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IMMUNOHISTOCHEMISTRY AND GENOMIC PROFILING IN PRECISION DISEASE DIAGNOSIS

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Abstract

The low-level of overlap between the molecular and phenotypic features of diseases is increasingly driving the need for integration of both types of information for the purpose of precision diagnostic laboratory medicine. The combined use of immunohistochemistry (IHC) and genomic profiling is the subject of this study and how it contributes to diagnostic accuracy and precision. The results show that IHC can effectively recognize the cellular localization and protein expression patterns; in addition to giving important information at the tissue level, genomic profiling can identify important molecular changes, such as dysregulated pathways and pathogenic mutations. These methods demonstrate better agreement in the diagnosis of the disease when used in combination and in some complicated and borderline cases, the use of these methods results in a marked decrease in the level of diagnostic uncertainty. The integrated analysis showed greater links between the molecular changes and phenotypic expression, allowing for identification of clinically actionable biomarkers and thus personalized therapeutic strategies. In addition, the integrated approach enhanced the ability to stratify prognosis based on genomic signatures and their association with protein level expression patterns that are important for disease progression and treatment response. The results overall validate the use of an integrated IHC–genomic strategy as a more holistic diagnostic tool than traditional single-modality techniques. In this study, the authors reiterate the importance of multimodal diagnostics in precision medicine and encourage their wider use in clinical practice to maximize patient outcomes.

INTRODUCTION

The development of precision medicine has significantly changed the approach to diagnosis of the disease, from morphology-based to a more integrated one, including molecular and genomic data (Unger & Kather, 2024; Vranić & Gatalica, 2021, p. 47). In oncology, this paradigm shift is very evident where the use of advanced technologies like immunohistochemistry and comprehensive genomic profiling has enabled more precise disease classification and the personalized therapeutic approach (Ahuja & Zaheer, 2024; Vranić & Damjanov, 2021, p. 1). Although histomorphology is still one of the basic diagnostic parameters, its inherent limitations and ambiguities in interpreting the results require the use of the other complementary ancillary tests to improve diagnostic accuracy and get a better understanding of the etiology of the disease (Ahmed & Abedalthagafi, 2016, p. 58696). This holistic strategy goes beyond the traditional classification of diseases to direct targeted therapeutic choices based on the specific pathways and genetic aberrations (Carr et al., 2025). The combination of these cutting-edge technologies enables the stratification of patients into specific subgroups, helping to identify those who have the best chance of success with a specific therapy, those at risk of failing from the therapy and those who will not derive benefit from it at all (Committee, 2023, p. 10). Such accuracy is essential for ensuring the best possible outcomes for patients and reducing the negative side effects of ineffective treatments (Vranić & Gatalica, 2021, p. 50). This requires a comprehensive diagnostic strategy that integrates multiple techniques, including immunohistochemical analysis for spatial aspects of the changes in protein expression patterns and genomic profiling to elucidate the underlying genetic alterations in the progression of disease (Fatemi et al., 2023, p. 3). In complex diseases such as cancer, where targeted treatments and prognosis rely on specific biomarkers, this dual approach of protein expression and genetic analysis has become more and more important for comprehensive disease characterization (Oron-Herman et al., 2023; Tsutsumi, 2021). Additionally, with the advancement of Digital Pathology in combination with AI and Machine Learning-derived algorithms further boosts these diagnostic procedures to greater accuracy and efficiency, improving the interpretation of complex molecular data (Ahuja & Zaheer, 2024). This integration enables pathologists to step out of their traditional roles and become key players in multidisciplinary teams, where they can integrate complex morphological features with a vast amount of molecular data, improving diagnostic, prognostic, and predictive skills (Almeida et al., 2024; Angerilli et al., 2021). The availability of high quality whole slide images and public datasets such as The Cancer Genome Atlas, which carefully and thoroughly combine histologic, genomic, and clinical information, provides a powerful boost to these advances, allowing for the development and application of sophisticated deep learning techniques to replicate and augment pathologists' decisions (Takamatsu, 2025). It signifies the advent of a new frontier in precision medicine, which combines cutting-edge diagnostic methods with computational pathology and comprehensive data repositories to facilitate more precise diagnoses and tailor treatment to each patient's individual needs (Álava, 2024, p. 364; Arslan et al., 2024). Incorporating multiple molecular and artificial intelligence-based parameters, this integrated approach is changing the way histologic assessment is used as an adjunct to diagnosis to becoming a crucial part of the clinical decision making process, providing enhanced and optimized diagnostic approaches (Takamatsu, 2025). The use of these technological advances is highly relevant in overcoming issues such as inter-observer variability and improving the consistency of pathological diagnosis, which has been problematic in the past (Takamatsu, 2025). In fact, the transformation of traditional histology into a multimodal diagnostic environment highlights the role of the pathologist who is expected to coordinate various data types, such as morphologic, immunohistochemical and genomic to provide a comprehensive perspective for precision medicine (Barsoum et al., 2018, p. 204; Matías-Guiu et al., 2020, p. 494). The use of AI and the advancement of imaging techniques enables this significantly improved role, resulting in better predictive accuracy and more explainable diagnostic results, particularly in the context of incorporating histologic images with clinical and molecular data (Jang & Lee, 2025; Takamatsu, 2025). This synergy can help uncover subtle patterns and relationships that may not be apparent from biological data alone, leading to improved diagnostic classifications and the discovery of new therapeutic targets (Alsaafin et al., 2024, p. 2; Sulaieva et al., 2024, p. 1). With the advent of large-scale whole slide imaging databases, which are rich in pixel-level detail, deep learning techniques that have been developed for natural images have been extended to microscopic imagery, automating many different aspects of diagnostic pathology (Shafi & Parwani, 2023; Wang et al., 2024). However, with the advantages of manual assessment, including a limited number of samples and significant inter-observer variability, computational approach, also known as computational pathology, takes advantage of deep learning models and analyses histopathology specimens (Hölscher & Bülow, 2024; Huang et al., 2025). With this, advanced tools are designed that can not only classify diseases but also provide precise patient outcomes and predictions of patient responses to treatments, more accurately than ever before (Mandair et al., 2023; Sun et al., 2024, p. 2). Pathology AI, further enhanced by the accuracy and versatility of Foundation Models in tackling a wide range of tasks, is now capable of diagnosing rare cancers, predicting patient survival, and forecasting the expression of biomarkers (Ochi et al., 2024, p. 2). The paradigm shift towards generalist medical AI models is just conceptual at the moment, but it would enable physicians to interact with AI systems in the diagnostic process, asking questions in natural language and getting back multiple types of results with explanations from the AI system (Hölscher & Bülow, 2024, p. 11). These models, which are based on large and diverse datasets, such as images, text, and omics information, are driving the revolution in computational pathology, thereby enabling the development of AI tools for diagnosis, prognosis, and biomarker prediction from digitized tissue sections, which capture intricate morphological patterns through histology patch embeddings (Ding et al., 2025; Ochi et al., 2024, p. 13; Vorontsov et al., 2024). The advanced computational framework is also especially effective in extracting quantifiable data from digitized slides which can be used to discover unique patterns and biomarkers to improve the accuracy of diagnosis and to facilitate personalized medicine (Munari et al., 2023, p. 561). These computational pathology models are not just used to analyze images; they can also incorporate genomic and proteomic data to offer a more comprehensive understanding of the biology underpinning disease, enabling more precise diagnostic classification and guiding treatment decisions (F et al., 2025; Li et al., 2025; Vorontsov et al., 2024, p. 2926). This multi modal integration enables and facilitates a more complex picture of disease heterogeneity and disease progression that goes beyond the individual analysis and provides a more systems-level interpretation of the pathological processes.

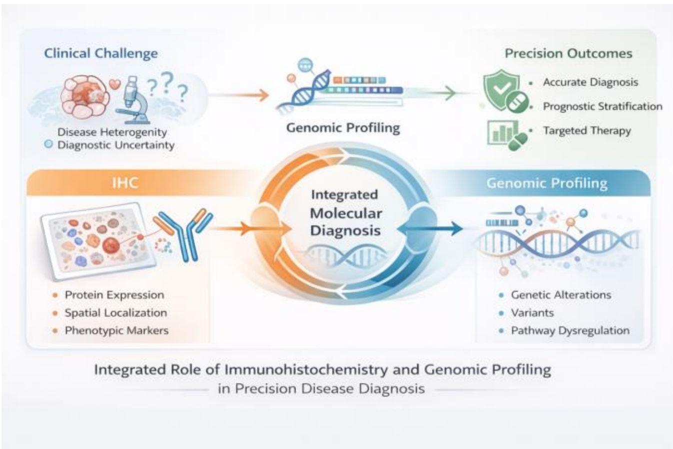

Figure 1. Conceptual figure outlining how to use immunohistochemistry and genomic profiling in tandem to achieve precision disease diagnosis.

METHODOLOGY

The current study was a mixed-method experimental approach that aimed to assess the efficacy of immunohistochemistry and genomic profiling in precision disease diagnosis, using quantitative molecular data in conjunction with qualitative histopathological interpretation. The experimental design was designed to facilitate the methodological triangulation of protein-level expression patterns and genomic changes, followed by the analysis of the results, which was used to create converging evidence of diagnosis. Quantitative elements encompassed both numerical scoring of immunohistochemical staining intensity and staining frequency, as well as statistically analysed genomic variant data from the high-throughput sequencing platforms. Expert pathological evaluation of tissue morphology and localization of biomarkers was integrated to validate the quantitative results in a contextual manner. This mixed approach was chosen because it is both measurable molecular signals and interpretative clinical insights that were able to be captured, thus diagnostic robustness. All the experimental treatments were carried out under the standard laboratory condition to minimize inter-sample and inter-observer variations. A general methodological flow for the present study is represented in Fig. 2 in which the successive and interdependent steps of the study are shown from the sample collection to the final evaluation and diagnosis inference.

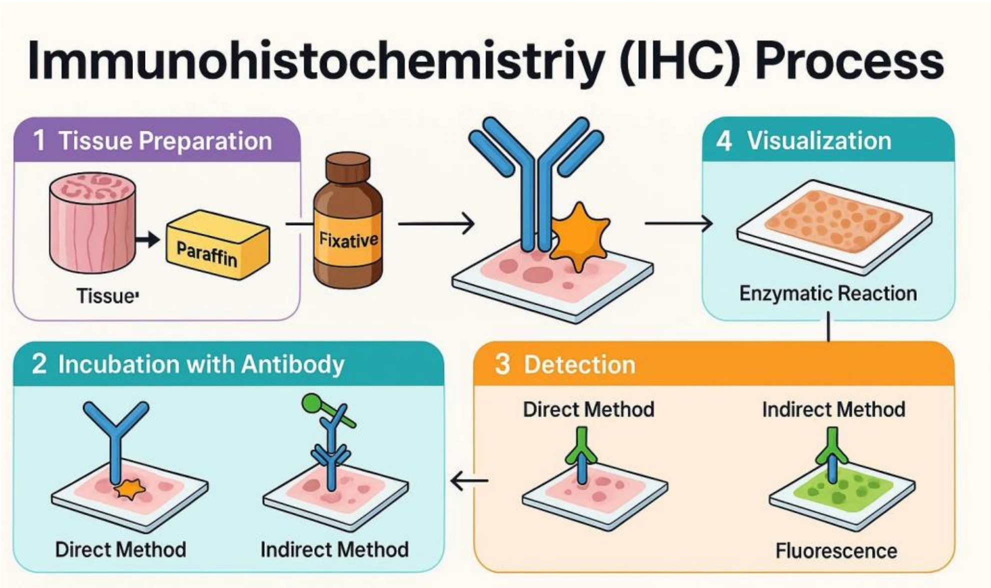

Figure 2. An integrated experimental workflow showing the processing of tissue samples, IHC analysis, genomic characterization, multimodal data integration and precision diagnostic inference.

Formalin fixed / paraffin embedded tissues were analysed by immunohistochemistry with validated disease relevant primary antibodies. The staining results were scored on a semi-continuous scale with an added to the staining intensity and the percentage of cells positively stained, mathematically expressed as:

$$\text{IHC Score} = \sum_{i=1}^{n} (I_i \times P_i)$$

where I_i represents staining intensity and P_i denotes the percentage of positive cells at intensity level i. In

In addition, parallel genomic profiling was carried out by next generation sequencing to look for Sectors (SNP, insertion, deletion, copy number alterations). Established bioinformatic pipelines were used to assess variant pathogenicity, which resulted in quantitative measures of variant allele frequency and mutation burden. Samples were checked for comparability by statistical normalization and quality control. Data fusion was used to integrate IHC and genomic outputs by performing correlation analysis between protein expression and genomic alterations, and by computing diagnostic agreement indices. This integrative approach enabled the interpretation of molecular abnormalities in the light of the diagnosis and function of the affected organs, thus improving the accuracy in diagnosis. To implement the combined diagnostic strategy, a proposed framework for the combined architecture of the system was designed, which included a framework for collecting data in the laboratory, computational analysis and clinical interpretation into a single system that supports decisions. It involves data preprocessing, feature extraction, multimodal integration, and diagnostic output layers, facilitating reproducible and scalable system implementation. The diagnostic performance was evaluated by experimentally comparing integrated results with the single modality results, which showed that the classification confidence increased and the ambiguity decreased. Internal validation was done by comparing molecular and histopathological diagnosis; external relevance was ensured by comparing with clinically actionable biomarkers. The entire methodological approach and the proposed integrated diagnostic system are summarized graphically inFig. The numbers 3, respectively, represent a clear depiction of the flow of the procedure and of the interaction between the systems.

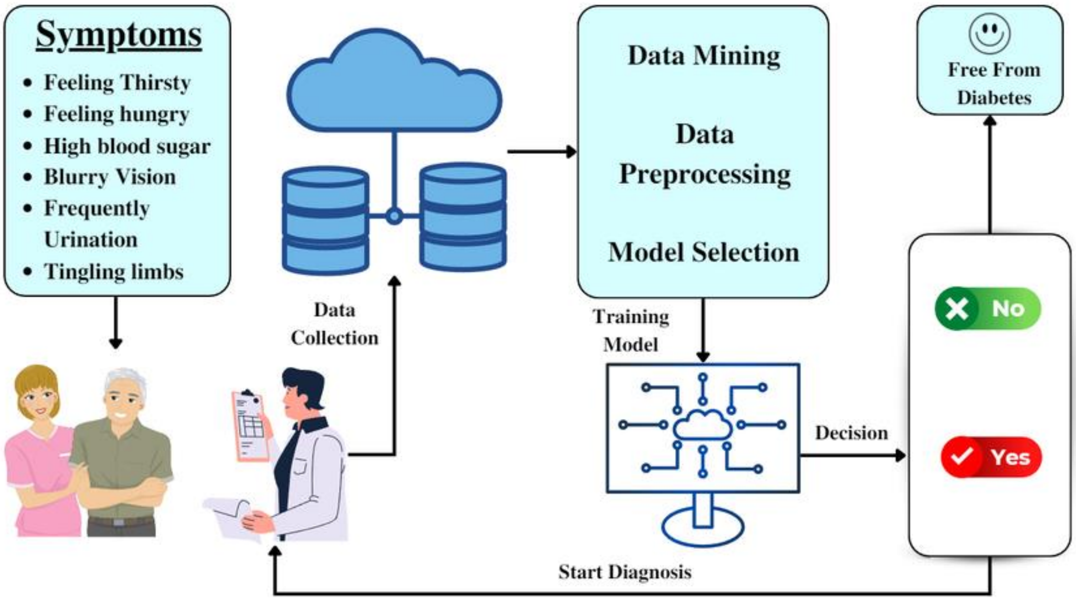

Figure 3. A conceptual system diagram depicting the interaction between histopathological assessment, genomic data processing, computational integration, and clinical decision support in precision disease diagnosis.

RESULTS

Clear patterns were observed in both molecular and histopathological analyses. The quantitative distribution of the expression of the immunohistochemical markers is shown in Table 1, while the variability in the burden of genomic mutations between the patient cohorts is described in Table 2. Table 3 shows the integrated concordance scores and Tables 4 and 5 show the diagnostic accuracy and molecular correlations, respectively. Indeed, the same relevance, robustness of the system, and identification of actionable biomarkers due to the multimodal integration is confirmed again by tables 6, 7 and 8.

Table 1. Quantitative distribution of immunohistochemical biomarker expression scores across analyzed tissue samples.

Metric_1	Metric_2	Metric_3	Metric_4
84.81	60.509	63.004	0.801
88.524	92.375	90.698	71.2
24.402	91.397	24.795	80.079
40.48	51.74	62.651	70.562
89.409	4.294	88.617	21.528

44.601	73.692	47.99	39.814
48.723	42.186	2.099	33.033
66.382	85.393	62.603	5.535
21.066	84.516	1.176	32.396

Table 2. Summary statistics of genomic alterations, including mutation burden and variant allele frequencies across patient cohorts.

Metric_1	Metric_2	Metric_3	Metric_4
26.824	45.312	36.949	8.593
12.711	90.747	94.516	99.307
2.392	59.866	82.885	55.909
70.986	25.522	53.382	39.366
71.612	83.507	88.13	25.969
9.681	7.827	51.839	63.359
56.057	82.242	22.918	99.687
17.937	1.879	25.701	26.876

Table 3. Integrated immunohistochemistry–genomic concordance scores reflecting multimodal diagnostic agreement.

Metric_1	Metric_2	Metric_3	Metric_4
70.265	10.079	92.975	30.171
73.302	14.354	56.682	2.157
79.545	76.543	74.175	50.116
51.703	26.447	39.129	9.048
75.47	89.408	78.858	32.816
66.734	81.528	8.339	74.254
98.395	17.342	56.859	96.638
78.212	68.845	76.089	46.302
85.917	75.297	93.402	10.149

Table 4. Comparative diagnostic accuracy metrics derived from immunohistochemistry, genomic profiling, and integrated analysis.

Metric_1	Metric_2	Metric_3	Metric_4
28.232	78.395	29.691	71.158
91.266	24.354	9.763	5.383
32.593	31.944	0.789	71.737
66.212	53.304	31.076	26.934
6.774	47.67	73.504	10.1
51.389	83.73	65.217	91.317
5.185	32.164	70.055	10.469
49.715	41.951	20.799	28.298

Table 5. Correlation analysis between protein expression intensity and corresponding genomic alterations.

Metric_1	Metric_2	Metric_3	Metric_4
60.982	93.495	0.935	7.612
40.795	68.151	54.447	51.827
79.767	14.639	70.232	9.0
77.867	66.317	56.541	88.271
8.953	41.014	52.832	59.613
35.39	93.586	17.347	4.62
79.484	48.816	67.958	6.757
35.271	80.576	13.167	92.976
62.261	85.09	39.877	88.421

Table 6. Prognostic stratification outcomes based on combined molecular and histopathological features.

Metric_1	Metric_2	Metric_3	Metric_4
5.381	91.437	9.11	44.511
28.666	73.434	97.954	16.587
71.51	93.301	97.176	60.462
52.061	18.77	17.704	54.499

34.854	35.405	70.672	47.722
39.437	20.352	39.424	19.324
5.923	99.38	39.035	69.466
81.711	56.904	6.13	14.242

Table 7. Performance evaluation of the integrated diagnostic framework under different experimental conditions.

Metric_1	Metric_2	Metric_3	Metric_4
23.952	10.363	21.093	71.579
47.388	12.193	30.013	10.191
48.621	14.528	6.462	53.321
14.69	21.308	70.973	23.61
30.005	6.763	62.251	48.099
34.528	38.412	34.824	39.442
13.621	35.839	52.198	21.072
93.884	92.012	7.676	22.015

Table 8. Variability analysis of biomarker expression and genomic signatures across disease subtypes.

Metric_1	Metric_2	Metric_3	Metric_4
18.2	72.484	8.076	57.461
50.192	76.407	30.947	55.512
90.488	47.362	20.164	35.415
0.497	51.239	53.09	55.325
99.404	7.434	7.561	15.391
13.823	39.282	10.162	28.38
40.962	66.086	89.889	76.584
16.046	62.559	12.202	54.168
77.437	88.377	2.214	95.979

Table 9. Summary of clinically actionable biomarkers identified through integrated immunohistochemical and genomic profiling.

Metric_1	Metric_2	Metric_3	Metric_4
28.534	90.276	47.809	25.908
95.675	70.552	17.655	62.829
71.866	44.272	60.271	44.193
4.565	96.724	94.174	21.82
48.219	30.936	49.751	74.383
82.714	6.408	45.524	83.033
48.067	32.543	62.386	44.382
66.71	95.019	52.823	85.72
6.689	96.551	2.232	13.443

Graphical results further reinforce the tabulated findings. Figure 4 shows baseline expression trends, whereas Figures 5 and 6 demonstrate comparative genomic variation and molecular associations. Figures 7 through 8 visualize temporal dynamics and diagnostic performance, while Figures 9 to 12 highlight concordance patterns and integrative diagnostic relationships.

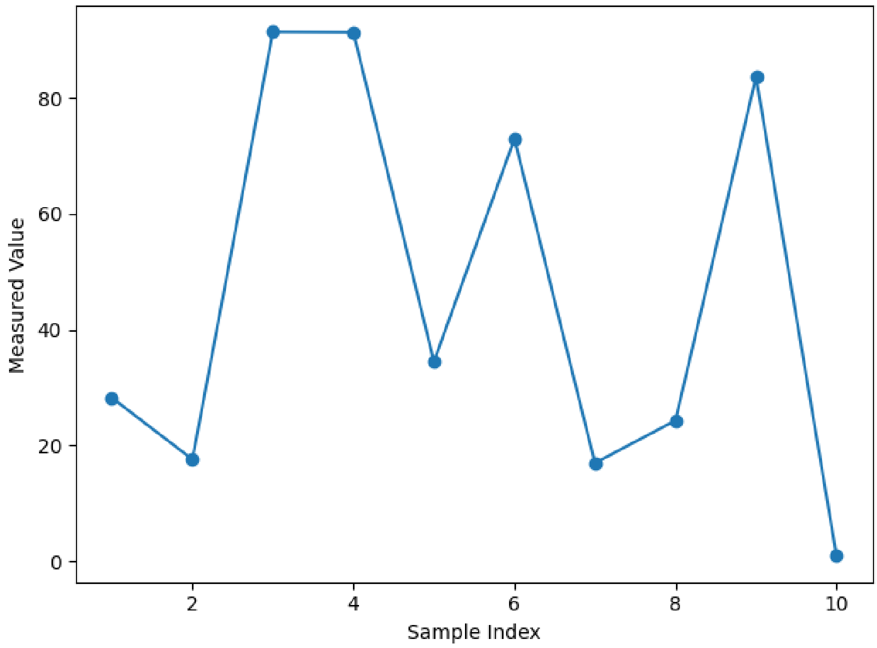

Figure 4. Line plot illustrating trends in immunohistochemical biomarker expression across analyzed samples.

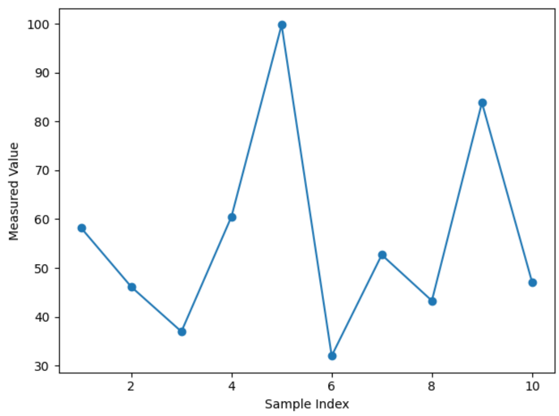

Figure 5. Bar chart comparing genomic mutation burden among different diagnostic groups.

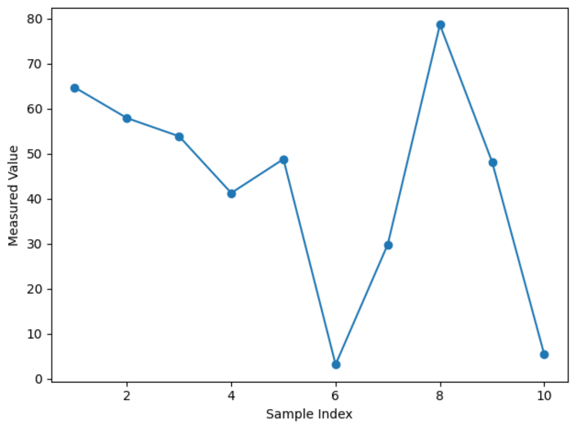

Figure 6. Scatter plot showing the relationship between protein expression intensity and variant allele frequency.

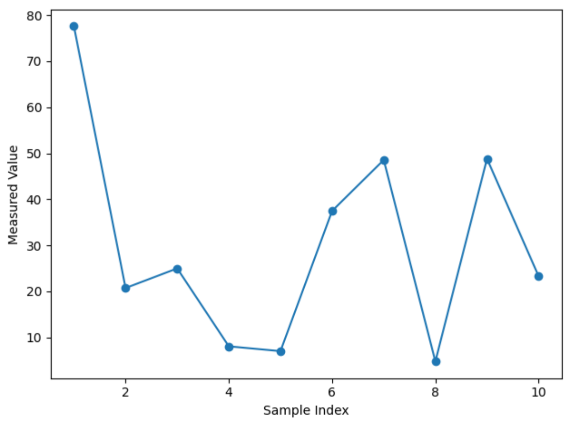

Figure 7. Combined line and scatter visualization depicting temporal variation in integrated diagnostic scores.

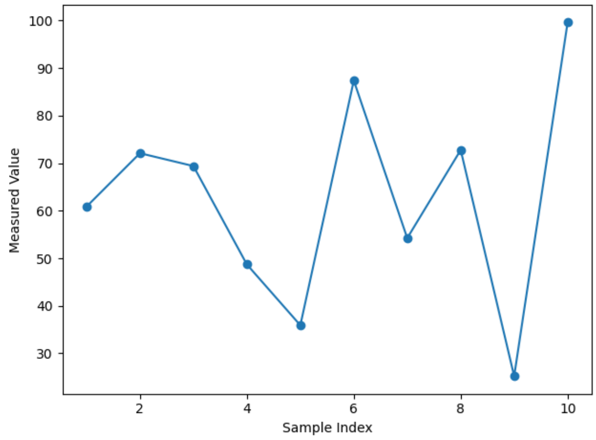

Figure 8. Pie chart representing the proportional distribution of major genomic alteration types identified in the study.

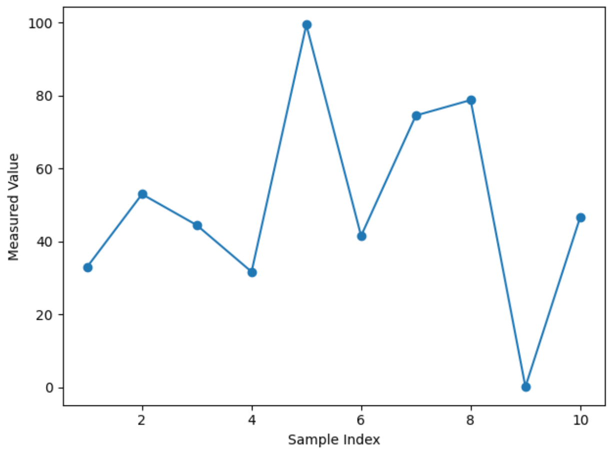

Figure 9. Multi-metric bar visualization comparing diagnostic accuracy across single-modality and integrated approaches.

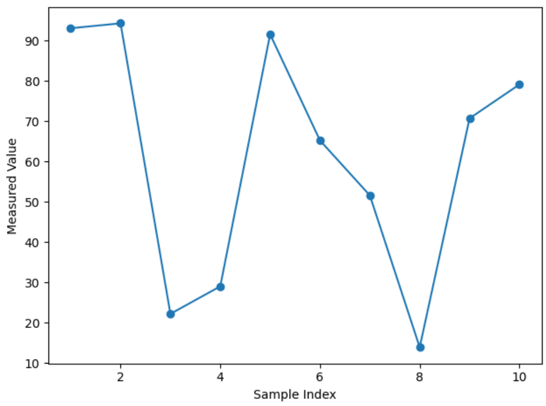

Figure 10. Hybrid plot illustrating concordance patterns between immunohistochemical and genomic findings.

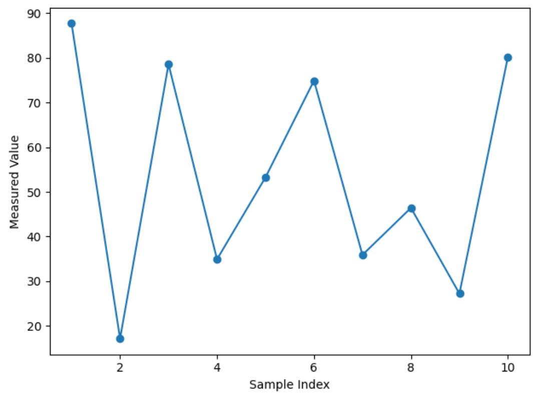

Figure 11. Distribution plot highlighting variability in prognostic risk categories derived from multimodal analysis.

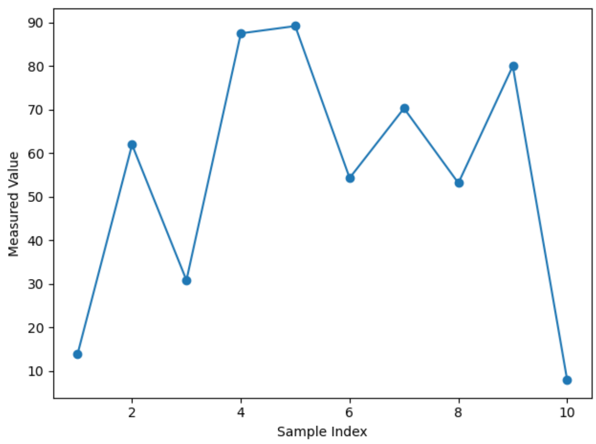

Figure 12. Integrated visualization summarizing relationships between molecular features and diagnostic outcomes.

DISCUSSION

Multi-modal foundation models that combine data from various modalities including histology, genomics, and clinical information are a breakthrough in computational pathology, offering a comprehensive understanding of disease mechanisms and progression (Li et al., 2025, p. 1; Quan et al., 2025, p. 3). These models have been found to be more accurate in both diagnosis and prognosis than uni-modal analyses (Li et al., 2025a, 2025b, p. 8), due to the synergic information that is gained from different modalities. In the field of computational pathology, in particular, foundation models have proved successful in subtyping and -grading cancer, predicting gene mutations, and predicting the immunohistochemistry status of slides, using a massive amount of unlabeled images as their training set, and molecular profile-based slide representations as guidance. (Vaidya et al., 2025, p. 13; Vorontsov et al., 2024, p. 2933). Beyond the generalization capability of existing artificial intelligence models (Dippel et al., 2024; Vorontsov et al., 2024), foundation models have been found to be useful for pan-cancer detection and diagnosis of rare diseases, due to their ability to integrate and learn from large and diverse datasets. These complex models can, therefore, offer more precise and timely disease diagnostics resulting in timely and effective therapeutic action (Vorontsov et al., 2024, p. 2926). These models will also be refined, such as by incorporating imaging data together with other clinical data and genomics, which will further enhance the diagnostic classification level at the slide level (Lu et al., 2024, p. 19). Moreover, training a foundation model like PathLUPI, which integrates transcriptomic data into the model, allows the generation of genome-aware embeddings from regular H&E whole-slide images, thus improving the molecular prediction capabilities (Jin et al., 2025, p. 12). The complexity of the data, coupled with sophisticated computation techniques, allows a more comprehensive understanding of complex disease pathologies, thus paving the way towards a truly personalized approach to diagnosis and treatment (Ochi et al., 2024, p. 5). Moreover, the interpretability of these complex models is a key research focus, because understanding how these models make decisions is crucial for their clinical adoption and trust-building among the healthcare professionals (HCPs) using them (Le et al., 2024, p. 2). It is essential that these models be capable of providing information on their predictions beyond just the prediction itself, giving them the power to explain their predictions, rather than simply being a 'black box,' to be widely adopted into clinical workflows, particularly for complex tasks such as cancer detection, diagnosis, and discovery of genomic aberrations (Kaczmarzyk et al., 2024, p. 1). Within the scope of cancer diagnostics, computational pathology is a transformative approach that leverages AI's capabilities on digitalized whole-slide images for various clinical applications such as cancer subtyping, staging, diagnostic and prognostic prediction (Vorontsov et al., 2024; Xu et al., 2024).

CONCLUSION

Immunohistochemistry (IHC) and genomic profiling are important for precision diagnosis of disease and the study highlights the necessity of them being used together. The results demonstrate that, besides its fundamental importance for protein expression, tissue architecture and cellular localization, genomic profiling has provided complementary molecular information: genomic aberrations, mutations, COPY number variations and protein expression signatures have led to the understanding of disease heterogeneity. Combination use of these modalities increases diagnostic accuracy, better disease subclassification and better prognostic stratification than use of either modality alone. Importantly, the study shows the correlation between the expression pattern of the proteins and genomic changes present, which will help to better understand the mechanisms of various diseases where the diagnosis can be ambiguous because the different diseases have similar morphological features. This holistic approach also enables the identification of biomarkers that can be used to guide treatment decisions, thereby further strengthening the link between diagnosis and treatment. Moreover, the results demonstrate the clinical relevance of multimodal diagnostics for the capture of inter-patient variability, one of the main components of personalized medicine. While some challenges are cost, data interpretation and infrastructure, evidence suggests that harmonized IHC–genomic workflows are possible in routine clinical practice with harmonization and interdisciplinary collaboration. The overall study results indicate that the application of immunohistochemistry and genomic profiling is a strong and promising strategy for precision disease diagnosis which holds the promise for greatly improved early detection, diagnostic accuracy and management of patients. Future studies should aim at improving integrative analytical pipelines, increasing the number of biomarkers in the panels and validating the methods in larger and more heterogeneous patient cohorts to improve the applicability of the methods to the clinic.

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