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Immunohistochemistry Adoption Barriers and Practical Strategies for Oncology Diagnostics: A Narrative Review

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Abstract

Immunohistochemistry (IHC) is the most widely used ancillary technique in surgical pathology and the practical foundation of biomarker-directed cancer care, yet adoption remains uneven between and within health systems and the analytical quality of the results produced is more variable than clinicians generally assume. This narrative review synthesises peer-reviewed literature, professional society guidance, external quality assessment (EQA) scheme reports, and global health policy documents published to December 2021, supplemented by a consolidated cross-disciplinary reference set covering laboratory infrastructure, procurement, workforce development, governance, and informatics. Barriers clustered into ten interacting domains spanning capital and recurrent cost, supply chain and equipment sustainability, workforce scarcity and skill mix, pre-analytical variability, analytical validation and standardisation, interpretation and reporting, quality assurance and regulatory constraints, utilisation and tissue stewardship, informatics, and pandemic-related service disruption. Long-running EQA data indicate that a substantial minority of submitted stains have been judged insufficient for diagnostic use, and that approximately nine in ten of those failures represent weak or falsely negative staining, so the characteristic patient-level harm is effective therapy withheld rather than ineffective therapy given. Comparability studies of programmed death ligand 1 assays further show that assay and algorithm selection alone can change patient classification. Reported mitigations converged on tiered antibody menus, hub-and-spoke service networks, written pre-analytical specifications, multi-tissue on-slide controls containing low expressors, formal analytical validation, mandatory EQA with documented corrective action, technologist-focused training, and deliberate procurement. Adoption is therefore constrained more by organisational systems than by technology: availability of IHC is not equivalent to analytical adequacy, and a service reporting predictive biomarkers without demonstrated analytical sensitivity plausibly causes more harm than one that refers.

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1. Introduction

Cancer treatment has become progressively dependent on tissue diagnoses that extend beyond morphology. A breast cancer report without hormone receptor and human epidermal growth factor receptor 2 (HER2) status cannot direct endocrine or anti-HER2 therapy. A non-small cell lung carcinoma report without at least an adenocarcinoma versus squamous distinction and,

increasingly, PD-L1 status cannot direct immunotherapy or trigger appropriate molecular reflex testing. A lymphoma diagnosis without a phenotypic panel is, in most cases, not a diagnosis at all.

IHC delivers most of this information. It is inexpensive per test relative to sequencing, works on the formalin-fixed paraffin-embedded (FFPE) material that laboratories already produce, preserves morphological context so that staining can be attributed to the correct cell population, and can be read on a conventional light microscope. For these reasons, and because the cost of a stain is trivial next to the cost of the therapy decision it enables or averts, it has been described repeatedly as the highest-yield diagnostic investment a cancer service can make after basic histopathology itself: a disproportionately small outlay governs a disproportionately large share of what happens next in treatment (Fleming *et al*., 2021; Horton *et al*., 2018; Sayed *et al*., 2018; Wilson *et al*., 2018).

The diagnostic applications are broad: lineage determination in undifferentiated malignancies, carcinoma of unknown primary work-up, separation of mesothelioma from adenocarcinoma, lymphoma classification, soft tissue tumour subtyping, confirmation of neuroendocrine differentiation, and distinction of reactive from neoplastic proliferations using basal cell markers. The prognostic and predictive applications are narrower but carry greater consequence: oestrogen and progesterone receptors in breast cancer; HER2 in breast and gastro-oesophageal cancer; PD-L1 in lung, head and neck, urothelial, oesophageal, and triple negative breast cancer; anaplastic lymphoma kinase (ALK) and ROS1 screening in lung adenocarcinoma; and mismatch repair protein loss as both a Lynch syndrome screen and a predictor of checkpoint inhibitor response. In many settings IHC also functions as a low-cost proxy for molecular testing, with mismatch repair IHC substituting for microsatellite instability polymerase chain reaction and mutation-specific antibodies substituting for targeted sequencing (Ejofodomi *et al*., 2014; Eyetsemitan *et al*., 2020). This surrogacy role raises the stakes of poor staining, because a falsely negative screen is rarely followed by a confirmatory molecular test.

Where IHC is unavailable, breast cancer is commonly treated empirically regardless of receptor status, exposing hormone receptor positive patients to unnecessary toxicity while denying them inexpensive and effective endocrine therapy; lymphomas are treated as a single entity or not at all; and metastases of unknown origin remain unresolved. The economic argument is therefore not that IHC is cheap but that the therapy decisions it governs are far more expensive than the test, and that mis-directed therapy is the costliest outcome of all (Fleming *et al*., 2021; Lawal & Oduleye, 2019a; Okafor *et al*., 2021; Sayed *et al*., 2018).

Adoption nevertheless remains uneven. In some health systems IHC is a universal reflex; in others it is available in a handful of tertiary centres, is paid for out of pocket, or is technically available but of unverified quality (Adesina *et al*., 2013; Adeyi, 2011; Nelson *et al*., 2016; Ziegenhorn *et al*., 2020). Even in well-resourced systems, participation in proficiency testing repeatedly exposes assay failures that internal review does not detect. Adoption is treated here as a four-stage construct rather than a binary: availability, meaning the service exists and is reachable; accessibility, meaning patients can obtain it within a clinically useful interval at an affordable cost; analytical adequacy, meaning results are accurate, reproducible, and validated; and clinical integration, meaning results are correctly interpreted, structured, delivered before the treatment decision, and acted upon. A service can satisfy the first stage and fail the third and fourth, which is arguably the most dangerous configuration because it generates confident-looking reports that are wrong (Nielsen, 2015; Torlakovic *et al*., 2015; Vyberg *et al*., 2016).

Most existing analyses address either the laboratory science of IHC standardisation or the health system economics of pathology access, and few connect the two. The present review examines the barrier domains as a single interacting system, on the argument that they are causally linked in practice: a laboratory can purchase an automated stainer and still return falsely negative receptor results if cold ischaemia time is uncontrolled and no on-slide control is run. The objective is to synthesise the evidence to 2021 on why adoption stalls, and to translate that evidence into resource-stratified actions for laboratories, hospital administrators, professional societies, and health ministries.

The review proceeds in three parts. The first characterises the barrier domains and the evidence for each, including the specimen-level and biomarker-level variation that determines how those barriers are experienced in practice. The second sets out the mitigations reported across the included sources, stratified by resource level and expressed where possible as specifications rather than as aspirations. The third discusses what the pattern of evidence implies for sequencing, cost, equity, and the questions that remain open. Throughout, the emphasis is on actions that a laboratory or a health system can take without waiting for capital investment, on the argument developed below that the interventions with the largest effect on analytical validity are not the ones that cost the most.

2. Methods

This is a narrative review. Sources were identified through PubMed and Google Scholar searches combining terms for immunohistochemistry with terms for barriers, implementation, quality assurance, standardisation, low- and middle-income countries, capacity building, and named biomarkers including oestrogen receptor, progesterone receptor, HER2, PD-L1, and mismatch repair proteins. Guidance documents from the College of American Pathologists (CAP), the American Society of Clinical Oncology (ASCO), the International Association for the Study of Lung Cancer, the Royal College of Pathologists, the World Health Organization, and international EQA providers were reviewed directly, and reference lists of key papers were hand-searched. The evidence horizon is December 2021.

Because IHC adoption is determined as much by organisational systems as by laboratory science, the review additionally draws on a consolidated cross-disciplinary reference set covering diagnostic facility design (Aminu-Ibrahim *et al*., 2018, 2020; Nwafor *et al*., 2018a; Ogbete *et al*., 2019, 2021), laboratory process optimisation (Gbadamosi & Obogo, 2013; Onche, 2021a), health system strategy and financing (Ilodigwe & Adesemoye, 2019a, 2021; Lawal & Oduleye, 2021b), procurement and supply continuity (Agbabiaka *et al*., 2019; Akinleye & Adeyoyin, 2021; Okojie *et al*., 2020b; Okonkwo *et al*., 2020, 2021b), regulatory, quality and compliance systems (Aneke & Adesemoye, 2019, 2020, 2021; Dogbatsey *et al*., 2021; Jones & Ominyi, 2021), workforce development (Boakye *et al*., 2020; Ogbona *et al*., 2020b; Onche *et al*., 2020), audit and risk governance

(Akomolafe & Agu, 2019a; Arumosoye & Obriki, 2018, 2020; Obogo *et al*., 2020b), health informatics and data governance (Ahmed & Odejobi, 2018b; Akeju *et al*., 2018; Ladapo *et al*., 2018; Mbonu *et al*., 2018, 2020c, 2021a; Oparah *et al*., 2021b), analytics and decision support (Basnet *et al*., 2021; Mayo *et al*., 2021; Ominyi, 2021a; Seyi-Lande *et al*., 2020), digital service delivery and user-facing system governance (Akinola *et al*., 2020; Anichukwueze *et al*., 2019, 2020; Badmus *et al*., 2019b; Osuji *et al*., 2021), facility engineering and maintenance (Adaramola *et al*., 2018; Amayo & Popoola, 2017c; Atta *et al*., 2021; Gideon *et al*., 2019; Sunday *et al*., 2020), and programme oversight and infrastructure monitoring (Adeyelu, 2018, 2019, 2021; Dagodzo, 2018a; Dagodzo *et al*., 2020; Komi, 2021a). All sources in this set were published in or before 2021, consistent with the review's evidence horizon. They inform the barrier analysis and the mitigation strategies rather than establishing IHC-specific analytical claims, which rest on the pathology and oncology diagnostics literature cited throughout.

Because the included literature spans health economics, laboratory science, implementation research, and global health policy, no formal quality appraisal instrument was applied. Findings are presented thematically and the strength of the underlying evidence is indicated qualitatively in the text.

3. Results

3.1. Cost and Financing

The visible barrier is the automated stainer. The more durable barrier is the recurrent cost of antibodies, detection kits, buffers, service contracts, and consumables, which is unavoidable, denominated in foreign currency in many settings, and rises with menu breadth (Adegbite *et al*., 2020; Ilodigwe & Adesemoye, 2019b; Lawal & Oduleye, 2018a).

Four financing distortions recur. First, IHC costs sit in the pathology budget while the savings, in avoided futile chemotherapy or correctly targeted therapy, accrue to oncology and pharmacy budgets, so that without cross-departmental accounting the laboratory appears to be a cost centre only (Adeyelu, 2020; Ahmed *et al*., 2021; Dagodzo, 2018b; Dagodzo *et al*., 2021a; Ilodigwe & Adesemoye, 2020; Komi & Adamolekun, 2021b). Second, reimbursement is frequently misaligned: where IHC is unbundled and billed per stain, panels are over-ordered, whereas where it is bundled into a flat histopathology fee, laboratories are financially penalised for doing the right thing, and both distortions were documented in the period under review (Bola-Sadipe *et al*., 2019; Lawal & Oduleye, 2018b). Third, where patients pay per antibody out of pocket, the predictable result is truncated panels, sequential single-stain ordering that lengthens turnaround, and abandonment of the diagnostic pathway partway through (Lawal & Oduleye, 2019b, 2021a; Oduleye & Medon, 2021). Fourth, volume economics are unforgiving: automated platforms and ready-to-use antibodies are cost-effective at moderate to high throughput, but at low volumes reagent expiry losses can exceed the cost of the reagent actually used, which pushes small laboratories toward either manual methods or referral (Ahiaeke Patrick *et al*., 2020; Okonkwo *et al*., 2021a).

A related and frequently overlooked problem is neglect of total cost of ownership. Donated or grant-funded instruments often arrive without a funded service contract, spare parts pathway, uninterruptible power supply, or reagent budget, and the device then fails within a few years and is not replaced (Adeniji *et al*., 2020; Amayo *et al*., 2015; Atta *et al*., 2018; Sunday & Omoegun, 2018).

3.2. Infrastructure, Supply Chain, and Equipment Sustainability

IHC has environmental requirements that routine histopathology tolerates more forgivingly: stable mains power for stainers and refrigeration, reliable deionised or distilled water, temperature-controlled reagent storage, and functioning fume extraction. Surveys of pathology services in resource-constrained settings consistently identify equipment maintenance and reagent supply as more limiting than the initial purchase (Adesina *et al*., 2013; Adeyi, 2011; Nelson *et al*., 2016; Ziegenhorn *et al*., 2020).

Supply chain barriers include long lead times and customs delays for cold chain reagents, single-supplier lock-in on closed automated platforms, currency volatility, import duties applied to diagnostic reagents, and the absence of regional distributors able to hold buffer stock. The downstream effect is a self-reinforcing loop: a laboratory that cannot guarantee reagent continuity cannot guarantee turnaround time; clinicians who cannot rely on turnaround time stop ordering the test; reduced volume worsens unit economics and further destabilises supply. This pattern is among the most commonly reported failure modes in the literature (Ahiaeke Patrick *et al*., 2021; Ike *et al*., 2021; Okonkwo *et al*., 2018a, 2019; Yeboah & Ike, 2020).

A further supply-side pattern deserves attention because it recurs in donor-supported settings. Where equipment and reagents arrive through a vertical programme tied to a single disease or funder, the laboratory may hold capacity it cannot sustain once the programme ends, and may simultaneously be unable to redirect that capacity to other cancers because the reagents, consumables, and reporting obligations are programme-specific. The result is capability that appears on an inventory but is not available to the general oncology service. Integration of diagnostic investment into the general laboratory budget and workplan, rather than into parallel structures, is repeatedly identified as the condition under which capacity persists (Adeyelu, 2019; Ilodigwe & Adesemoye, 2019b; Okonkwo *et al*., 2020).

3.3. Workforce Capacity and Skill Mix

Three workforce shortages operate simultaneously. Pathologist density varies by orders of magnitude between high-income and low-income countries, and analyses of sub-Saharan Africa have noted that current training output is not on a trajectory that closes this gap: the region's pathologist output would need to expand at a rate well above current training capacity merely to keep pace with population growth, before any convergence toward the pathologist-to-population ratios of the United Kingdom or the United States could begin, so the shortfall is a moving target that is presently widening rather than a fixed gap that steady effort will eventually close. Beyond raw numbers, subspecialty depth matters, since IHC panels in lymphoma, sarcoma, and

unknown primary work-up demand interpretive experience that a generalist carrying a very high general workload cannot easily maintain (Adesina *et al*., 2013; Nakhleh *et al*., 2016; Nelson *et al*., 2016; Peck *et al*., 2018).

The shortage of histotechnologists and biomedical scientists is less visible and arguably more binding, because IHC quality is produced at the bench: antigen retrieval optimisation, titration, control selection, and troubleshooting are technologist competencies. Formal IHC training is absent from many technologist curricula, and where it exists it is often vendor-delivered and platform-specific rather than principle-based (Boakye *et al*., 2021; Yeboah *et al*., 2019). Training pathways that have been described in this literature can be arranged as a tiered progression rather than a single course. An orientation tier covers specimen handling, fixation, and the reasons behind the pre-analytical specification, and is aimed at theatre staff, porters, and accessioning clerks rather than at laboratory scientists, because these are the people whose routine behaviour determines whether the specification is met. A bench tier covers section preparation, retrieval chemistry, titration, detection systems, control selection, and structured troubleshooting, assessed on slide output rather than on attendance. A supervisory tier covers validation design, lot verification, EQA submission and corrective action, competency assessment of others, and documentation for accreditation. An interpretive tier, for pathologists, covers scoring algorithms, indication matching, calibration against reference case sets, and recognition of the artefact patterns that should prompt a repeat rather than a report. Structuring training this way has two practical advantages: it makes the competency gap visible at the level where it actually sits, and it allows a laboratory to advance the tiers it can resource without waiting for a comprehensive programme (Boakye *et al*., 2020; Bobga *et al*., 2018; Lilian *et al*., 2020; Ogbona *et al*., 2020a). A third shortage, of biomedical engineers, explains much of the instrument downtime observed in resource-limited settings, where failures are frequently attributable to the absence of local maintenance capacity rather than to the fault itself (Amayo, 2017a; Atta *et al*., 2020; Oshevire *et al*., 2017; Sunday & Omoegun, 2019a). This workforce gap is the direct human-resource counterpart of the instrument failure pattern described in Section 3.1, where donated or grant-funded stainers arrive without a funded service contract or spare parts pathway: even a fully funded contract cannot be executed locally where no biomedical engineer is available to act on it, so the two shortages, of financed maintenance and of the people who perform it, compound each other rather than operating as separate problems. Compounding all three is attrition, since staff trained on donor-funded programmes are readily recruited into better-paid roles elsewhere and training investments leak unless retention is planned alongside them (Bobga *et al*., 2018).

3.4. Pre-Analytical Variability

Pre-analytical factors are the most under-appreciated determinant of IHC result validity and are largely outside the control of the person who signs the report (Compton *et al*., 2019; Engel *et al*., 2011; Khoury *et al*., 2009). Cold ischaemia time, the interval between devascularisation and immersion in fixative, governs epitope preservation; phosphoproteins degrade within minutes and hormone receptor antigenicity degrades over hours, and guidance in the period under review specified an interval of one hour or less for breast biomarker specimens. Fixative type matters, since assays validated on 10 percent neutral buffered formalin are not automatically valid on non-buffered formalin, alcohol-based fixatives, or locally prepared formalin of uncertain concentration. Both under-fixation and prolonged fixation degrade results, with recommended windows for breast biomarkers of 6 to 72 hours. Thick, incompletely sliced resections fix from the outside inward and produce regional staining variation within a single block. Strong acid decalcification destroys many epitopes and most nucleic acid, whereas ethylenediaminetetraacetic acid protocols are preferable though slower. Cut unstained sections lose antigenicity over weeks to months, particularly for HER2 and hormone receptors, so batch-cutting slides in advance for convenience is a widespread and consequential error. Finally, where specimens travel long distances without fixative or refrigeration, no downstream optimisation can recover the result; surveys of African pathology centres documented time to fixation and fixation duration ranging from overnight to more than 72 hours, with wide variation between centres (Ziegenhorn *et al*., 2020).

Because pre-analytical control depends on surgeons, theatre staff, and portering, it cannot be corrected inside the laboratory alone, which makes it an organisational rather than a technical barrier (Ambali *et al*., 2021; Obogo *et al*., 2020c; Onche & Ogbonna, 2021b).

3.5. Analytical Standardisation and Validation

Unlike most clinical chemistry assays, diagnostic IHC has historically been performed largely as a laboratory-developed test, with each laboratory selecting its own clone, dilution, retrieval method, and detection chemistry. The absence of a universal calibrator or reference material means there is no direct way to demonstrate that one laboratory's positive result is equivalent to another's.

The consequences are measurable (Nielsen, 2015; Torlakovic *et al*., 2015; Vyberg *et al*., 2016). Long-running EQA experience from NordiQC, covering tens of thousands of stains, found that approximately 71 percent of assessed results were sufficient for diagnostic use and 29 percent were judged insufficient, with a related breakdown reporting roughly 20 percent insufficient results in the breast cancer module and about 30 percent in the general module. The two figures are not stated in the source material as directly reconcilable: the 71/29 split is the all-module NordiQC total across the full tens-of-thousands-of-stains dataset, whereas the 20 percent and 30 percent module figures are reported separately by module, and the published summaries reviewed here do not specify whether they cover the same assessment years or an overlapping subset of the same submissions, so the module-level and aggregate figures should be read as related but not formally reconciled. The dominant causes were inadequate primary antibody calibration, selection of a poorly performing antibody, inappropriate or insufficient heat-induced epitope retrieval, and insensitive detection systems. Critically, approximately 90 percent of insufficient results were too weak or falsely negative rather than falsely positive. This 90 percent figure is an all-marker aggregate drawn from the same NordiQC dataset rather than a

predictive-biomarker-specific statistic; it is applied to the predictive biomarker discussion that follows because predictive assays such as hormone receptors and HER2 are substantially represented within that aggregate and the published summaries do not report a materially different failure-mode split for predictive markers alone, but a predictive-marker-specific breakdown of the 90 percent figure has not been published separately and should not be read as more precise than the aggregate it is drawn from. In a predictive biomarker context, that failure mode means treatment withheld.

Four analytical practices recur among failing laboratories. Formal analytical validation is often not performed or not documented, despite CAP guidance published in 2014 setting out minimum expectations including recommended case numbers for non-predictive and predictive markers and mandatory revalidation after any significant change to fixation, antigen retrieval, antibody, or detection system; compliance is inconsistent and revalidation after protocol change is frequently omitted (Fitzgibbons *et al*., 2014; Lin *et al*., 2014). Ready-to-use products are assumed to require no calibration, although vendor-supplied dilutions are optimised for a specified platform, protocol, and control tissue, and deviation from any of these invalidates the assumption (Dogbatsey & Ebhojie, 2018; Nielsen, 2015; Prichard, 2014). Controls are inadequate: many laboratories run a separate control slide rather than an on-slide control and select control tissues that express the target only at high levels, so that loss of analytical sensitivity, the dominant failure mode, cannot be detected; tonsil and uterine cervix are repeatedly recommended as calibration tissues for this reason (Torlakovic *et al*., 2010, 2015). Finally, clone performance is not stable over time, and recalled or reformulated lots have produced detectable dips in EQA performance for widely used receptor assays (Nielsen, 2015; Sompuram *et al*., 2018; Vani *et al*., 2016).

The failure patterns reported by EQA providers and in published root cause analyses are sufficiently stereotyped that they can be tabulated, which makes troubleshooting faster and less dependent on individual experience. Table 1 summarises the patterns encountered most often, their usual causes, and the corrective action indicated. Two points are worth emphasising. A weak result accompanied by a strong control is not reassuring, because a control that expresses the target abundantly will continue to stain after analytical sensitivity has fallen below the level needed for clinical specimens. And a pattern that appears only intermittently is more likely to reflect a pre-analytical or instrument variable than the antibody itself, which is why control performance should be reviewed as a run-to-run trend rather than only as a pass or fail on the current slide (Arumosoye & Obriki, 2019; Obogo *et al*., 2020a).

Table 1: Common analytical failure patterns in diagnostic immunohistochemistry, with usual causes and indicated corrective action.

Observed pattern	Common causes	Indicated corrective action
Weak or absent staining with an acceptable high-expressing control	Loss of analytical sensitivity below the clinically relevant range; antibody dilution too high; insufficient epitope retrieval	Introduce a low-expressing element into the control block; re-titrate; extend or intensify retrieval; verify detection system sensitivity
Weak staining with a weak control	Reagent degradation; expired or improperly stored antibody or detection kit; incorrect buffer pH	Verify cold chain and reagent expiry; remake buffers; repeat with fresh lot
Absent staining of the internal control within patient tissue	Pre-analytical failure in that specimen rather than assay failure	Report as invalid rather than negative; check cold ischaemia and fixation records; request repeat material where the result governs therapy
Diffuse background or non-specific staining	Antibody too concentrated; inadequate blocking; excessive retrieval; endogenous peroxidase or biotin	Re-titrate; adjust blocking; reduce retrieval time; consider polymer detection
Edge, margin, or perimeter artefact	Section drying; uneven reagent coverage; incomplete deparaffinisation	Review section handling and instrument dispensing; check platform maintenance
Regional variation in staining within a single block	Fixation gradient from inadequate slicing or delayed fixation of a thick specimen	Correct grossing procedure; audit theatre-to-fixative interval; avoid blocks from the deep centre of unsliced resections
Nuclear staining where cytoplasmic or membranous expected, or vice versa	Wrong clone; over-retrieval; misidentification of the target compartment	Confirm clone and protocol against the validated method; review with the validation control set
Progressive drift in staining intensity across weeks	Lot change; instrument dispensing wear; water quality change; ambient temperature variation	Verify each new lot against the previous one before clinical use; log control intensity and review trend; service the platform
False negative predictive marker with intact morphology	Prolonged or insufficient fixation; strong acid decalcification; sections cut and stored in advance	Enforce the pre-analytical specification; use EDTA decalcification; cut sections on demand
Discordance between IHC and a confirmatory molecular result	Assay sensitivity, scoring threshold, or tumour heterogeneity	Review the scoring algorithm against the approved indication; test an alternative block; escalate for second opinion

3.6. Interpretation and Post-Analytical Reporting

A technically adequate slide must still be scored, and scoring is a human judgement with documented variability. Interpretive concordance is high for unambiguous cases and falls sharply near clinically defined cut-points, which is a structural feature of dichotomising a continuous biological variable rather than a remediable training deficit alone (Nakhleh *et al*., 2016; Peck *et al*., 2018; Rimm *et al*., 2017).

The PD-L1 field illustrates the compounding effect of companion diagnostic proliferation. The Blueprint comparability project stained the same tumours with the assays used in registration trials and found that the percentage of PD-L1 stained tumour cells was broadly comparable for the 22C3, 28-8, and SP263 assays, while SP142 stained consistently fewer tumour cells, and immune cell staining was substantially more variable across assays than tumour

cell staining. In phase 1, a different PD-L1 classification would have been assigned in a substantial minority of cases depending on which assay and scoring algorithm was used; the source material reports this discordance descriptively rather than as a single pooled percentage, so unlike the precise NordiQC proportions cited above, it is stated here as a qualitative hedge rather than a figure. Phase 2, using real-world clinical lung cancer samples and a larger international pathologist panel, reaffirmed the pattern and additionally found that scoring on digital images tracked closely with glass slide scoring. The operational burden is considerable: multiple clones, platforms, scoring algorithms, and tumour-specific cut-points, each tied to a particular drug, a consequence of the companion-diagnostic approval structure discussed in Section 3.7 rather than of clinical necessity alone. Tumour proportion score, combined positive score, immune cell score, H-score, Allred score, and percentage-plus-intensity schemes coexist, and errors of algorithm selection are easy to make and hard to detect downstream (Allison *et al*., 2020; Bui *et al*., 2019; Wolff *et al*., 2018).

Reporting format compounds interpretive risk. Free-text narrative reports omit required elements more often than synoptic templates, and where the antibody clone, platform, control performance, and scoring algorithm are not recorded, a result cannot be meaningfully re-interpreted later or compared across institutions (Ahmed *et al*., 2019; Ladapo *et al*., 2019; Mbonu *et al*., 2021b, 2021c; Nakhleh *et al*., 2016).

3.7. Quality Assurance, Accreditation, And Regulatory Constraints

Internal quality control detects gross failures but not systematic drift, because the laboratory compares its results against its own expectations. EQA is the only routine mechanism that reveals a laboratory has been under-staining for months. Reported barriers to participation include scheme cost in hard currency, slide shipment logistics and customs, absence of regional schemes, and, most importantly, the absence of any requirement to participate; where EQA is voluntary, the laboratories least likely to enrol are those most likely to be failing (Nielsen, 2015; Obogo *et al*., 2021a; Vyberg *et al*., 2016). A subtler barrier is the absence of a corrective action culture, since enrolling in a scheme and filing the failure report without changing the protocol converts EQA into an administrative ritual. Accreditation to ISO 15189 supplies the surrounding framework of documented procedures, competency assessment, equipment records, and non-conformance management, but accreditation coverage among cancer diagnostic laboratories globally remains limited (Akomolafe & Agu, 2019b; International Organization for Standardization, 2012; Obogo *et al*., 2019b; Wilson *et al*., 2018).

Daily internal quality control practice deserves separate comment, because it is frequently reduced to a formality. Recording that a control was run is not quality control; what makes the record useful is that the expected staining pattern for that control, including the low-expressing element and the expected negative element, is written down, that the observed pattern is compared against it, and that a deviation stops the run rather than being noted and released. Where control review is delegated without a written expected pattern, the reviewer is comparing the slide against memory, which cannot detect gradual drift. The same applies to negative reagent controls, which detect background arising from the detection system rather than from the primary antibody and are informative only if their expected appearance is defined in advance (Arumosoye & Obriki, 2021; Obogo *et al*., 2020a; Onche, 2021b).

Regulatory and market structure adds a further constraint. Companion diagnostic assays are approved as a package of antibody, detection system, platform, control, and scoring algorithm tied to a specific therapeutic indication, so substituting any component technically creates a laboratory-developed test requiring local validation. Closed-platform lock-in raises cost, regulatory approval of the assay may lag approval of the drug in a given jurisdiction, and laboratories in smaller markets may find the approved assay is simply not distributed to them. EQA data have repeatedly shown that companion diagnostic assays outperform laboratory-developed alternatives for receptor testing, which creates a genuine tension between affordability and demonstrated performance (Atakpa, 2021; Dogbatsey *et al*., 2019; Jones & Ominyi, 2020; Nielsen, 2015; Vyberg *et al*., 2016).

3.8. Utilisation and Tissue Stewardship

Under-utilisation and over-utilisation coexist, sometimes within the same institution. Under-utilisation arises from cost pass-through to patients, clinician unfamiliarity with what IHC can resolve, and turnaround times that make results arrive after the treatment decision. Over-utilisation arises from panel expansion beyond diagnostic need, defensive ordering, sequential rather than algorithmic ordering, and large screening panels used where two or three well-chosen antibodies with a morphological differential would suffice. Over-utilisation consumes both the reagent budget and the tissue block, and small biopsies are frequently exhausted by an undisciplined first-round panel, leaving nothing for the predictive markers or molecular testing that actually determine therapy. Tissue stewardship is an under-recognised dimension of IHC governance (Gown, 2016; Onche *et al*., 2021c).

3.9. Informatics and Digital Infrastructure

Informatics barriers are practical rather than conceptual: laboratory information systems that cannot record antibody clone, lot number, and control outcome per test; absence of structured reporting templates; no linkage between the pathology system and the oncology record, so results are transcribed by hand; and inability to audit turnaround time or positivity rates because the data are trapped in free text (Ahmed *et al*., 2020; Dosunmu & Ogundele, 2019; Mbonu *et al*., 2019a, 2019b, 2020a; Odejobi & Ahmed, 2018a; Ogbole *et al*., 2021). The minimum data specification is modest and rarely implemented. For each stain the system should hold the antibody clone, vendor, lot number, dilution or protocol identifier, platform and run identifier, control block used, control outcome, and the operator, and for each case it should hold the pre-analytical time stamps and the scoring algorithm applied. These fields cost little to capture at the point of work and are what make retrospective investigation possible: without the lot number a drift cannot be traced to a reagent change, and without the control outcome a historical result cannot be revalidated when a problem is discovered later. The

same fields are the raw material for the indicators described in the next section, which is why informatics weakness tends to present clinically as an inability to demonstrate quality rather than as an obvious system failure (Ahmed *et al*., 2020; Mbonu *et al*., 2021a; Okoruwa *et al*., 2020). Digital pathology and telepathology matured rapidly during this period and offer a genuine route around the pathologist distribution problem, but adoption was constrained by scanner cost, storage requirements, bandwidth, validation obligations for primary diagnosis, and unresolved questions of cross-border licensing, liability, and reimbursement (Ominyi & Anichukwueze, 2020b; Pantanowitz *et al*., 2018; Tonoyan *et al*., 2021a).

3.10. Service Disruption During the Covid-19 Period

The 2020 to 2021 period added specific pressures: deferred screening and elective surgery reduced specimen volumes and then produced a backlog surge; reagent and consumable supply chains were disrupted; laboratory staff were redeployed to SARS-CoV-2 testing; and in-person training, fellowships, and EQA slide circulation were interrupted. One durable positive effect was the accelerated normalisation of remote reporting, digital slide review, and virtual multidisciplinary meetings, which lowered a barrier that had previously been more cultural than technical (Aminu-Ibrahim *et al*., 2021; Anichukwueze *et al*., 2021; Badmus & Olamide, 2019a; Badmus *et al*., 2019c; Vigliar *et al*., 2020).

3.11. Specimen Type and Tissue Adequacy

Barriers differ systematically by specimen type, and much of the variation attributed to laboratories is in fact variation in what they are sent.

Core needle biopsies and small endoscopic or bronchoscopic samples now constitute the majority of material on which predictive biomarker decisions are made in advanced disease, because many such patients never proceed to resection. These specimens fix quickly and therefore avoid some of the fixation gradients seen in resections, but they carry two distinct risks. The first is exhaustion: an undisciplined diagnostic panel can consume the tumour before the predictive markers are reached, and where the block is exhausted the patient must undergo a repeat procedure or be treated without the result. The second is representativeness, since a small sample may not capture heterogeneous marker expression, which is a particular concern for PD-L1 and for HER2 in gastro-oesophageal cancer where expression is frequently focal.

Cytology cell blocks introduce a separate problem. Many cytology preparations use alcohol-based fixatives or a combination of alcohol and formalin, and an assay validated on 10 percent neutral buffered formalin is not automatically valid on such material. Where cell blocks are used for predictive testing, the fixation protocol must be specified and the assay validated on material prepared that way, which in practice means either standardising cytology fixation to formalin for biomarker work or maintaining a separately validated protocol (Compton *et al*., 2019; Fitzgibbons *et al*., 2014). Minimum tumour cellularity also matters, since scoring algorithms for several predictive markers assume a defined minimum number of viable tumour cells and results reported below that threshold are not interpretable in the terms the algorithm intends.

Bone specimens and bone marrow trephines require decalcification, and the choice of agent has a larger effect on downstream testing than is generally appreciated. Strong acid protocols are fast and convenient but destroy many epitopes and most nucleic acid, so a laboratory that decalcifies routinely in strong acid has effectively removed the option of predictive testing on those specimens. EDTA protocols preserve antigenicity at the cost of turnaround, and the practical compromise is to reserve EDTA for specimens where biomarker testing is foreseeable and to record the decalcification method in the report so that a negative result can be interpreted correctly.

Necrotic, crushed, and cauterised tissue produces uninterpretable staining, and the appropriate response is to state that the material is inadequate rather than to report a result of unknown validity. Documenting inadequacy is itself a quality activity: an audit of the proportion of specimens deemed inadequate, broken down by referring source and procedure type, identifies remediable problems in sampling and handling that no amount of laboratory optimisation will fix (Eyetsemitan *et al*., 2020; Onche, 2021a).

A related adequacy question concerns block selection when several are available. Where a resection yields multiple tumour blocks, the block chosen for predictive testing determines the result, and the criteria for that choice are rarely written down. The block with the highest tumour content is not automatically the right one if it was taken from the deep centre of a thick, late-fixed specimen, and the periphery of a large tumour may differ in marker expression from its centre. A defensible rule is to select a peripheral, well-fixed block with adequate viable tumour and minimal necrosis, to record which block was used, and to test a second block where the result is discordant with morphology or with a prior sample from the same patient. Recording the block identifier costs nothing and is what allows a discordant result to be investigated rather than merely disbelieved (Compton *et al*., 2019; Onche, 2020).

3.12. Biomarker-Specific Requirements and The Consequences of Error

The general barriers described above manifest differently across tumour types, because the marker set, the scoring rule, and the clinical decision at stake all differ. Table 2 summarises the minimum expectations for the tumour types that account for most oncology workload, together with the decision each biomarker governs and the characteristic consequence of a false negative result.

Table 2: Minimum immunohistochemistry expectations by tumour type, with the decision governed and the consequence of a false negative result.

Tumour type	Minimum IHC expectation	Decision governed	Consequence of a false negative
Breast carcinoma	ER, PR, HER2, Ki-67	Endocrine therapy; anti-HER2 therapy; chemotherapy intensity	Effective endocrine or anti-HER2 therapy withheld; unnecessary chemotherapy given
Non-small cell lung carcinoma	TTF-1, p40, PD-L1; ALK and ROS1 screening	Histological subtyping; immunotherapy eligibility; targeted therapy referral	Immunotherapy or targeted therapy withheld; incorrect chemotherapy regimen
Colorectal carcinoma	MLH1, PMS2, MSH2, MSH6	Lynch syndrome screening; immunotherapy eligibility in metastatic disease	Missed inherited cancer syndrome affecting the family; checkpoint inhibitor eligibility missed
Gastro-oesophageal adenocarcinoma	HER2, PD-L1	Anti-HER2 therapy; immunotherapy eligibility	Targeted therapy withheld in a disease with limited alternatives
Lymphoma	Lineage and subtype panel including CD20, CD3, CD5, CD10, BCL2, BCL6, cyclin D1, Ki-67	Subtype assignment determining the entire treatment pathway	Wrong regimen or no regimen; curable disease treated as incurable
Melanoma	S100, SOX10, and lineage confirmation	Diagnosis; referral for mutation testing	Misdiagnosis as undifferentiated carcinoma or sarcoma
Prostate carcinoma	Basal cell markers with AMACR	Distinction of carcinoma from mimics on limited biopsy material	Over-diagnosis and unnecessary treatment, or under-diagnosis
Endometrial and ovarian carcinoma	Mismatch repair panel, p53, hormone receptors as indicated	Molecular classification; Lynch screening; systemic therapy selection	Misclassification with direct effect on adjuvant therapy
Carcinoma of unknown primary	Algorithmic panel from CK7, CK20, TTF-1, CDX2, GATA3, PAX8 and related markers	Identification of a treatable primary site	Empirical broad-spectrum chemotherapy in place of site-directed treatment
Soft tissue tumours	Lineage panel with entity-specific markers	Subtype assignment; surgical planning; systemic therapy	Inappropriate surgery or systemic therapy for a misassigned entity

Two patterns are visible across the table. First, the consequence of analytical error is asymmetric in almost every row: a false negative typically denies an effective and often inexpensive therapy, whereas a false positive typically exposes the patient to an ineffective one, and since the dominant analytical failure mode is weak or falsely negative staining, the realised harm skews toward therapy withheld. Second, the marker sets that matter most clinically are small. The core and expanded tiers together, described in Section 3.14, cover the majority of the decisions listed, which supports concentrating validation and control effort on a defined, tiered menu rather than distributing it thinly across an unbounded one (Ilodigwe & Adesemoye, 2020; Lawal & Oduleye, 2019b).

3.13. Turnaround Time and Integration with Clinical Decision-Making

A result that is analytically perfect but arrives after the treatment decision has no clinical value, and turnaround failures are a common and under-reported form of adoption failure.

Total turnaround decomposes into intervals that are owned by different people: the theatre-to-laboratory interval, accessioning and grossing, processing and embedding, initial reporting, the decision to order IHC, the staining run itself, interpretation, and delivery of the report into the clinical record. Laboratories typically measure only the intervals they control, which conceals the largest delays. Where IHC is ordered sequentially rather than as a planned panel, each round adds a full staining and reporting cycle, and three sequential rounds can consume more time than the whole preceding histology workflow. Where the result must be transcribed by hand from the pathology system into the oncology record, both delay and transcription error are introduced (Mbonu *et al*., 2020a; Oparah *et al*., 2021a).

Several practical measures shorten the path. Reflex protocols that trigger predictive testing automatically on a confirmed diagnosis remove the ordering delay entirely and are appropriate for markers required in every case of a given tumour type. Planned panels replace sequential rounds. Scheduled staining runs on defined days give clinicians a predictable date rather than an open-ended wait, which matters more for multidisciplinary planning than a marginally shorter average. Interface between the laboratory system and the oncology record removes transcription. And publishing turnaround performance to the multidisciplinary team converts a laboratory metric into a shared clinical one, which in reported experience is what sustains improvement (Adeyelu, 2020; Ilodigwe & Adesemoye, 2021; Osuji *et al*., 2021).

Turnaround also interacts with the financing barriers described earlier. Where patients pay per antibody and must return to arrange payment between rounds, the delay is not a laboratory process problem at all, and no amount of internal optimisation will resolve it (Lawal & Oduleye, 2021a).

3.14. Reported Mitigation Strategies

Strategies described across the included sources converged on a consistent set of actions, summarised against their corresponding barrier domains in Table 3.

Table 3: Barrier domains and corresponding mitigation strategies.

Barrier domain	Reported strategies
Cost and financing	Tiered antibody menu; pooled procurement; cross-departmental business case; reimbursement reform; referral of low-volume tests
Supply chain and infrastructure	Minimum stock policy; regional distribution; funded maintenance contracts; power conditioning; open-platform options where clinically acceptable
Workforce	Technologist-focused training; twinning partnerships; competency-based assessment; retention planning; regional training hubs
Pre-analytical variability	Written specification with theatre engagement; time stamping; audit; no advance batch slide cutting; EDTA decalcification
Analytical standardisation	Formal validation and revalidation; multi-tissue on-slide controls including low expressors; tonsil and cervix calibration tissues; lot verification
Interpretation	Indication-matched assay and algorithm; scoring calibration sets; second opinions; image analysis as an adjunct
Quality assurance	Mandatory EQA with corrective action loop; ISO 15189 accreditation; internal audit
Regulatory and market structure	Approved companion diagnostics where available; documented local validation otherwise; advocacy for timely local registration
Utilisation	Algorithmic panels; tissue stewardship policy; ordering audit with feedback; multidisciplinary review
Informatics	Structured fields for clone, lot, and control; synoptic templates; oncology record integration; auditable data
Service disruption	Backlog planning; buffer stock; remote reporting capability; distributed staffing

Three strategies warrant expansion because they recur across settings and because their implementation detail determines whether they work.

Menu stratification: Attempting a comprehensive menu is the most common strategic error in a new or constrained service; a resource-stratified panel concentrates spend on the antibodies with the highest decision yield per unit cost (Anderson *et al*., 2011; Ginsburg *et al*., 2020; Masood *et al*., 2008). Table 4 gives an illustrative stratification. The governing principle is that the referral tier exists deliberately, since referring low-volume tests is not a failure of the service whereas running them at volumes too low to validate or control is.

Table 4: Illustrative tiered antibody panel for a resource-stratified IHC service.

Tier	Purpose	Representative antibodies
Core	Establish lineage; deliver breast biomarkers; basic lymphoid screen	Pan-cytokeratin (AE1/AE3), CD45, S100 or SOX10, vimentin, ER, PR, HER2, Ki-67, CD20, CD3
Expanded	Common primary-site and subtype resolution	CK7, CK20, TTF-1, napsin A, p40/p63, CDX2, GATA3, PAX8, synaptophysin, chromogranin, CD34, desmin, SMA, MLH1, PMS2, MSH2, MSH6, CD5, CD10, BCL2, BCL6, cyclin D1
Specialised	Therapy selection and specialist subtyping	PD-L1 (indication-matched clone), ALK, ROS1, p16, BRAF V600E, IDH1 R132H, ATRX, INSM1, extended haematolymphoid and sarcoma panels
Referral	Rare or very low-volume markers	Sent to a designated reference centre rather than maintained in-house

Pre-analytical specification: This is the highest-yield and lowest-cost intervention available to most laboratories (Compton *et al*., 2019; Engel *et al*., 2011; Khoury *et al*., 2009). Table 5 sets out a workable specification with verification methods. Implementation depends on engaging theatre and clinical teams rather than on laboratory instruction alone, and a short jointly owned protocol printed on the request form and audited quarterly is more effective than a policy document (Arumosoye & Obriki, 2021; Eyetsemitan *et al*., 2021; Obogo *et al*., 2021b).

Table 5: Pre-analytical specification for biomarker-bearing specimens.

Variable	Specification	Verification
Cold ischaemia time	1 hour or less	Excision and fixative times on the request form; audited monthly
Fixative	10 percent neutral buffered formalin, verified pH and concentration	Batch records; periodic pH check
Fixative volume	Minimum 10:1 fixative to tissue	Theatre and grossing procedure
Fixation duration	6 to 72 hours	Recorded at accessioning
Resection slicing	Serially incised at approximately 5 mm within the specified window	Grossing procedure with photographic reference
Decalcification	EDTA-based where biomarkers are required	Protocol logged per block and noted in the report
Unstained sections	Cut on demand, not stored beyond the locally validated interval	Stock control; no advance batch cutting
Transport	Placed in fixative in theatre, never transported fresh over long distances	Courier procedure and audit

Control and quality assurance practice: Practical control strategy is disproportionately effective relative to its cost (Compton *et al*., 2019; Torlakovic *et al*., 2010, 2015). On-slide controls ensure the control experiences the same conditions as the patient tissue; multi-tissue control blocks should contain high, low, and negative expressing elements, because the low expressor is what detects loss of analytical sensitivity before it reaches the patient; internal controls within the patient section, such as normal ducts for oestrogen receptor or lymphocytes and stroma for mismatch repair

proteins, should be recorded, and an absent internal control treated as an invalid rather than a negative result; and control performance should be logged per run and reviewed as a trend rather than only as pass or fail per slide. EQA participation should be treated as non-negotiable for any laboratory issuing predictive biomarker results, and where cost or logistics obstruct enrolment in an international scheme, workable intermediate options include regional slide exchange between hub laboratories, a national scheme run by a professional society, and structured inter-laboratory comparison of split samples (Akomolafe & Agu, 2019c; Nielsen, 2015; Obogo *et al*., 2019a; Vyberg *et al*., 2016). Because the dominant failure mode is weak or falsely negative staining, the first troubleshooting question after an unsatisfactory result should be whether the assay's analytical sensitivity has been demonstrated on a low-expressing control, not whether the pathologist misread the slide (Nielsen, 2015; Sompuram *et al*., 2018; Torlakovic *et al*., 2010, 2015; Vani *et al*., 2016; Vyberg *et al*., 2016).

Remaining strategies can be stated more briefly. Concentrating IHC in a smaller number of adequately resourced hubs, with spoke laboratories performing grossing, processing, and routine histology and forwarding blocks, lifts hub volume into the range where automation and EQA participation are economic, concentrates scarce technologist expertise, and standardises protocols across a region; the model requires a reliable block courier system with tracking, agreed turnaround targets and escalation routes, a shared requisition and reporting format, and a funding flow that does not penalise the hub for absorbing referred work (Aminu-Ibrahim *et al*., 2019; Gil-Ozoudeh *et al*., 2018; Komi & Adeniji, 2020; Nwafor *et al*., 2018b; Ogbete *et al*., 2018, 2020). Validation policy should follow CAP principles, with a defined minimum number of cases spanning expected positive and negative results, comparison against a reference method or established diagnostic standard, documented concordance targets, and revalidation on any material change; validation records must be retrievable, since an undocumented validation does not exist for audit purposes (Fitzgibbons *et al*., 2014; International Organization for Standardization, 2012; Obogo *et al*., 2019c). Training programmes that persist share two design features, namely competency assessed against slide output rather than attendance, and coupling to a retention plan, since a trained technologist who leaves takes the capability with them (Lilian *et al*., 2020; Orise & Niniola, 2020), with effective delivery models including structured manual IHC training for technicians, twinning arrangements with established reference laboratories, regional training hubs, and vendor-independent curricula covering retrieval, titration, detection chemistry, and troubleshooting rather than the operation of one instrument (Falemi *et al*., 2020; Ogbona *et al*., 2020a). Automation is not a prerequisite for adequate IHC: a disciplined manual method with correct controls, verified reagent storage, and documented validation outperforms an unmaintained automated platform running an uncontrolled protocol, and the decision should be made on sustainable throughput and maintenance access rather than on prestige (Amayo & Popoola, 2017b; Prichard, 2014; Shittu *et al*., 2021; Sunday *et al*., 2019b). Procurement should be managed deliberately, including pooled purchasing across a hospital group, region, or national network to gain volume pricing and buffer stock (Akin-Oluyomi *et al*., 2020; Ogunwole *et al*., 2021; Okonkwo *et al*., 2018b), negotiation of service and consumable terms at the point of instrument acquisition rather than afterwards, refusal of donations that do not include a funded maintenance and reagent pathway, advocacy for removal of import duties on diagnostic reagents, and a minimum stock policy with defined reorder points for core antibodies so that service continuity does not depend on a single shipment (Aifuwa *et al*., 2020; Efobi *et al*., 2021; Fadayomi *et al*., 2021; Nnabueze *et al*., 2021; Okojie & Abioye, 2020a). Reporting should be synoptic, and a predictive biomarker report should record antibody clone, vendor, platform, scoring algorithm and cut-point, control performance, known pre-analytical parameters, the block tested, and the therapeutic indication to which the result applies, which turns the report into an auditable artefact and permits later re-interpretation when guidelines change (Ahmed & Odejobi, 2018a; Badmus *et al*., 2020; Dosunmu & Ogundele, 2020; Mbonu *et al*., 2020b; Nakhleh *et al*., 2016; Okoruwa *et al*., 2020; Oparah *et al*., 2021a). Utilisation should be governed through algorithm-based panels for common diagnostic problems, a tissue stewardship policy reserving small biopsy material for predictive testing, periodic audit of antibodies ordered per case with individual feedback, and multidisciplinary review where panels exceed a defined threshold, with the goal of fewer and better-chosen stains rather than simply fewer stains (Gown, 2016). Digital tools are best introduced through second-opinion and quality-review use cases rather than primary diagnosis, since these carry lower validation and regulatory burdens (Badmus *et al*., 2018; Ominyi & Anichukwueze, 2021b; Pantanowitz *et al*., 2018; Tonoyan *et al*., 2021b), and quantitative image analysis, covered by CAP guidance in this period, offers reproducibility gains but requires its own validation and pathologist oversight and is not a substitute for a well-controlled stain (Bui *et al*., 2019; Ominyi, 2020a; Oziri *et al*., 2020). Finally, the economic case is best framed in terms of downstream therapy cost rather than laboratory cost, comparing receptor testing for a breast cancer cohort against the cost and toxicity of empirical treatment, or PD-L1 testing against a single course of checkpoint inhibitor therapy given to a patient unlikely to benefit; costing analyses in the pathology strengthening literature and the Lancet Commission on diagnostics provide the framing, in which diagnostics are a disproportionately small fraction of health expenditure that governs a disproportionately large fraction of downstream spending, the same asymmetry noted for IHC specifically in Section 1 (Fleming *et al*., 2021; Horton *et al*., 2018; Sayed *et al*., 2018).

4. Discussion and Conclusion

4.1. Principal Findings

Three findings follow from the synthesis. The first is that availability and adequacy are separable, and that the literature has concentrated disproportionately on the former. Most descriptive surveys of IHC access report whether a service exists; comparatively few report whether the results it produces have been validated or externally assessed. This measurement gap has a specific mechanism: an unvalidated result is reported with the same apparent confidence as a validated one, so the clinician using it cannot distinguish the two at the point of decision, whereas a referral is an explicit, visible non-result that prompts the clinician to seek the answer elsewhere. A laboratory that issues unvalidated predictive biomarker results therefore plausibly causes more harm than one that refers, because the harm of the former is

silent while the harm of the latter is at least declared. In the four-stage adoption framework set out in Section 1, this finding addresses specifically the gap between the availability and analytical adequacy stages, and it is a gap that is not closed by capital investment.

The second is that the dominant analytical failure mode has a specific direction. EQA data indicate that the great majority of insufficient results are weak or falsely negative rather than falsely positive, which means the characteristic patient-level harm of poor IHC is effective therapy withheld rather than ineffective therapy given. This asymmetry has a direct design implication that is frequently missed in practice: quality systems must be built to detect loss of analytical sensitivity, which requires low-expressing control material and external assessment, because internal review of a laboratory's own high-expressing controls cannot reveal it. This finding sits within the analytical adequacy stage, since it concerns whether a result already produced is accurate and reproducible, and it carries directly into the clinical integration stage, because a falsely negative result that is not caught before reporting reaches the treatment decision undetected.

The third is that scope discipline functions as a quality strategy rather than as a concession. A narrow, well-validated, well-controlled menu with a functioning referral pathway serves patients better than a broad menu that cannot be sustained, because validation and control burden scales with menu breadth while diagnostic yield does not. This finding spans two stages of the framework: it protects analytical adequacy by keeping validation and control burden within what a laboratory can actually sustain, and it protects accessibility by routing markers that exceed that capacity to a defined referral pathway rather than abandoning them or reporting them unreliably.

A fourth observation follows from the first three. The interventions with the largest effect on analytical validity are also among the cheapest, while the interventions with the highest visibility are among the most expensive. Controlling cold ischaemia time costs a recorded time stamp and a conversation with theatre; building a multi-tissue control block costs a few blocks of surplus tissue and a technologist's afternoon; enrolling in external assessment costs a modest annual fee. Purchasing an automated platform costs several orders of magnitude more and, on its own, changes none of the failure modes that dominate proficiency testing. This inversion between cost and effect is a recurring feature of the reviewed evidence and has an obvious programmatic implication, namely that capital-led strengthening initiatives should be sequenced behind the process interventions rather than ahead of them (Aminu-Ibrahim *et al*., 2019; Ogbete *et al*., 2020). This sequencing argument concerns availability and clinical integration jointly, since it is a claim about the order in which capability should be built so that a service, once available, is also one whose results are safely integrated into treatment decisions rather than merely present. Taken together, these observations support treating the barrier domains as one system. Financing determines menu breadth; menu breadth determines validation burden; validation burden interacts with workforce capacity; workforce capacity determines whether pre-analytical and control discipline is maintained; and the resulting analytical performance determines whether the service is clinically useful at all. Interventions aimed at a single domain, most commonly instrument procurement, therefore tend to underperform. This systemic framing, together with the barrier-to-strategy mapping in Table 3, the sequencing in Table 7, and the indicator set in Table 9, is the principal contribution of this review; earlier syntheses have generally addressed the laboratory science and the health system dimensions separately.

4.2. Cost Structure and The Economics of Menu Breadth

The financing barrier is easier to act on when the cost structure is disaggregated, because the elements behave very differently as volume changes. Table 6 sets out the principal elements, their behaviour, and the lever available for each.

Table 6: Cost structure of an immunohistochemistry service, with behaviour under changing volume and the available management lever.

Cost element	Nature	Behaviour as volume rises	Management lever
Staining platform	Capital, or lease	Fixed; cost per test falls steeply	Match platform capacity to realistic throughput; consider manual methods at low volume
Service contract and parts	Recurrent fixed	Fixed; cost per test falls	Negotiate at acquisition; pool across a network
Primary antibodies	Recurrent variable, with wastage	Falls, since expiry losses shrink as usage rises	Restrict menu; concentrate volume in a hub; use concentrated formats at low volume
Detection kits and buffers	Recurrent variable	Broadly proportional	Volume purchasing; standardise on one detection system
Slides, consumables, reagent water	Recurrent variable	Proportional	Stock control; waste audit
Control material	Recurrent, low	Broadly fixed	Build multi-tissue control blocks in-house
Validation of each new antibody	One-off per antibody, then on change	Independent of volume	Limit menu breadth; revalidate only on material change
EQA participation	Recurrent fixed per marker enrolled	Fixed	Prioritise predictive markers; use regional schemes where available
Staff time	Semi-fixed	Falls per test until a capacity step	Batch runs; competency-based task allocation
Power, backup, and environmental control	Recurrent fixed	Fixed	Conditioning and backup sized to the instrument load
Referral of specialised markers	Variable	Proportional to referral volume	Deliberate referral tier rather than unplanned send-outs
Accreditation and quality management	Recurrent fixed	Fixed	Integrate with the wider laboratory quality system

Two implications follow. The first is that menu breadth is expensive in a way that unit reagent cost conceals, because each additional antibody carries a one-off validation cost, a recurring control and EQA obligation, and a wastage exposure that is largest at low usage. An antibody used twice a month may cost several times its nominal price once expiry and validation are included. The second is that the largest fixed elements, namely the platform, the service contract, staff, and the quality system, reward concentration of volume, which is the economic argument for the hub-and-spoke arrangement described earlier and the reason that dispersing small stainers across many sites tends to produce high unit costs and low quality simultaneously (Ahiaeke Patrick *et al*., 2021; Okonkwo *et al*., 2021b; Sunday & Omoegun, 2019b).

Framing the case for investment therefore depends less on reducing the cost of IHC than on demonstrating what it prevents. A cohort-level comparison between the cost of receptor testing and the cost and toxicity of empirical treatment for the same cohort is more persuasive to a finance committee than a per-slide price, and the same logic applies to predictive markers governing high-cost systemic therapy (Bola-Sadipe *et al*., 2019; Lawal & Oduleye, 2018b).

A second consideration concerns how a service should behave while it is still building capability. The intermediate position, in which a laboratory offers some markers reliably and others without validation, is common and is rarely made explicit to clinicians. Stating the position openly, by listing which markers are validated and externally assessed, which are offered as diagnostic aids without predictive claims, and which are referred, allows the multidisciplinary team to weigh a result appropriately rather than treating every reported number as equivalent. It also protects the laboratory, since a marker reported without a validation claim is not the same undertaking as one reported as a predictive result. Published quality frameworks in adjacent sectors make the same point in different language: declared scope, with the limits of assurance stated, is a component of assurance rather than an admission of weakness (Akomolafe & Agu, 2019c; Dogbatsey *et al*., 2021; Jones & Ominyi, 2021).

4.3. Equity and Geographic Access

Because IHC concentrates in tertiary and urban centres, the barriers described in this review are distributed unequally, and the distribution follows existing patterns of disadvantage. Patients distant from a centre face travel cost, time away from work, and a higher probability of loss to follow-up between the biopsy and the result, which is compounded where the diagnostic pathway requires several visits to arrange payment. Where testing is paid out of pocket, the truncated panel is not a clinical decision but an economic one, and its consequences fall on those least able to absorb them.

The equity consequences are not distributed evenly across tumour types either. Breast and cervical cancer carry a large share of the cancer burden in many low- and middle-income settings, and, although individual diagnoses such as lymphoma subtyping can be more strictly dependent on IHC at the level of a single case, breast cancer management depends on IHC across a far larger caseload than almost any other common malignancy in these settings; it is this combination of population-level burden and per-case dependency, rather than per-case dependency alone, that gives a weak IHC service a disproportionate effect on outcomes for women (Ginsburg *et al*., 2020; Wilson *et al*., 2018).

Three of the strategies described earlier have equity effects that are worth stating explicitly. Referral networks with reliable block transport extend access without requiring the patient to travel, shifting the movement burden from people to specimens. Reflex testing protocols remove the requirement for the patient to be present, or to pay, at the moment the decision to test is made. And telepathology and remote reporting decouple interpretive capacity from geography, which is the only mechanism in the current toolkit capable of addressing an absolute shortage of pathologists in the short term (Akinola *et al*., 2020; Anichukwueze *et al*., 2021; Pantanowitz *et al*., 2018). None of these substitutes for financing reform, but each reduces the extent to which analytical capability is rationed by location.

4.4. Implementation Sequence

Sequencing matters as much as content. Launching predictive biomarker testing before pre-analytical control and EQA are in place produces confident false negatives, which is worse for patients than an honest referral (Nielsen, 2015; Nwafor *et al*., 2019a, 2019b; Shittu *et al*., 2019; Torlakovic *et al*., 2015; Vyberg *et al*., 2016). Table 7 sets out a phased sequence consistent with the evidence reviewed.

Table 7: Phased implementation sequence for an IHC service.

Phase	Objective	Key actions	Indicative timeframe
Assessment	Establish the current state	Baseline audit of specimen flow, cold ischaemia and fixation times, menu, volumes, staff competencies, equipment status, turnaround, and referral patterns	1 to 3 months
Foundation	Make existing histology reliable	Correct formalin quality and fixation procedures; engage theatre on cold ischaemia; standardise processing; record clone and lot in the information system; write the quality manual	3 to 6 months
Core service	Launch the core tier with demonstrated quality	Commission staining capability; build multi-tissue control blocks; validate core antibodies; train technologists; enrol in EQA; publish turnaround targets	6 to 12 months
Expansion	Add expanded and predictive markers	Sequential validation of additional antibodies; adopt synoptic reporting; formalise referral for specialised markers; begin utilisation audit	12 to 24 months
Consolidation	Sustain and accredit	ISO 15189 accreditation; continuous EQA with documented corrective action; digital second-opinion pathway; workforce succession planning; periodic menu review	24 months onward

Sequencing alone is insufficient if no one owns each step. A recurring finding across the reviewed sources is that pre-analytical and quality obligations fail not because they are disputed but because they sit between departments, and the remedy is an explicit allocation of accountability of the kind set out in Table 8.

Table 8: Allocation of responsibility across the diagnostic pathway, with the associated control and the consequence of leaving it unowned.

Step	Accountable role	Key control	Consequence if unowned
Specimen excision and placement in fixative	Operating surgeon and theatre team	Recorded time of excision and time into fixative	Uncontrolled cold ischaemia; falsely negative receptor results
Transport to the laboratory	Theatre coordinator or portering service	Specimen in fixative before transport; tracked handover	Prolonged transit of unfixed tissue; unusable material
Accessioning	Laboratory reception	Verification and recording of pre-analytical time stamps	Missing data; inability to interpret a negative result
Grossing and slicing	Pathologist or trained assistant	Serial incision within the specified window; block selection	Fixation gradients; regional staining variation
Processing and embedding	Histotechnologist	Validated schedule; monitored reagent rotation	Under-processing; poor sections and weak staining
Staining run and controls	IHC technologist	On-slide multi-tissue control; run log with lot numbers	Undetected loss of analytical sensitivity
Validation and lot verification	Laboratory supervisor	Documented validation and revalidation records	Assays in clinical use without evidence of performance
EQA submission and corrective action	Quality manager	Enrolment, root cause analysis, protocol change, re-challenge	External failure recorded but not remedied
Interpretation and scoring	Reporting pathologist	Indication-matched algorithm; internal control checked	Wrong algorithm applied; invalid result reported as negative
Report structure and delivery	Reporting pathologist with informatics support	Synoptic template; interfaced delivery to the clinical record	Missing elements; transcription delay and error
Reagent continuity and maintenance	Procurement and biomedical engineering	Reorder points; funded service contract	Stockouts and downtime presenting as clinical unreliability
Utilisation and tissue stewardship	Multidisciplinary team with pathology lead	Agreed panels; audit with feedback	Block exhaustion before predictive testing

Allocation of this kind is also what makes the indicators in the next section actionable, since an indicator that drifts without a named owner generates discussion rather than change (Adeyelu, 2021; Akomolafe & Agu, 2019b; Obogo *et al*., 2021b).

4.5. Monitoring

Adoption progress is measurable, and Table 9 proposes indicators spanning the pre-analytical, analytical, post-analytical, service, utilisation, and sustainability dimensions. Reporting these indicators to a laboratory quality committee and to the cancer multidisciplinary team keeps the service accountable to clinical users rather than only to itself (Akomolafe & Agu, 2018; Arumosoye & Obriki, 2019; Dagodzo, 2018c; Dagodzo *et al*., 2021b; Obogo *et al*., 2020a).

Table 9: Suggested performance indicators for an IHC service.

Domain	Indicator	Suggested target
Pre-analytical	Biomarker specimens with recorded cold ischaemia time of 1 hour or less	Greater than 90 percent
Pre-analytical	Specimens with fixation duration within 6 to 72 hours	Greater than 95 percent
Analytical	EQA results assessed as sufficient across enrolled markers	Greater than 90 percent, trending upward
Analytical	Unsatisfactory EQA results with documented root cause and protocol change	100 percent
Analytical	Runs with acceptable on-slide control performance	Greater than 98 percent
Analytical	In-use antibodies with current, retrievable validation records	100 percent
Post-analytical	Biomarker reports containing all required synoptic elements	Greater than 95 percent
Post-analytical	Second-opinion concordance on predictive markers	Monitored, with discordance reviewed
Service	Turnaround from receipt to biomarker report	Locally defined, commonly 5 to 10 working days
Service	Eligible cancers with the indicated biomarker result available before the treatment decision	Greater than 90 percent
Utilisation	Mean antibodies per case by diagnostic category	Monitored against agreed algorithms
Utilisation	Small biopsies exhausted before predictive testing	Minimised; each occurrence reviewed
Sustainability	Instrument uptime and stockout days for core antibodies	Greater than 95 percent uptime; zero stockout days

4.6. Gaps in The Evidence Base

Several questions material to practice remain inadequately answered by the literature reviewed here, and they define a reasonable agenda for further work.

Implementation evidence is the largest gap. Most published accounts of IHC capacity building are descriptive single-site reports without a comparison group, so the relative effectiveness of the interventions described in this review, for example twinning versus regional training hubs, or hub-and-spoke consolidation versus distributed provision, is essentially unmeasured. Prospective evaluations with defined outcome measures, including EQA performance and turnaround, would be feasible at network scale and are largely absent.

Economic evidence is similarly thin. Costing studies specific to IHC implementation are few, are rarely transferable across financing systems, and seldom capture the downstream therapy costs that constitute the main argument for investment. Analyses that link biomarker testing coverage to realised treatment patterns and outcomes at population level would materially strengthen the policy case (Ilodigwe & Adesemoye, 2019a).

On the analytical side, the absence of a stable, widely available reference material with defined low-level expression remains the central unsolved problem in IHC standardisation. Quantitative calibrator approaches have been described but are not in routine use, and without them analytical sensitivity remains assessed indirectly through control tissue and periodic EQA challenge rather than measured directly (Sompuram *et al*., 2018; Vani *et al*., 2016). Finally, the interaction between computational scoring and the barriers described here is unresolved. Image analysis promises reproducibility gains at the interpretive step, but it operates on the output of the analytical step and cannot compensate for a poorly calibrated stain, so its benefit in settings where weak or falsely negative staining is prevalent may be smaller than expected. Evaluation of computational tools under realistic pre-analytical and analytical variation, rather than on curated high-quality slide sets, would clarify where they belong in the sequence (Bui *et al*., 2019; Mayo *et al*., 2021; Tonoyan *et al*., 2021a).

4.7. Limitations

This is a narrative review and is therefore subject to selection bias in the sources considered. Much of the evidence on adoption barriers in resource-constrained settings derives from surveys of tertiary centres, which are systematically better equipped than the average laboratory, so the true burden is likely understated. Cost-effectiveness data specific to IHC implementation are sparse and difficult to generalise across health financing systems. Several of the strategies described are supported by expert consensus and programme experience rather than by controlled comparative evaluation, and implementation research in this field remains underdeveloped. This general concession applies with particular force to the recurring claim in this review that a laboratory reporting unvalidated predictive biomarker results plausibly causes more harm than one that refers: no study identified in this review directly compares patient outcomes between an unvalidated-result arm and a refer-onward arm, so the claim is a reasoned inference from the direction of the dominant EQA failure mode and from the asymmetry of harm described throughout, not a directly measured comparison, and it should be read with that evidentiary limitation in mind. The cross-disciplinary sources drawn on for the organisational dimensions of adoption are largely conceptual, framework, and review literature in adjacent sectors including laboratory infrastructure, procurement, workforce development, informatics, and governance, and are cited to support organisational reasoning by analogy rather than as direct empirical evidence about immunohistochemical assay performance. Finally, the evidence horizon is 2021; readers applying this synthesis later should check current guideline versions, particularly for HER2 and PD-L1 scoring thresholds, which have been revised as new therapeutic indications have emerged.

4.8. Conclusion

IHC adoption in oncology diagnostics fails for organisational reasons far more often than for technological ones. Instruments can be purchased, whereas disciplined cold ischaemia times, validated protocols, low-expressing controls, EQA-driven corrective action, trained technologists, and sustainable reagent supply cannot be purchased as a package and must be built.

Three implications follow for practice. Availability is not adequacy: the operational consequence is that a laboratory should stop issuing a predictive biomarker result for any antibody it has not formally validated and cannot control with a low-expressing on-slide element, and should refer that marker instead of reporting it provisionally, since an unvalidated report is silently misleading in a way that a referral is not. The dominant failure mode is weak or falsely negative staining, so quality systems should be designed specifically to detect loss of analytical sensitivity through low-expressing on-slide controls and external assessment rather than internal review alone. And scope discipline is itself a quality strategy, since a narrow, well-controlled menu with a functioning referral pathway serves patients better than an unsustainable broad one. A fourth implication is organisational rather than technical. Most of the failures described in this review occur at boundaries between roles, in the interval between excision and fixation, in the handover between the laboratory and the oncology record, in the gap between an external assessment result and a protocol change. Naming an owner for each step, and auditing the handovers rather than only the outputs, is therefore not administrative overhead but the mechanism through which the technical measures described here actually take effect.

For health systems, the corresponding policy implication is that pathology strengthening should be funded as cancer treatment infrastructure rather than as laboratory overhead, because the value of IHC lies in the therapy decisions it makes possible (Fleming *et al*., 2021; Horton *et al*., 2018; Nwafor *et al*., 2019c; Sayed *et al*., 2018; Wilson *et al*., 2018).

Declarations

Ethics approval and consent to participate: Not applicable. This is a narrative review that does not involve human participants, human tissue, or identifiable patient data.

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