Missing             | 14 (1.2) | 1 (0.2) | 0 (0.0) | 4 (1.6) | 9 (3.8) |   |
| Tumor grade         |       |       |       |       |     | < .001 |
| Reported            | 1,067 (92.1) | 424 (97.5) | 227 (93.8) | 202 (82.4) | 214 (90.7) |   |
| Missing             | 91 (7.9) | 11 (2.5) | 5 (2.6) | 43 (17.6) | 22 (9.3) |   |
| LVI                 |       |       |       |       |     | < .001 |
| Reported            | 982 (84.8) | 402 (92.4) | 217 (89.7) | 177 (72.2) | 186 (78.8) |   |
| Missing             | 176 (15.2) | 33 (7.6) | 25 (10.3) | 68 (27.8) | 50 (21.2) |   |
| Closest invasive margin |       |       |       |       |     | < .001 |
| Reported            | 904 (78.1) | 385 (88.5) | 208 (86.0) | 118 (48.2) | 193 (81.8) |   |
| Missing             | 254 (21.9) | 50 (11.5) | 34 (14.0) | 127 (51.8) | 43 (18.2) |   |
| Pathologic staging  |       |       |       |       |     | < .001 |
| Reported            | 1,097 (94.7) | 418 (96.1) | 237 (97.9) | 215 (87.8) | 227 (96.2) |   |
| Missing             | 61 (5.3) | 17 (3.9) | 21 (5) | 30 (2.2) | 9 (3.8) |   |
| Tumor size          |       |       |       |       |     | .974 |
| Reported            | 1,079 (93.2) | 406 (93.3) | 225 (93.0) | 227 (92.7) | 221 (93.6) |   |
| Missing             | 79 (6.8) | 29 (6.7) | 17 (7.0) | 18 (7.3) | 15 (6.4) |   |

Abbreviations: CHBAH, Chris Hani Baragwanath Academic Hospital; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; GH, Grey’s Hospital; IALCH, Inkosi Albert Luthuli Central Hospital; LVI, lymphovascular invasion.

# TABLE 4 Specimen TATs

| Report                  | Total     | CHBAH     | CMJAH     | IALCH     | GH        | P       |
|-------------------------|-----------|-----------|-----------|-----------|-----------|---------|
| Core biopsy specimen    | 11.9 ± 10.8 | 8.0 ± 6.2 | 12.0 ± 8.3 | 18.6 ± 15.8 | 10.9 ± 15.8 | < .001  |
| Surgical specimen       | 16.1 ± 11.3 | 15.4 ± 9.9 | 20.3 ± 11.2 | 12.9 ± 9.2 | 15.5 ± 13.8 | .010    |

Abbreviations: CHBAH, Chris Hani Baragwanath Academic Hospital; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; GH, Grey’s Hospital; IALCH, Inkosi Albert Luthuli Central Hospital; SD, standard deviation; TAT, turnaround time.
a drop that was almost exclusively noted within KZN units. Although Ki-67 has caused many controversies with interobserver, interlaboratory, and intraobserver variations, most of these have been addressed by international working groups, and there are clear guidelines for preanalytical, analytical, and data handling.14 Ki-67 is used in various predictive models, some of which estimate Oncotype DX (Genomic Health, Redwood City, CA) recurrence scores, which adds clinical utility, especially in settings where multigene assays are unavailable.15,16 Ki-67 interpretation can be significantly improved through application of digital image analysis technology, removing a subjective component to interpretation.17 Strict quality control, national standardization, and laboratory accreditation will further result in more consistent and robust Ki-67 results.

The significant differences in tumor grade and IHC subtype distribution among the sites need additional investigation. The majority of patients had luminal B tumors across all sites, with the exception of IALCH that had more luminal A tumors. Exploratory analyses, including only Black patients to remove confounding around ethnicity and adjusting the Ki-67 cutoff to ≤ 14%, made no difference (Appendix Tables A1 and A2). It is probable that these differences are due to interlaboratory variations in Ki-67 scoring and not due to true differences in tumor biology. This illustrates, however, that allocations to subtypes are flawed: Grading and Ki-67 evaluation do not seem to be uniformly reproducible among our sites. In the absence of multigene assays, it is important that these results are improved to assist clinicians with treatment decisions.

The mean TATs for core biopsies and surgical specimens were 11.9 and 16.1 days, respectively, and need to be improved. In comparison, TATs for breast biopsies in Botswana were reported at 8 days and 57 days for surgical specimens, which the authors hypothesized to be due to preanalytical delays with a reported goal TAT of < 7 days for all specimens in the future.18 In HICs, reported mean TATs for surgical pathology specimens and mastectomies are 2.7 and 3.8 days, respectively.19,20 There is no international recommendation on TATs for histopathology reports and certainly no national consensus. CHBAH aims to process uncomplicated surgical specimens within 5 working days, but excision breast specimens are often complex and may require a second review of the macroscopic specimen for additional sections to be taken and additional analyses. Furthermore, TATs for teaching units in the public sector cannot be expected to equal those of private laboratories because trainees need supervision at each stage of the work-up before reports are authorized. This may delay TATs but is critical for teaching and to increase local pathology capacity over the longer term.

The EUSOMA QIs were selected because they are most reflective of local practice, and all mandatory parameters are included as essential pathology parameters in the Breast Cancer Control Policy published by the South African National Department of Health in 2017.21 It needs to be acknowledged that histopathologists are scarce and often overburdened in South Africa, a situation that has already led to the outsourcing of government patient specimens to the private sector in some provinces. Although South Africa has the second highest number of pathologists in sub-Saharan Africa, with one pathologist/224,897 population, this is still in stark contrast to one pathologist/15–20,000 population estimated for HICs.4 Most pathology departments lack specialists in breast pathology, and while we do have pathologists with special interests, the limited number of pathologists in South Africa, particularly in the public sector, means that it is probably not feasible to have pathologists who are purely breast pathologists.

Although EUSOMA standards were not met in this cohort, the results must be seen in context with other audits in the literature. They are far superior compared with other countries in sub-Saharan Africa. A study from Ethiopia showed that only 61% of specimens included basic-level reporting of T and N staging, tumor grading, and histologic type and only 1% included ER status, margins, and LVI.22 Two studies from West Africa reported grading in only 12% of patients, and only 26% had hormone receptors tested.23,24 Compared with first audits in HICs, only 64.7% had complete reports according to the College of American Pathologists guidelines in an audit from 2010,25 and only 28% fulfilled all recommendations in an audit from Australia in 1995.26 Report completeness improves over time, and with ongoing audits, more recent European studies have shown > 94% complete reports according to EUSOMA standards.

In this audit, the variation in report quality among sites is more worrisome than the overall results and point toward differences in provincial health care administration and resources and interlaboratory differences between academic NHLS laboratories and the private laboratories that process the outsourced state patient specimens. Although Gauteng units did not meet EUSOMA standards, they consistently reported on most parameters, including grade and Ki-67. Both units had almost all their specimens reported by the respective NHLS laboratories, whereas the majority of reports in KZN were from private, nonacademic laboratories. One of the most pertinent differences is the use of standardized synoptic reports at both CMJAH and CHBAH NHLS laboratories, whereas the reporting in KZN was predominantly free text at the time of the study. Templates and synoptic reporting increase report completeness, they ensure a clearer communication of core data to the treating multidisciplinary team, they increase satisfaction among all team members, and they may also increase awareness of QIs among pathologists.29,30 In our study, the most disadvantageous effect of free text reporting was observed at IALCH, where clear documentation of
tumor grade, a critical oncology parameter for clinical decision making, was missing in an extremely high number of cases. There are three interventions that have consistently led to higher quality of reporting in the literature. First, pathology departments that have reporting templates with checklists and synoptic reports have shown higher report completeness. Second, the process of audits has facilitated increasing completeness after each audit process, and third, the implementation of national recommendations or a guideline often improves report adequacy.

There are several limitations to this study. First, this is a retrospective review. However, data were collected in a prospective manner for the SABCHO study, and missing data were minimal. All reports with missing parameters were rechecked in the clinical database and with laboratories. This data set only includes two provinces and is therefore not fully representative of all South African provinces. In addition, the audit was of a clinical cohort, and the results may not be entirely reflective of the laboratories’ overall standards. Although the majority of specimens in KZN were reported by private laboratories, there are no specific data on private versus public laboratory sites to enable precise comparisons. Nevertheless, there are also clear strengths to this study, such as the large sample size and multicenter design. To our knowledge, this is the largest breast histopathology audit from an LMIC to date. In conclusion, the quality of histopathology reporting of breast cancer specimens in South Africa is not uniform among academic breast units and can be improved. Special efforts should be made to improve reporting of tumor grade and HER2 confirmatory tests as well as excision margins, pathologic staging, and LVI. From a clinical point of view, we also recommend routine testing and guideline-adherent reporting of Ki-67 for more accurate risk assessment in the absence of multigene arrays. Reporting standards vary across laboratories, and a South African pathology consensus is required, including a national target for TATs. All pathology services should use data sheets and synoptic reports to improve completeness and communication to the clinician. Increasing pathology resources and ongoing quality audits or accreditation processes within pathology services should be encouraged to continually improve standards countrywide. In the absence of a consensus and standardized reporting, the responsibility will remain with the treating clinician to request clinically adequate reports and ensure patient safety.

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### APPENDIX

**TABLE A1** Subanalysis of IHC-Based Subtype in Black Patients Only

| Reporting Element | Total   | CHBAH   | CMJAH   | IALCH   | GH      | P      |
|-------------------|---------|---------|---------|---------|---------|--------|
| No. of patients   | 1,417   | 590     | 322     | 225     | 280     |        |
| IHC-based subtype |         |         |         |         |         | < .001 |
| Luminal A         | 227 (17.6) | 68 (12.2) | 61 (20.1) | 68 (31.9) | 30 (13.8) |        |
| Luminal B + HER2 negative | 508 (39.3) | 237 (42.5) | 113 (37.2) | 58 (27.2) | 100 (46.1) |        |
| Luminal B + HER2 positive | 239 (18.5) | 131 (23.5) | 55 (18.1) | 28 (13.1) | 25 (11.5) |        |
| HER2 enriched     | 110 (8.5)  | 33 (5.9)  | 27 (8.9)  | 26 (12.2) | 24 (11.1) |        |
| Triple negative   | 207 (16.0) | 88 (15.8) | 48 (15.8) | 33 (15.5) | 38 (17.5) |        |
| Unknown           | 126      | 33      | 18      | 12      | 74      |        |

**Abbreviations:** CHBAH, Chris Hani Baragwanath Academic Hospital; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; GH, Grey’s Hospital; HER2, human epidermal growth factor receptor 2; IALCH, Inkosi Albert Luthuli Central Hospital; IHC, immunohistochemistry.

**TABLE A2** IHC-Based Subtype With Ki-67 Cutoff ≤ 14%

| Variable                          | Total   | CHBAH   | CMJAH   | IALCH   | GH      | P      |
|-----------------------------------|---------|---------|---------|---------|---------|--------|
| No. of patients                   | 1,850   | 643     | 442     | 409     | 356     |        |
| IHC-based subtype for core biopsy |         |         |         |         |         | < .001 |
| Luminal A                         | 302 (17.8) | 57 (9.4)  | 80 (19.1) | 132 (34.1) | 33 (11.7) |        |
| Luminal B + HER2 negative         | 703 (41.5) | 279 (46.0) | 178 (42.5) | 108 (27.9) | 138 (48.9) |        |
| Luminal B + HER2 positive         | 285 (16.8) | 144 (23.8) | 62 (14.8)  | 47 (12.1)  | 32 (11.3)  |        |
| HER2 enriched                     | 136 (8.0)  | 35 (5.6)  | 34 (8.1)  | 41 (10.6) | 27 (9.6)  |        |
| Triple negative                   | 268 (15.8) | 92 (15.2)  | 65 (15.5)  | 59 (15.2)  | 52 (18.4)  |        |
| Unknown                           | 156      | 37      | 23      | 22      | 74      |        |

**Abbreviations:** CHBAH, Chris Hani Baragwanath Academic Hospital; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; GH, Grey’s Hospital; HER2, human epidermal growth factor receptor 2; IALCH, Inkosi Albert Luthuli Central Hospital; IHC, immunohistochemistry; Ki-67, protein encoded by the *MKI67* gene.