Breast cancer molecular diagnostics in Rwanda: a cost-minimization study of immunohistochemistry versus a novel GeneXpert® mRNA expression assay

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Abstract

Objective To compare the financial and time cost of breast cancer biomarker analysis by immunohistochemistry with that by the Xpert® STRAT4 assay.

Methods We estimated costs (personnel, location, consumables and indirect) and time involved in breast cancer diagnosis at the Butaro Cancer Centre of Excellence, Rwanda, using time-driven activity-based costing. We performed a cost-minimization analysis to compare the cost of biomarker analysis for estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 status with immunohistochemistry versus STRAT4. We performed sensitivity analyses by altering laboratory-specific parameters for the two methods.

Findings We estimated that breast cancer diagnosis in Rwanda costs 138.29 United States dollars (US$) per patient when conducting biomarker analysis by immunohistochemistry. At a realistic immunohistochemistry antibody utilization efficiency of 70%, biomarker analysis comprises 48.7% (US$ 67.33) of diagnostic costs and takes 33 min. We determined that biomarker analysis with STRAT4 yields a reduction in diagnosis cost of US$ 7.33 (10.9%; 7.33/67.33), and in pathologist and technician time of 20 min (60.6%; 20/33), per patient. Our sensitivity analysis revealed that no cost savings would be made in laboratories with antibody utilization efficiencies over 90%, or where
only estrogen and/or progesterone receptor status are assessed; however, such operational efficiencies are unlikely, and more laboratories are pursuing human epidermal growth factor receptor-2 analysis as targeted therapies become increasingly available.

**Conclusion** Breast cancer biomarker analysis with STRAT4 has the potential to reduce the required human and capital resources in sub-Saharan Africa laboratories, leading to improved treatment selection and better clinical outcomes.

**Introduction**

Breast cancer is the most common cancer worldwide and the leading cause of cancer death among women.\(^1\) With ongoing demographic transitions, breast cancer incidence and mortality rates are rising in low- and middle-income countries, especially in sub-Saharan Africa.\(^1\) To combat the persistent global inequity in breast cancer mortality, the World Health Organization (WHO) recently launched the Global Breast Cancer Initiative, which identifies timely and accurate breast cancer diagnostics as one of its three central pillars.\(^1\) The WHO Science Council has also recommended avenues to increase access to molecular and genomic diagnostic technologies in low- and middle-income countries.\(^2\)

The breast cancer diagnostic pathway includes tissue biopsy, tissue processing, histopathology and, if histopathology reveals invasive cancer, biomarker analysis for three breast cancer biomarkers, including estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 status. Biomarker analysis – routinely performed by immunohistochemistry – is essential for staging and systemic therapy selection. Patients with non-metastatic breast cancer positive for estrogen receptor and/or progesterone receptor have a 50% reduced recurrence risk with five years of adjuvant endocrine therapy, which is widely available as an oral medication in low- and middle-income countries.\(^3\) Similarly, patients with non-metastatic breast cancer positive for human epidermal growth factor receptor-2 have a greater than 40% reduction in recurrence risk with targeted therapies such as trastuzumab or biosimilars, which are becoming increasingly available in low- and middle-income country markets.\(^4,5\) Tailored use of endocrine therapies and therapies targeting human epidermal growth factor receptor-2 also yield significant survival benefits for eligible patients with metastatic breast cancer.\(^6\)

However, limited access to reliable immunohistochemistry for biomarker analysis in sub-Saharan Africa represents a major gap in breast cancer care, contributing to poor breast cancer survival in the region.\(^7\) Immunohistochemistry is a technically complex process that requires
robust supply chains, extensive personnel training and continued quality control; recent surveys across sub-Saharan Africa report that only 42–50% of centres that process breast tissue perform biomarker analysis. Of the centres that do perform immunohistochemistry, many struggle to maintain consistent services because of a lack of local suppliers and/or regular stock-outs of reagents (often for months).

Innovations in molecular diagnostics may help overcome barriers to breast cancer biomarker analysis. One such example is the Xpert® STRAT4 Assay, a near point-of-care molecular diagnostic technology that runs on the GeneXpert® platform technology. STRAT4 quantitates the mRNAs (messenger ribonucleic acid) for $ESR1$, $PGR$, $ERBB2$ and $MKi67$ (a proliferation marker) in a closed-system, fully standardized cartridge using reverse transcription polymerase chain reaction. The assay has shown high concordance with immunochemistry and fluorescence in situ hybridization for $ESR1$-estrogen receptor, $PGR$-progesterone receptor and $ERBB2$-human epidermal growth factor receptor-2, with overall percentage agreements of 98, 90 and 93%, respectively. A recent study in Rwanda was the first to show immunohistochemistry–STRAT4 in sub-Saharan Africa, with an overall percentage agreement of 93% for $ESR1$-estrogen receptor and 98% for $ERBB2$-human epidermal growth factor receptor-2.

STRAT4 is especially attractive for low-resource settings because most of its reagents are available in a single kit, and its simple manual steps and internal quality controls overcome the need for extensive personnel training. Furthermore, GeneXpert® is a cross-cutting platform that is widely disseminated across Africa and is used across several disease processes, including tuberculosis and human immunodeficiency virus detection. Although the adoption of STRAT4 could streamline and increase access to breast cancer molecular diagnostics in sub-Saharan Africa, little is known about the real-world impact of STRAT4 implementation in low- and middle-income countries, including its financial and time cost. Moreover, robust costing data for breast cancer diagnosis are lacking in sub-Saharan Africa, including for biomarker analysis; in a recent scoping review of breast cancer costing studies in low- and middle-income countries, only two studies were identified from sub-Saharan Africa. These studies (from Kenya and Nigeria) only reported costs of histopathology, but not biomarker analysis. A cost comparison of breast cancer biomarker analysis with STRAT4 and with immunohistochemistry could help to quantify the impact of STRAT4 adoption on hospital and government budgets.
The objectives of our study were therefore to: (i) estimate the cost of the breast cancer diagnostic pathway at a low-resource hospital in sub-Saharan Africa using a micro-costing approach; (ii) identify the main drivers of breast cancer diagnosis costs, including the role of biomarker analysis; and (iii) conduct a cost-minimization analysis of breast cancer biomarker analysis by comparing immunohistochemistry with STRAT4.

Methods

Study setting and design
We conducted a cost-minimization study to compare the cost of breast cancer diagnosis, including biomarker analysis, using immunohistochemistry and STRAT4 at the Butaro Cancer Centre of Excellence in Rwanda. The laboratory provides comprehensive breast cancer diagnosis, including tissue processing, histological diagnosis and biomarker analysis for estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 status with manual immunohistochemistry on formalin-fixed paraffin-embedded samples. As part of a immunohistochemistry–STRAT4 concordance study, we also performed biomarker analysis with STRAT4 for select formalin-fixed paraffin-embedded samples. We estimated costs using a health-care perspective with time-driven activity-based costing, a micro-costing approach that estimates the costs of health-care resources consumed as a patient moves along a care process (referred to as a process map). This method was used to quantify differences in cost, time, personnel and consumables required for the two methods of biomarker analysis.

Process map
We developed the breast cancer diagnosis process map, starting with a patient’s initial visit for breast mass evaluation and ending with the delivery of a breast cancer diagnosis result to the patient, from interviews with involved personnel and shadowing of patients. We interviewed 10 personnel (a pathologist, an oncologist, two internists, a general practitioner, two nurses, two laboratory technicians and a pharmacist) using a semi-structured questionnaire (data repository). We followed patients until no new process map branches were identified ($n = 40$ patients; 20 patients over days 1 and 3 combined, and a further 20 patients during day 2). For non-patient care processes (laboratory steps), we followed breast tissue samples throughout the laboratory process; we shadowed laboratory technicians twice for standard tissue fixation, processing, histopathology and biomarker analysis with immunohistochemistry and STRAT4.
We recorded time estimates during shadowing, and extracted laboratory repeat rates and batching estimates from personnel interviews.

**Costing analysis**

We included the cost categories of personnel, location, consumables and indirect costs in estimating the cost of the breast cancer diagnosis pathway. After recording costs in Rwandan francs (₣), we report these in 2021 United States dollars (US$) using the conversion rate of 990.9 Rwandan ₣ = US 1. We rounded final cost and time estimates to the nearest cent and minute, respectively. We report costs according to the Consolidated Health Economic Evaluation Reporting Standards (data repository), and provide cost calculations in an Excel calculator (data repository).

**Personnel and location**

To estimate personnel and location cost for each process step, we multiplied the cost per minute (or capacity cost rate) of personnel and location by the probability-weighted time of personnel and location involvement, respectively. Personnel capacity cost rate is defined as the annual salary and benefits of personnel divided by the total minutes of availability per year. Location capacity cost rate is defined as the cost of equipment, electricity per metre and construction per metre (accounting for annual depreciation) divided by the total minutes of availability (when staffed and operational) of the location per year. Given the equipment inventory and energy needs of the laboratory, we assumed the laboratory used 25% of the total electricity consumption of the hospital. For laboratory equipment costing more than US$ 3000, we calculated a separate cost capacity rate per item (accounting for annual depreciation and maintenance costs) and multiplied it by the probability-weighted time of machine use per sample to estimate the cost of each laboratory machine per sample. We added the calculated laboratory machine cost per sample to the total laboratory location cost. Laboratory steps accounted for the grouping of samples into batches (average number of samples per batch: 40 for immunochemistry, 28 for STRAT4 sample preparation and 4 for STRAT4 cartridge analysis).

**Consumables and indirect costs**

We estimated the costs of consumables by multiplying the unit price per consumable by the probability of patient consumption. The STRAT4 cartridge is not commercially available in the region, but we estimated a price similar to the Xpert® BCR-ABL Ultra cartridge (i.e. US$ 50.00
per cartridge kit) that is available across sub-Saharan Africa for an oncology indication (chronic myelogenous leukaemia). For consumables in which the price of a single unit per patient could not be calculated (such as laboratory reagents), we used the annual ordering frequency and volume of samples requiring the consumable to estimate the consumable cost per patient. We estimated annual sample volumes by performing an inventory of tissue blocks, haematoxylin and eosin slides, and immunohistochemistry slides (including for three breast cancer biomarkers) processed during a 3-month period (October–December 2019). We used annual antibody ordering frequency and breast cancer immunohistochemistry volume to estimate the estrogen receptor antibody utilization efficiency (i.e. percentage of antibody vial used). We estimated indirect costs by dividing overhead hospital costs for outpatient clinics in 2019 by the number of outpatients served at Butaro Hospital that year. We outline all data sources and assumptions in the data repository.²¹

**Sensitivity analyses**

We performed two sets of sensitivity analyses, the first of which was to calculate extremity bound estimates for breast cancer diagnostic costs at Butaro Cancer Centre of Excellence. We altered parameters including time estimates from patient shadowing (25th percentile versus 75th percentile), electricity consumption by the laboratory (15% versus 35% hospital electricity costs), and the estimated annual volume of tissue blocks, haematoxylin and eosin slides, and immunohistochemistry slides (+10% versus −10% estimate). Alterations in laboratory volume estimates affect consumable cost and the antibody utilization efficiency of the laboratory. Our second set of sensitivity analyses aimed to make cost estimates generalizable to other laboratories in sub-Saharan Africa. We altered laboratory-specific variables for immunohistochemistry (e.g. batching volumes, number of receptors evaluated and antibody utilization efficiency) and STRAT4 (e.g. batching volumes and estimated cartridge price) individually.

**Results**

**Process map**

We identified a 3-day breast cancer diagnosis pathway: initial consultation (day 1), breast mass biopsy (78% by core needle biopsy; 22% by incisional or excisional biopsy) and laboratory analysis (day 2), and follow-up consultation with diagnosis (day 3) (Fig. 1 and data repository).²¹
The laboratory processed 360 breast cancer cases in 1 year, which required 1080 immunohistochemistry stains for the three breast cancer biomarkers. We observed a utilization efficiency of the estrogen receptor antibody of 70%, and assumed antibodies for progesterone receptor and human epidermal growth factor receptor-2 to have the same utilization efficiency. We estimated a laboratory test repeat rate for immunohistochemistry and STRAT4 of 10%.

**Cost of immunohistochemistry**

We calculated a cost of breast cancer diagnosis using immunohistochemistry of US$ 138.29 (lower–upper bound estimate: US$ 126.98–149.41; Table 1). Laboratory steps comprised 58.5% (80.88/138.29) of costs: 9.8% (US$ 13.55) for histological diagnosis and 48.7% (US$ 67.33) for biomarker analysis. Consumables were the primary cost drivers, comprising 72.8% (US$ 100.72) of costs. Core needle biopsy was the most expensive consumable, costing US$ 25.35 per patient (data repository).21 Personnel costs contributed 18.0% (US$ 24.85) to costs (Table 1), of which physician specialists, the most expensive, comprised 57.8% (US$ 14.37) of personnel costs (data repository).21

**Immunohistochemistry versus STRAT4**

We calculated that biomarker analysis by STRAT4 cost US$ 7.33 (lower–upper bound estimate: US$ 1.52 to 14.15) or 10.9% (7.33/67.33) less per patient than for biomarker analysis by immunohistochemistry (Table 2). We noted that the decrease in cost of consumables (US$ 57.38 for STRAT4 versus US$ 61.67 for immunohistochemistry; difference US$ 4.29) contributed the largest portion (58.6%; 4.29/7.33) of the cost saving of STRAT4. Consumables comprised 91.6% (61.67/67.33) of immunohistochemistry costs and 95.6% (57.38/60.00) of STRAT4 costs; biomarker analysis by immunohistochemistry requires 17 consumables, while biomarker analysis by STRAT4 requires only four. For immunohistochemistry, 76.2% (46.97/61.67) of consumable costs were from monoclonal antibodies for estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 (US$ 12.97, 10.27 and 9.58, respectively, per patient), and for the Dako REAL EnVision Detection System (US$ 14.15 per patient). For STRAT4, 98.8% (56.71/57.38) of consumable costs were from the STRAT4 cartridge kit (US$ 56.71 per patient; data repository).21

Biomarker analysis using STRAT4 saves 20 min or 60.6% (20/33) of personnel time per patient compared with immunohistochemistry (13 min for STRAT4 versus 33 min for immunohistochemistry; Table 2). The decreased personnel time corresponds to US$ 2.37 in cost.
savings, which accounts for 32.3% (2.37/7.33) of the savings made by using STRAT4. Of the 20 min saved with STRAT4 (note that data are subject to rounding errors), 15 min were saved by the laboratory technician (11 min for STRAT4 versus 26 min for immunohistochemistry) and 6 min were saved by the pathologist (1 min for STRAT4 versus 7 min for immunohistochemistry; data repository).21 With an annual volume of 360 breast samples at the laboratory for biomarker analysis, using STRAT4 instead of immunohistochemistry could save US$ 2638.53 (lower–upper bound estimate: US$ 603.22 to 4585.58) and 122.6 hours of personnel time annually (note that data in Table 2 are rounded to the nearest minute).

**Sensitivity analysis**

We did not observe any major effect on cost or personnel time when increasing batch volumes of immunohistochemistry and STRAT4 analyses (Table 3). However, the antibody utilization efficiency of immunohistochemistry impacted the cost savings made by using STRAT4: the cost of biomarker analysis by STRAT4 is almost the same as by immunohistochemistry for laboratories that operate at 90% antibody utilization efficiency (difference: US$ 0.07). We noted that the number of receptors assessed substantially affects the cost comparison: biomarker analysis by STRAT4 costs US$ 38.23 (175.6%) or 13.76 (29.8%) more per patient than by immunohistochemistry at laboratories that only assess estrogen receptor status or estrogen and progesterone receptor status (relative to assessing three breast cancer biomarkers), respectively. For laboratories that assess the status of proliferation marker Ki67 (in addition to the other three biomarkers), the use of STRAT4 results in a saving of US$ 22.78 (27.5%) per patient. We also observed that the cost of the cartridge is important; if the STRAT4 cartridge is made available at the same price as the Xpert® severe acute respiratory syndrome coronavirus 2 (US$ 14.90 per kit) or the *Mycobacterium tuberculosis* /rifampin resistance Ultra (US$ 9.98 per kit) cartridges, the use of STRAT4 instead of immunohistochemistry would result in a cost saving of US$ 45.94 (68.2%) or US$ 51.35 (76.3%) per patient, respectively.

**Discussion**

For a real-world immunohistochemistry antibody utilization efficiency of 70%, we demonstrated that STRAT4 is a moderate cost-saving and robust time-saving alternative to immunohistochemistry for biomarker analysis of three breast cancer biomarkers. However, our sensitivity analysis showed that when laboratories operate at antibody utilization efficiencies of 90% or greater, STRAT4 is more expensive than immunohistochemistry. Although there are no reports in the
literature of antibody utilization efficiencies for laboratories in sub-Saharan Africa, operational and supply chain challenges likely prevent them from achieving 90% efficiency, as was the case at Butaro Cancer Centre of Excellence (which has an antibody utilization efficiency of 70%). Less-specialized laboratories may operate at even lower immunohistochemistry efficiencies, meaning that STRAT4 could yield even greater cost and time savings for these facilities.

We also demonstrated that the cost savings of STRAT4 were also sensitive to the number of breast cancer molecular markers assessed. While all four biomarkers (ESRI, PGR, ERBB1 and Mki67) reported with the STRAT4 assay are clinically meaningful, their results are not always actionable in low- and middle-income countries. STRAT4 has fixed costs irrespective of the intended number of biomarkers, and may cost more for cancer programmes that are currently performing immunohistochemistry only for hormone receptor status (estrogen and/or progesterone). However, as therapies targeting human epidermal growth factor receptor-2 (including biosimilars) become increasingly available, more laboratories in sub-Saharan Africa (including Butaro Cancer Centre of Excellence) are pursuing routine human epidermal growth factor receptor-2 analysis.

Given the expanding footprint of GeneXpert® across Africa, there is growing interest in the potential of STRAT4 to streamline and decentralize breast cancer molecular diagnostics to less-specialized facilities. Many laboratories across sub-Saharan Africa have the capability to process tissue and diagnose breast cancer, but do not perform immunohistochemistry because of financial, technical and supply-chain limitations. Our results suggest that STRAT4 has the potential to reduce the human and capital resources necessary for these laboratories to perform breast cancer biomarker analysis. Given the scarcity of pathologists and laboratory technicians in sub-Saharan Africa, the time saved by personnel with STRAT4 is incredibly valuable and can enable personnel to complete additional laboratory processes. Preliminary data also suggest that the STRAT4 assay has similarly favourable diagnostic performance with fine-needle aspirate samples, yielding the potential to expand availability of breast cancer molecular diagnostics to smaller district-level hospitals where traditional biopsies and tissue processors are not available.

Although STRAT4 may reduce human and capital barriers for breast cancer biomarker analysis, its absolute cost of US$ 60 will likely limit its wide adoption in sub-Saharan Africa (where the annual health-care spending per capita is US$ 84). The primary cost of diagnostics
with GeneXpert® is the price of the cartridge. In the past decade, global multisectoral investments have helped to lower the price of the Xpert® tuberculosis diagnostic assays to approximately US$ 10 per cartridge, transforming tuberculosis care in sub-Saharan Africa. Driving down the price for STRAT4 could similarly revolutionize access to breast cancer molecular analysis.

The adoption of STRAT4 instead of breast immunohistochemistry by laboratories will likely be influenced by several implementation factors beyond cost, such as assay training, turn-around time and supply-chain feasibility. First, in our experience, training for STRAT4 (conducted over 2 days via video teleconference) was substantially less burdensome than that for manual immunohistochemistry, which required extensive and repeated in-person trainings to maintain reproducible results. Facilities with fewer skilled personnel may therefore be more willing to adopt STRAT4. Second, given that STRAT4 requires substantially less personnel time, it may also decrease turn-around time for breast cancer diagnostic results (currently about 2 weeks at Butaro Cancer Centre of Excellence), which is critical for initiating optimal therapy. Finally, given that STRAT4 requires substantially fewer consumables, it may be less vulnerable to supply-chain challenges. The 17 reagents required for immunohistochemistry rely on complex supply chains; when one reagent is out of stock, the entire process is halted, leading to diagnostic delays (a common issue for immunohistochemistry implementation in sub-Saharan Africa). Although GeneXpert® testing relies on fewer reagents, its use in sub-Saharan Africa has also been limited by stock-outs and non-functional modules.

Our study has several limitations. First, this cost-minimization analysis assumes that the diagnostic outcomes for immunohistochemistry and STRAT4 are equivalent: a reasonable assumption for laboratories with high-quality immunohistochemistry and in turn high concordance with STRAT4. For laboratories that struggle to maintain high-quality immunohistochemistry, STRAT4 may be more accurate; a cost–effectiveness analysis is therefore needed to account for downstream cost implications of inaccurate immunohistochemistry results. Second, we did not consider the cost of performing fluorescence in situ hybridization for immunohistochemistry-equivocal cases of human epidermal growth factor receptor-2, because it is not currently available in Rwanda. If potential fluorescence in situ hybridization costs were added to immunohistochemistry costs, STRAT4 would yield even greater cost savings. Third, training costs for both methods of biomarker analysis were not
included in this cost analysis. Given that the cost of biomarker analysis was primarily driven by consumables, we estimate that training cost differences between the two methods may not impact long-term costs but would likely impact upfront costs. Fourth, estimates for laboratory repeat rates and sample batching were drawn from personnel interviews, and therefore vulnerable to recall bias.

Given the challenges of maintaining efficient immunohistochemistry services in low-resource settings such as many sub-Saharan African laboratories, we consider that STRAT4 adoption could reduce the capital and human resource barriers to performing breast cancer biomarker analysis, leading to improved treatment selection and better clinical outcomes.

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Competing interests

LNS received research funding from the Breast Cancer Research Foundation. DR received institutional research funding from Cepheid, including salary for a research assistant, compensation for a laboratory technician and purchase of laboratory reagents and consumables for STRAT4 testing. TF received institutional research funding for a STRAT4 and immunohistochemistry comparison study, including for a GeneXpert® machine, STRAT4 supplies and consumables, and salary for a research assistant. Other authors declare no conflicts.

References


2. Accelerating access to genomics for global health: promotion, implementation, collaboration, and ethical, legal, and social issues: a report of the WHO Science


Table 1. **Cost of breast cancer diagnosis pathway with immunohistochemistry, Rwanda, 2021**

<table>
<thead>
<tr>
<th>Type of cost</th>
<th>Cost, US$(^a) Step along breast cancer diagnosis pathway</th>
<th>Type-of-cost total (% of absolute total) [lower–upper bound estimate](^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-laboratory: histologic diagnosis</td>
<td>Laboratory: biomarker analysis(^b)</td>
</tr>
<tr>
<td>Personnel</td>
<td>18.25</td>
<td>3.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location(^d)</td>
<td>1.42</td>
<td>3.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consumables</td>
<td>31.87</td>
<td>7.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect(^e)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Step cost (% of absolute total)(^f)</td>
<td>51.54 (37.3)</td>
<td>13.55 (9.8)</td>
</tr>
<tr>
<td></td>
<td>[47.22 to 54.58]</td>
<td>[12.76 to 14.42]</td>
</tr>
</tbody>
</table>

NA: not applicable; ND: not defined; US$: United States dollars.

\(^a\) Cost in US$ converted from Rwandan francs in 2021. Time and cost data rounded to nearest minute and cent, respectively, for inclusion in table; totals calculated using unrounded data (see data repository).

\(^b\) Biomarker analysis at Butaro Cancer Centre of Excellence includes manual immunohistochemistry for estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 status.

\(^c\) Lower bound estimates include 25th percentile time estimates (non-laboratory steps), 15% of electricity costs attributed to laboratory and estimated annual laboratory volume plus 10% (altering the cost of consumables per patient). Upper bound estimates include 75th percentile time estimates (non-laboratory steps), 35% of electricity costs attributed to laboratory and estimated annual laboratory volume minus 10% (altering the cost of consumables per patient).

\(^d\) For laboratory equipment costing more than US$ 3000, a separate capacity cost rate was calculated per item of equipment. Based on the length of equipment utilization per sample, an allocated capacity cost rate per item of equipment was added to the location cost.

\(^e\) Indirect costs include fuel, telephone, internet, security services, cleaning services, office supplies, maintenance, patient food and patient housing.

\(^f\) Percentage of total costs for non-laboratory and laboratory steps do not add up to 100% because indirect costs (4.2%) are not assigned to any individual step.
Table 2. Comparison of time and cost for breast cancer biomarker analysis by immunohistochemistry and by Xpert® STRAT4 assay, Rwanda, 2021

<table>
<thead>
<tr>
<th>Type of cost</th>
<th>Immunohistochemistry</th>
<th>Xpert® STRAT4</th>
<th>Absolute saving (relative saving, %) achieved by using STRAT4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time, minutes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cost, US$&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Time, minutes&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Personnel</td>
<td>33</td>
<td>3.27</td>
<td>13</td>
</tr>
<tr>
<td>Location&lt;sup&gt;b&lt;/sup&gt;</td>
<td>54</td>
<td>2.39</td>
<td>33</td>
</tr>
<tr>
<td>Consumables&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>61.67</td>
<td>–</td>
</tr>
<tr>
<td>Biomarker analysis</td>
<td></td>
<td>67.33</td>
<td>–</td>
</tr>
<tr>
<td>[lower–upper bound estimate]&lt;sup&gt;d&lt;/sup&gt;</td>
<td>[61.13 to 74.55]</td>
<td></td>
<td>[59.61 to 60.40]</td>
</tr>
<tr>
<td>Total annual saving [lower–upper bound estimate]&lt;sup&gt;e&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

US$: United States dollars.

<sup>a</sup> Cost in US$ converted from Rwandan francs in 2021. Time and cost data rounded to nearest minute and cent, respectively, for inclusion in table; totals calculated using unrounded data (see data repository).

<sup>b</sup> For laboratory equipment costing more than US$ 3000, a separate capacity cost rate was calculated per item of equipment. Based on the length of equipment utilization per sample, an allocated cost capacity rate per equipment was added to the location cost.

<sup>c</sup> Immunohistochemistry requires 17 consumables; STRAT4 requires 4 consumables. The antibody utilization efficiency for estrogen receptor was 70%; progesterone receptor and human epidermal growth factor receptor-2 antibodies were assumed to have the same utilization efficiency. The price of Xpert® STRAT4 was assumed to be similar to that of the Xpert® BCR-ABL Ultra cartridge at US$ 50 per cartridge kit.

<sup>d</sup> Lower bound estimates include 15% of electricity costs attributed to laboratory, estimated annual laboratory volume plus 10% (altering cost of consumables per patient); upper bound estimates include 35% of electricity costs attributed to laboratory, estimated annual laboratory volume minus 10% (altering cost of consumables per patient).

<sup>e</sup> Butaro Cancer Centre of Excellence laboratory assesses 360 breast samples for estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 annually.
Table 3. Sensitivity analyses of laboratory-specific parameters to compare time and cost estimates of breast cancer biomarker analysis using immunohistochemistry and Xpert® STRAT4 assay, Rwanda, 2021

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Immunohistochemistry</th>
<th>Xpert® STRAT4</th>
<th>Absolute saving (relative saving, %) achieved by using STRAT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost estimate per patient&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunohistochemistry batches (primary: 40 slides)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 slides</td>
<td>33</td>
<td>63.33</td>
<td>13</td>
</tr>
<tr>
<td>20 slides</td>
<td>38</td>
<td>68.53</td>
<td>13</td>
</tr>
<tr>
<td>Antibody utilization efficiency (primary: 70%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90% of antibody vial used</td>
<td>33</td>
<td>60.07</td>
<td>13</td>
</tr>
<tr>
<td>80% of antibody vial used</td>
<td>33</td>
<td>63.27</td>
<td>13</td>
</tr>
<tr>
<td>60% of antibody vial used</td>
<td>33</td>
<td>72.85</td>
<td>13</td>
</tr>
<tr>
<td>No. receptors analysed (primary: three)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One (estrogen receptor)</td>
<td>11</td>
<td>21.77</td>
<td>13</td>
</tr>
<tr>
<td>Two (estrogen and progesterone receptors)</td>
<td>22</td>
<td>46.24</td>
<td>13</td>
</tr>
<tr>
<td>Four (estrogen and progesterone receptors, human epidermal growth factor receptor-2, Ki67)</td>
<td>44</td>
<td>82.78</td>
<td>13</td>
</tr>
<tr>
<td>STRAT4 batching (primary: 4-module GeneXpert® system)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-module GeneXpert® system</td>
<td>33</td>
<td>67.33</td>
<td>13</td>
</tr>
<tr>
<td>2-module GeneXpert® system</td>
<td>33</td>
<td>67.33</td>
<td>13</td>
</tr>
<tr>
<td>Xpert® cartridge price (primary: 50.00)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US$ 50.00</td>
<td>33</td>
<td>67.33</td>
<td>13</td>
</tr>
<tr>
<td>US$ 30.00</td>
<td>33</td>
<td>67.33</td>
<td>13</td>
</tr>
<tr>
<td>US$ 20.00</td>
<td>33</td>
<td>67.33</td>
<td>13</td>
</tr>
<tr>
<td>US$ 14.90 (price of Xpert® SARS-CoV-2 cartridge kit)</td>
<td>33</td>
<td>67.33</td>
<td>13</td>
</tr>
<tr>
<td>US$ 9.98 (price of Xpert® MTB/RIF Ultra cartridge kit)</td>
<td>33</td>
<td>67.33</td>
<td>13</td>
</tr>
</tbody>
</table>


<sup>a</sup> Estimates are taken from Table 2.

<sup>b</sup> The antibody utilization efficiency was based on the estrogen receptor antibody utilization efficiency of the laboratory.

<sup>c</sup> 2-, 4- and 16-module batching for STRAT4 corresponds to 14-, 28- and 112-sample batching for preparation, respectively, assuming that the GeneXpert® system can be run seven times in 1 day (each run takes 70 min).

<sup>d</sup> The price of the 2-, 4- and 16-module Xpert® machines was US$ 12,030, 17,500 and 64,350, respectively. The price of Xpert® STRAT4 was assumed to be similar to that of the Xpert® BCR-ABL Ultra cartridge, that is, US$ 50 per cartridge kit.

Note: Cost in US$ converted from Rwandan francs in 2021. Time and cost data rounded to nearest minute and cent, respectively, for inclusion in table.
Fig. 1. Process map for breast cancer diagnosis pathway, based on personnel interview and patient shadowing at Butaro Cancer Centre of Excellence, Rwanda, 2021

1a. Initial Consultation (Day 1)

1b. Biopsy (Day 2)

1c. Follow up Consultation (Day 3)

A total of 40 patients were shadowed: 20 patients were shadowed at the clinic, representing patients presenting for initial consultation (day 1) or follow-up consultation (day 3), and 20 additional patients were shadowed for the biopsy (day 2).

For Step 8b, Laboratory (diagnosis), time estimates are weighted according to biopsy type.

All processes in Laboratory (biomarker analysis) have an occurrence of 110% because both biomarker analysis methods had an estimated repeat rate of 10%.

Note: All steps have a 100% probability of occurrence unless otherwise noted.