Predicting and replacing the pathological Gleason grade with automated gland ring morphometric features from immunofluorescent prostate cancer images

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Abstract. The Gleason grade is the most common architectural and morphological assessment of prostate cancer severity and prognosis. There have been numerous algorithms developed to approximate and duplicate the Gleason scoring system, mostly developed in standard H&E brightfield microscopy. Immunofluorescence (IF) image analysis of tissue pathology has recently been proven to be robust in developing prognostic assessments of disease, particularly in prostate cancer. We leverage a method of segmenting gland rings in IF images for predicting the pathological Gleason, both the clinical and the image specific grades, which may not necessarily be the same. We combine these measures with nuclear specific characteristics. In 324 images from 324 patients, our individual features correlate well univariately with the Gleason grades and in a multivariate setting have an accuracy of 85% in predicting the Gleason grade. Additionally, these features correlate strongly with clinical progression outcomes [concordance index (CI) of 0.89], significantly outperforming the clinical Gleason grades (CI of 0.78). Finally, in multivariate models for multiple prostate cancer progression endpoints, replacing the Gleason with these features results in equivalent or improved performances. This work presents the first assessment of morphological gland unit features from IF images for predicting the Gleason grade, and even replacing it in prostate cancer prognostics. © 2017 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: [10.1117/1.JMI.4.2.021103](https://doi.org/10.1117/1.JMI.4.2.021103)]

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1 Introduction

Prostate cancer is the most prevalent form of cancer and the second most common cause of cancer deaths among men in the United States. Accurate prognosis is important as it is the principal factor in determining the treatment plan. Prostate cancer is primarily assessed by the Gleason grading system which classifies the tissue architecture into five patterns of increasing severity.^{1–3} The Gleason grade characterizes tumor differentiation, i.e., the degree of tumor resemblance to normal tissue. In the lower risk Gleason grades of 1 to 3 the architecture consists primarily of isolated or touching gland rings surrounded by fibromuscular stromal tissue. Each gland is composed of a ring of epithelial cells surrounding a duct, the lumen. The connected glandular cytoplasm, or “epithelial unit,” contains just one gland ring. As the cancer progresses to grade 4, epithelial units fuse together creating chains of gland rings, or “cribriform” sheets of rings. A second axis of variation in grades 4 and 5 disease is the increasing fragmentation of rings resulting in sheets of isolated cells and nonring epithelial fragments (the terms “glandular” and “epithelial” are interchangeable). As shown in Fig. 1, normal tissue consists of gland units surrounded by fibromuscular stroma which mechanically support the gland units. As the cancer progresses, epithelial cells replicate

in an uncontrolled manner, disrupting the regular arrangement of gland units.

The Gleason grade is assessed by pathologists in light microscopy images of tissue stained using conventional H&E. While common in clinical practice, such images often present significant challenges in automated analysis of glandular objects due to uneven contrast between glands and stroma, and the frequent tearing of the tissue.²

In multispectral immunofluorescence (IF) microscopy,^{2–7} multiple proteins in the tissue specimen are simultaneously labeled with different fluorescent dyes. Each dye has a distinct emission spectrum and its associated antibody binds to its target protein within a tissue compartment (i.e., nuclei or cytoplasm). The stained slide is illuminated under a fluorescence microscope with a light source for a specific wavelength. This excitation light is absorbed by the fluorescent dye causing it to emit light of a longer wavelength. The intensity of the emitted light is a measure of the target protein’s concentration. In multiplexed IF images, the tissue is labeled with several antibodies at the same time. Each antibody is labeled with a unique fluorescent dye with distinct spectral characteristics. The tissue is then imaged with a multispectral camera, then spectrally unmixed to yield multiple images with one image per individual dye/antibody. Two common dyes that reveal the tissue structures are DAPI (a nuclear stain) and CK18 (stains epithelial cytoplasm). Nuclear objects are segmented and then separated using a colocalization

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Fig. 1 Samples of hematoxylin and eosin (H&E) stained prostate tissue illustrating varying degrees of differentiation: (a) normal, (b) grade 2 well-differentiated cancer, and (c) grade 5 poorly differentiated cancer.

scheme into epithelial nuclei positive for both DAPI and CK18 and stromal nuclei positive for DAPI but not CK18. Subsequently, prognostic biomarkers such as androgen receptor may be evaluated within each colocalized compartment.⁵⁻⁷

Because of its highly specific identification of molecular components and accurate delineation of tissue compartments, as compared to the stains in (H&E) light microscopy, multiplex IF microscopy offers the advantage of more reliable and accurate image segmentation and consequent feature extraction.²

It has long been a focus of prostate image analysis to create quantitative morphometric replacements for the Gleason grade, due to its inherent variability and reproducibility challenges. We leverage recently published² techniques for glandular characterization and epithelial nuclear dispersion in prostate IF images. Notably, the contributions of this paper explore the heretofore unaddressed question of whether these quantitative IF glandular features represent similar information as the Gleason grade and could replace it in prognostic settings. We (1) explore these techniques for univariate correlation with the Gleason grade, as well as (2) in a multivariate context for predicting the actual Gleason grade. Additionally, we also (3) measure the correlation of these features with multiple prostate cancer prognostic outcomes and finally, (4) we explore replacing the Gleason grade in multivariate prognostic models with these new techniques to predict two different prostate cancer progression endpoints.

2 Methods

2.1 Segmentation of Cellular Components

This paper builds upon previous work in IF biomarker quantification.⁵⁻⁷ Specifically, we leverage an algorithm for joint segmentation of cellular cytoplasm and nuclei which incorporates procedures for reliably separating overlapping nuclei.⁵ The algorithm commences with an adaptive process which includes top-hat filtering, eigenvalues-of-Hessian blob detection, and distance. Next, a minimum-error-thresholding-based binarization process and seed-detection combining Laplacian-of-Gaussian filtering (constrained by a distance-map-based scale selection) is used to identify candidate seeds for nuclei segmentation. The initial segmentation is refined using minimum-error-thresholding including artifact removal and nuclear object classification. Multiple biomarker specific features are extracted from each cellular and biomarker component.

2.2 Minimum Spanning Tree Calculation

A number of studies have demonstrated the utility of features derived from the minimum spanning tree (MST) and other⁸ sub-graphs of the graph connecting epithelial nuclei for the diagnosis and prognosis of prostate cancer as well as other diseases such as melanoma, breast, cervical, and ovarian cancers.⁹⁻¹³ The MST of a graph is defined as the tree connecting all vertices (i.e., epithelial nuclei centroids) such that the sum of the lengths of the lines (edges) connecting the vertices is minimized. Many algorithms exist for constructing the MST of a graph. We leveraged the well-known Prim's algorithm.⁸ Figure 2 shows a sample MST construction.

A variety of MST characteristics have been considered in the literature for cancer diagnosis and prognosis. We selected three key characteristics based on their predictive value in previous studies as well as their ease of interpretation and qualitative validation.³ The first feature was the mean edge length of MST edges that connect epithelial nuclei within a gland, the “intragland” edge length. This feature characterizes the degree to which the epithelial nuclei are invading the stroma surrounding a gland. A gland was defined leveraging novel glandular morphology metrics described next in Sec. 2.3. The next two features were the “degree distribution” for vertices with edges 1 and 2. The “degree” of a vertex refers to the number of edges incident on the vertex. The MST degree distribution has an intuitive interpretation in terms of tumor architecture. Degree 1 vertices typically occur when an epithelial nucleus is fairly isolated from other epithelial nuclei, usually occurring during stromal invasion. Degree 2 vertices typically correspond to epithelial nuclei regularly arranged within a gland. Consequently, higher proportions of degree 1 vertices are expected to correspond to larger Gleason grades, whereas higher proportions of degree 2 vertices are expected to correlate negatively with the Gleason grade.

While useful, MST-based algorithms do not segment a gland into individual rings, and thus do not differentiate the fusion of rings into cribriform patterns in Gleason grade 4 versus the dense stroma separated rings in Gleason grade 3.

2.3 Quantitative Glandular Morphology

We leveraged a new class of automated glandular morphology characterizations we have developed.^{2,14} Following DAPI and CK18 segmentations, adjacent and/or touching CK18 units are separated, followed by segmentation of epithelial units into

Fig. 2 (a) The original multiplex IF image with the DAPI counterstain in blue and the CK18 biomarker in green. (b) The MST connecting the epithelial nuclei (EN). CK18 cytoplasm is marked in light gray, while stromal and other compartments are marked out for clarity. EN centroids and intragland MST edges are in yellow.

distinct gland rings, concluding with a final classification of the gland ring type which leads to predictive features. The features are defined by analyzing proportions of epithelial nuclei in several categories. The ring adjacency features are based on the observation that the fusion and fragmentation of gland rings tends to reduce the proportion of gland nuclei adjacent to stroma and lumens. The features are created to systematically sample the glandular architectural feature space. Table 1 and Fig. 3 show the novel ring metrics employed to develop families of ring adjacency features.

As described in Ref. 2, touching or almost touching CK18 (epithelial cytoplasm) areas are separated through a fast-marching algorithm. The speed function parameter of the algorithm is an experimentally derived heuristic. In the CK18 image, both lumen and stromal regions are dark, and it is important to distinguish them to generate meaningful architectural features. Not all stromal regions contain DAPI nuclei, and conversely some

lumens contain epithelial nuclei sloughed-off or cut through an indented gland. A heuristic lumen decision rule is developed to identify lumens. Subsequently, epithelial nuclei are clustered into rings around lumens using a graph-based algorithm. It is a customized watershed merging algorithm on the Delaunay triangulation/Voronoi graph.

Specifically, the algorithm synthesizes the standard bottom-up watershed and connected component labeling algorithms extensively employed in image analysis.¹⁵ These techniques are applied to the Voronoi diagram of epithelial nuclei, where the nodes represent Delaunay triangles. The weight or depth of each node is equal to the length of the triangle’s longest edge, and each edge in the graph represents triangle adjacency, again weighted by the length of the triangle’s edge. The algorithm visits the nodes in order of decreasing depth and merges touching regions while keeping track of the following properties for each region: area, boundary length, region diameter (the longest interior triangle edge), as well as the shortest and longest boundary edges. Compared to a pixel-based watershed, which maintains only the region depth, this graph-based approach has a richer set of region and shape information to use in the critical merging rule. The current implementation merges regions if the touching edge weight is less than 90% of both the regions’ diameters. Figure 4 presents the “algorithm recipe” for this procedure.

Finally, polygonal rings touching the image border are excluded, and the remaining polygonal regions are classified

Table 1 These six metrics (based on D, d and b in Fig. 3) characterize the shape of the gland ring and the degree to which the ring is adjacent to stroma and lumen areas. These metrics are then used to define a novel family of prognostic features.

Metric	Description
D	Outer diameter of ring = 4 area/perimeter
d	Inner clearing free of nuclei = second largest chord in nuclei triangulation
b	Border gap = second largest gap between nuclei around ring border
L	Lumen or clearing diameter = excess of inner diameter over border gap = $d - b$
Ltouch	Lumen touch = proportion of ring inner border touching inner clearing = L/D
Stouch	Stromal touch = proportion of ring outer border touching stroma
Density	Density of the border nuclei gaps compared to the interior gaps = d/b (good rings have dense nuclei around the border compared to the interior)

Fig. 3 Illustration of gland ring metrics described in Table 1.

Algorithm Recipe

1. Create a Delaunay triangulation with epithelial nuclei centers as vertices. The triangle connectivity graph is the Voronoi diagram.
2. Assign a “depth” to each triangle (graph node) = length of longest triangle edge.
3. Sort nodes by depth
4. Starting from the deepest triangles, examine the 3 neighboring regions and merge regions according to the following criteria, where region width is the largest triangle edge length in the region:
 - a. Merge touching regions if touching edge length > 0.75 microns (the minimum region width)
 - b. Merge touching regions if the smaller region has width < 10 pixels
 - c. Do not merge regions if the two regions overlap different epithelial nuclei.

Fig. 4 Algorithm recipe for merging gland regions.

Fig. 5 Calculation of gland units for four images. The (a) images are the CK18 segmentations, the (b) images are the DAPI segmentation (also used for MST calculations), the (c) images illustrate the centers of Voronoi diagrams and the final gland units are in (d). In the (c) and (d) images, red glandular units are those that represent intact gland rings and the green units are those which represent deteriorating or poorly differentiated gland units.

as epithelial or stromal according to a heuristic decision rule: that stromal regions must meet the following three criteria: (i) luminal areas (total of non-CK18 background areas not touching region edges) are <100 pixels, (ii) cytoplasm (CK18) represents less than 70% of the region area, and (iii) the region's edges cross through background areas, they are not totally included with CK18 positive pixels.

This graph segmentation algorithm clusters epithelial nuclei into individual gland rings and fragments.² Previous work in graph-based algorithms uses MST, Voronoi diagrams, and similar approaches to generate predictive features.¹⁶ The novelty of this approach is that it employs graph algorithms for glandular segmentation without initialization from a central lumen. This is important as high-grade disease often does not have lumens present. The algorithm is a watershed style graph algorithm which, when compared to a pixel-based one, supports a rich set of region merging rules, resulting in more accurate segmentations. Figure 5 shows the initials glands, intermediate steps, and final segmented gland units for four different images.

2.4 Related Work

There has been significant prior work on deriving architectural features from unsegmented graphs such as Minimum Spanning Trees (MSTs),⁸ Voronoi diagrams, and Delaunay triangulation in analyzing individual nuclei in both H&E and IF images.^{1,3,9} While glandular morphometry has been analyzed in whole prostate H&E images,^{16,17} analysis of microscopic H&E images has been a recent development.^{14,18–20} Most of the literature has focused on cancer versus benign classification with limited sets of images, often less than 100, and evaluates the morphometric features with respect to tumor architecture,^{19,20} rather than clinical outcomes of progression. Of note, Ref. 18 presented analysis of H&E images from 1027 patients yielding a set of “gland unit” features derived from semiautomated seeding of lumens. However, this paper employs one of the first efforts in automated glandular analysis from microscopic IF images² and builds on work recently presented at SPIE Medical Imaging 2016.¹⁴ As mentioned, earlier graph-based work usually generates features from the morphological graphs¹⁷ rather than employing them to create new morphological components, glandular as this work does. Furthermore, MST-based algorithms cannot differentiate between fused and dense rings.

Interestingly, cell cluster graph (CCG)²¹ features explore a similar area as this work. They are based on probabilistic connections within and between small clusters of nuclei, capturing the heterogeneity of the cellular architecture. However, a drawback of CCGs is that a cluster may include both stromal and epithelial nuclei, potentially hindering the development of epithelial features for gland fusion and fragmentation. Instead, the features in this work are based on discrete gland rings containing epithelial nuclei only. We employ Voronoi graph analysis solely as a segmentation aid, rather than a feature extraction method, so CCG features are not directly comparable.

The features presented in this work are based upon weighted area and length ratios of adjacent lumens, gland rings, and stroma, and are specifically designed to evaluate the fragmentation and fusion of gland patterns that drive disease progression. The pathological motivation is the fact that fusion is best captured by the loss of adjacency between glands and stroma, whereas fragmentation is characterized by reduced adjacency between gland rings and lumens. Unlike previous work, lumens in this effort are robustly defined by spacing between nuclei with

Fig. 6 Fully automatically segmented Gleason grade 4 image with fused gland rings in purple.

a ring,² not a lack of stain. The nuclei-lumen adjacency features proposed in Ref. 22, as well as the semiautomated lumen seeded features in Ref. 18 capture the effect of glandular fragmentation as they lost lumens in high-grade disease, but do not capture gland fusion as stroma between glands is lost. In contrast, the presented approach's features capture both fusion and fragmentation, through stromal, gland ring, and lumen adjacency measures. Figure 6 shows the fully automatically segmented fused gland rings in a Gleason grade 4 image.

3 Experimental Results

We evaluated these features in 324 prostate cancer images from 324 patients treated with a radical prostatectomy (RP).^{23,24} Two Gleason grades were assigned by pathologists. The first was the overall dominant clinical Gleason grade assigned to the patient representing the severity of the disease in the whole tissue sample. These were all assessed by a single pathologist. The second was a Gleason grade assigned specifically to the image being analyzed by our algorithms. Each image was captured from a tissue microarray (TMA) constructed from the whole prostate specimen, with the goal of capturing the region best corresponding to the total clinical Gleason grade. Subsequent sections of

Fig. 7 Distribution of clinical Gleason grades.

Fig. 8 Distribution of image specific Gleason grades.

the TMA were stained with both H&E and IF assays. Images were acquired at a 20× magnification. A second pathologist assessed an image's specific Gleason grade for the IF image, leveraging the corresponding H&E stained image from the adjacent pathological section for double checking. Due to potential sampling bias in the imaging process, the image-specific Gleason grade may not necessarily have been the same as the overall Gleason grade for the patient. Figure 7 shows the distribution of the clinical Gleason grades, and Fig. 8 shows the distribution of the corresponding image specific Gleason grades. Benign and precancerous (PIN) glands were manually masked out by a pathologist prior to analysis by our algorithms.

As the Gleason score requires multiple different views of the prostate to assign a dominant and secondary grade which are then combined into a score, and we were interested in simply

predicting for one view or image, this work focuses on predicting the Gleason grade.

3.1 Predicting the Gleason Grade

As a first step, we analyzed the univariate correlation of our features with both of the Gleason grades by employing the Pearson's correlation coefficient. These results are presented in Table 2. Subsequently, we built multivariate logistic regression models to predict high Gleason grades 4 and 5. We built models to predict both the clinical and image specific Gleason grades. These results are presented in Table 3.

It is interesting to observe that most of the features univariately correlate much better with the image specific Gleason than the overall clinical Gleason grade, which makes intuitive sense. Those images are the ones from which the automated features are derived. This is true in the multivariate results as well, where the accuracy of predicting the image-specific Gleason grade is higher than the clinical grade. Our features are particularly good at detecting low-grade disease, with noteworthy negative univariate correlations and specificities of the multivariate models.

3.2 Replacing the Gleason Grade in Post-RP Prognostic Models

The most common treatment for prostate cancer is the surgical removal of the prostate through a RP. Unfortunately, an RP is no guarantee of a cure. Approximately 9% to 18% of men post-RP experience significant clinical failure (CF) including metastasis and/or death-from-cancer.²³ While CF is a clinically meaningful endpoint, it can often take years to present; and when it does the disease maybe too advanced for effective treatment. Therefore, an earlier endpoint of prostate-specific-antigen-recurrence (PSAR) post-RP is frequently employed as a surrogate.²⁴ This is, however, a noisier endpoint, which 20% to 40% of men experience post-RP, not everyone with PSAR progresses to the more advanced stage of CF. Since PSAR

Table 2 Correlations of features with image specific and clinical Gleason grades.

Feature	Feature description	Correlation with clinical Gleason	Correlation with image Gleason
"RatioAreaENRingSoftStG40DeG15"	Proportion of epithelial nuclear area in "good" rings with stouch greater than 40 and density greater than 1.5	-0.2363	-0.3759
"MeanLtouchRingSoftStG50"	Mean of the SoftStG50 variable (stromal touching percentage >50%) weighted by the lumen touching proportion. This feature responds strongly to rings with relatively large lumens	-0.2705	-0.4322
"RatioPerimeterRingStouchvs12"	Ratio of the perimeter of good rings which touch stroma to the total perimeter length of good rings and fragments	-0.1517	-0.3304
"RatioAreaENRingStouchvs123"	Ratio of the total area of epithelial nuclei adjacent to stroma to the total area of all epithelial nuclei	-0.2055	-0.3500
"RatioAreaENRingSxLtouchvs123"	Product of proportion of epithelial nuclei which touch stroma and ratio of total area of epithelial nuclei that are lumen adjacent	-0.2314	-0.4004
"mstmeanlengthintra"	Mean MST edge length of intragland edges	0.1193	-0.0027
"proportionedge1"	Proportion of MST degree 1	0.1833	0.4832
"proportionedge2"	Proportion of MST degree 2	-0.1751	-0.4740

Table 3 Accuracy of multivariate logistic regression models in predicting high Gleason grades (4 and 5).

	Image Gleason (%)	Clinical Gleason (%)
Total accuracy	84	85
Sensitivity	62	19
Specificity	92	97
PPV	70	56
NPV	89	85

occurs years earlier though, a physician and patient can start to make complex decisions about treatment options and impact on quality of life. Accurate prognosis is important as it is the principal factor in determining the treatment plan. The Gleason grade is often included in multivariate prognostic models for predicting the risk of both CF and PSAR post-RP. We explored whether our IF glandular morphology features could not only predict the Gleason grade, but could actually replace it in these prognostic models.

We leveraged the concordance index (CI)^{2,3,25} as our measure of prognostic performance. The CI is the standard metric for assessing the predictive ability of a survival model or prognostic feature. The CI measures the concordance between a metric (individual features or model results) and the survival times of patients. Survival analysis is inherently a ranking problem and the CI measures the accuracy of ranking a model's results against the survival times. It is the probability that a patient with a shorter survival time will have a smaller predicted value. The CI is a linear transform of the Somers' *d* statistic and is similar in interpretation to the area-under-the-curve and the Mann-Whitney statistics.

3.2.1 Univariate analyses

First, we evaluated the univariate correlation of our features with the prognostic endpoints of significant disease progression via

Table 4 Correlation of glandular morphology IF features with prognostic disease progression as assessed by the CI.

Feature	CF CI	PSAR CI
Clinical Gleason	0.7774	0.6862
Image Gleason	0.7808	0.6434
"RatioAreaENRingSoftStG40DeG15"	0.8697	0.6337
"MeanLtouchRingSoftStG50"	0.8479	0.6629
"RatioPerimeterRingStouchvs12"	0.8038	0.5957
"RatioAreaENRingStouchvs123"	0.8261	0.6156
"RatioAreaENRingSxLtouchvs123"	0.8864	0.6477
"mstmeanlengthintra"	0.5519	0.5489
"proportionedge1"	0.7904	0.5598
"proportionedge2"	0.7746	0.5654

Table 5 Training and test performances of models to predict CF and PSAR.

	Model 1	Model 2	Model 3
CF training CI	0.84	0.84	0.84
CF test CI	0.80	0.82	0.83
PSAR training CI	0.71	0.70	0.86
PSAR test CI	0.62	0.65	0.76

the CI; these results are presented in Table 4. Of note is the fact that for the more important CF endpoint, our features are significantly better correlated with clinical outcomes than the manually assigned Gleason grades by the pathologists, whether at a clinical or image level. The clinical and image Gleasons, while different, are similar in their prognostic power, again manifesting a limitation of the human pathologist. For the more imprecise endpoint of PSAR, the features are able to match the predictive performance of the Gleason grade.

3.2.2 Multivariate prognostic models

Our cohort had seven clinical prognostic factors of risk per patient.^{23,24} Including the dominant Gleason grade and Gleason sum (dominant plus secondary grade), we had the clinical stage, preoperative PSA level, seminal vesicle invasion status, positive surgical margin status, and extra-capsular extension status. We split the cohort of patients into training and test sets, each representing 50% of the total cohort. In developing medical prognostics, it is usually necessary to maintain separate training and validation sets (rather than combined cross-validation type approaches) due to FDA regulatory requirements for independent testing and validation. We built models for CF and PSAR in the training set, and then tested them in the test set. Models were built using SVRC,²⁵ a support vector method for survival analysis which has previously been employed for prostate cancer prognostics.^{23,24}

For both CF and PSAR, three models were built. Model 1 employed just the seven clinical variables (including the Gleasons), model 2 employed eight variables, adding the pathologist assigned image-specific Gleason to the seven clinical variables, and model 3 dropped all three Gleasons and instead substituted in our IF glandular morphology features, combining them with the other six clinical variables.

Table 5 shows the multivariate training and test results. For the prognostic models to predict CF, the presented glandular morphometry features are able to match the performance of the Gleason grades. For the PSAR multivariate models, the IF features even outperform models with the Gleason grades.

4 Conclusions

This paper presents one of the first evaluations of morphometric features from immunofluorescent prostate cancer images for predicting Gleason grades manually assigned by expert pathologists. The new features predict the Gleason grade with 85% accuracy, and have improved performances for predicting the image-specific Gleason grades. The features are particularly good at detecting low-grade disease. Additionally, these features are able to replace the Gleason grades in multivariate prognostic

models for multiple prostate cancer progression endpoints in a postsurgical setting. We plan to further investigate and identify features in our framework that are optimized for high-grade cancer.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

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Gerardo Fernandez received his MD from Drexel University (MCP), Philadelphia, Pennsylvania, USA, residency and fellowship training were in anatomic and clinical pathology, surgical pathology and cytopathology, respectively, at New York University Medical Center. His early career was in oncologic pathology, specializing in tumor markers. In his later career, he has focused on tissue-based prognostic and predictive model assay development, in particular leveraging multiplexed image analysis, computer vision, deep learning techniques, and artificial intelligence modeling.