Frontiers of Predictive Oncology and Computing

From Pathology to Computation
The Path to Dynamic Models of Cancer

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Mount Sinai

FROM PATHOLOGY TO COMPUTATION
THE PATH TO DYNAMIC MODELS OF CANCER

Sick Care	→	**Health Care**
Data	→	**Knowledge**
Treating Symptomatology	→	**Treating Causation**

THEMATIC DEVELOPMENT

Integration of Multidimensional Studies to Precisely Classify Disease and Optimize Treatment

Development of Comprehensive Platforms
(From Workflow and Data Flow to "Solutions-as-a-Service")

Management of Knowledge
(From Personalized Medicine to Population Management)

Transform Practice into a Dynamic Interactive Learning Experience

A NEW PARADIGM IN PATHOLOGY

INTEGRATED APPROACH TO DISEASE MANAGEMENT

	Classical Pathology →	Molecular & Systems Pathology
Diagnosis & Staging	<u>Descriptive</u> analysis of clinical variables, histology, and biomarkers to categorize patients into broad disease stages; minimal to no predictive value to inform treatment selection.	<u>Objective, quantitative</u> and multidimensional analysis of clinical variables, tissue/cellular morphometrics, and molecular signatures to define individual patient tumor phenotype and genotype, guiding treatment decisions.
Prognostic Evaluation	Traditional population and cohort-based classification used to deduce disease progression and likelihood of treatment response; non-specific.	Patient-specific characteristics and molecular tumor profiles used to predict drug sensitivity and radiation response, thus optimizing treatment efficacy and outcome.
Treatment Selection	Group management approach that stratifies patients into disease categories, assigning therapies on pre-determined population-based protocols instead of being patient-specific.	Personalized and integrated care model drives selection of evidence-based treatment protocol to optimize clinical outcome; patient-tailored treatments improve survival and quality of life.

Diagnostic and prognostic approach that "groups" patients into disease categories.

Precise, predictive, and cost-effective; individualized patient management.

CENTER FOR COMPUTATIONAL AND SYSTEMS PATHOLOGY

Systems Pathology represents a novel, comprehensive approach to personalized medicine, based on the development of highly accurate predictive algorithms. Integrates clinical variables, histological/cellular features & molecular profiles through innovative technologies in the areas of image analysis, quantitative biomarker multiplexing, and deep learning.

Computational Pathology:
Mathematical characterization of phenotype.

+

Systems Pathology:
Analytical combination of multiple data sources.

- Board Certification in Clinical Informatics.
- Enhancing the development and funding of scientific research and clinical applications related to individualized and predictive medicine.

TRANSLATING DATA INTO KNOWLEDGE

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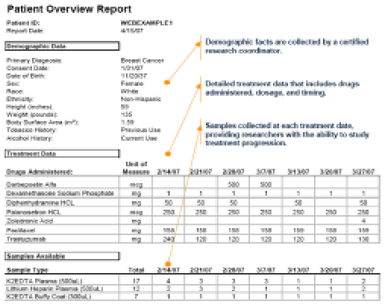
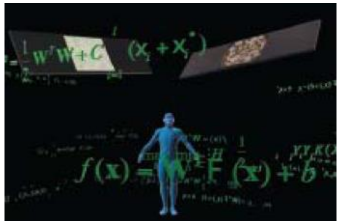
PRECISE Medical Diagnostics is a novel diagnostics platform to launch predictive/prognostic oncology-focused tests using deep learning and proprietary algorithms that combine:

(i) Clinical features and Outcomes Data } Annotated Records
(ii) Digital Morphology and Morphometric Statistics
(iii) Molecular Pathology Signatures
(iv) Clinical Laboratory Parameters } Phenotype
(v) Genomic Variables and Genetic Mutations } Genotype

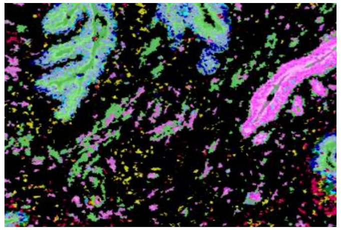
<u>Clinical and Outcomes Data</u>



<u>Morphometric Studies</u>

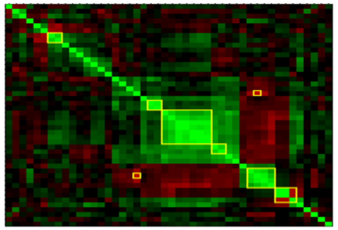


<u>Molecular Signatures</u>



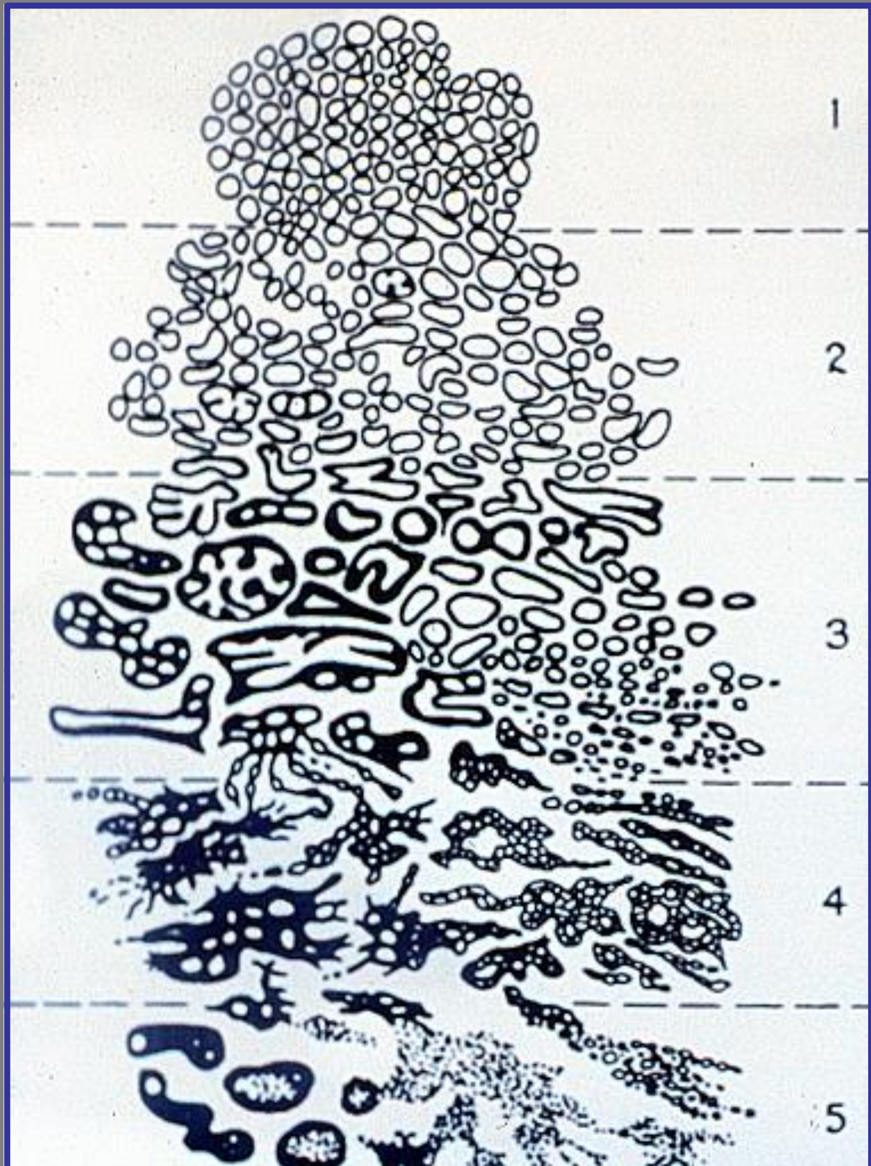
<u>Clinical Pathology</u>

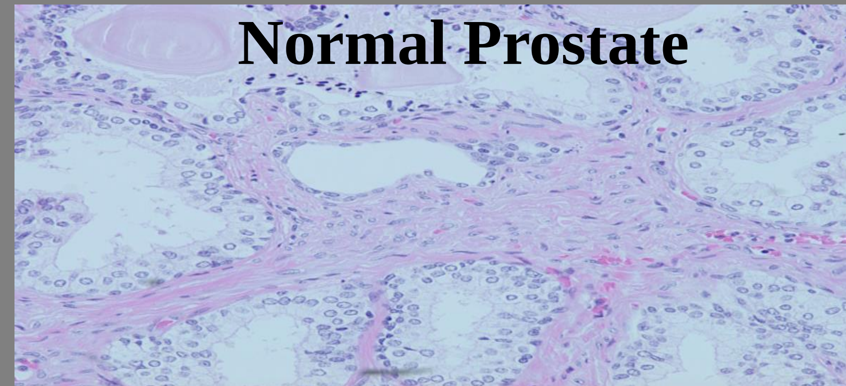
<u>Genomic and Genetics Variables</u>

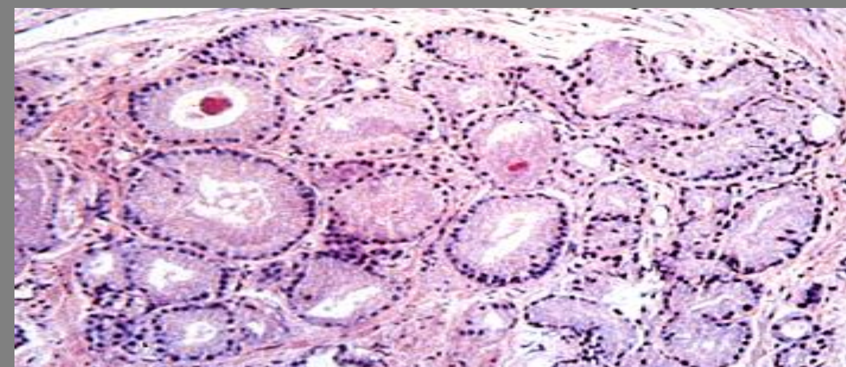


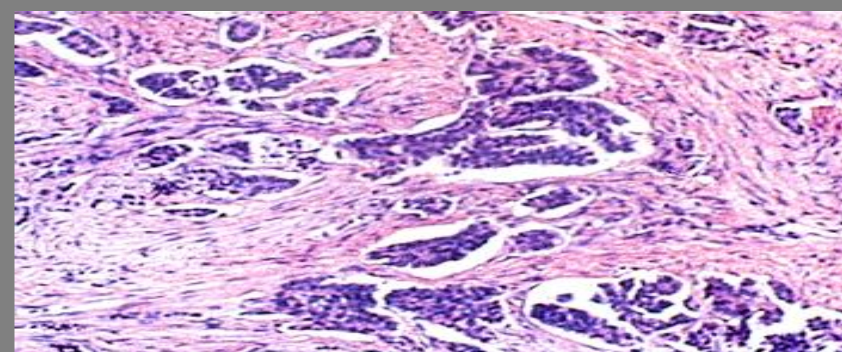
Algorithm-Based Platform for the Accurate Diagnosis and Better Management of Cancer Patients.
Tests with higher precision to render more effective and efficient patient care.

PROSTATE CANCER ANALYSIS: GLEASON TUMOR GRADE









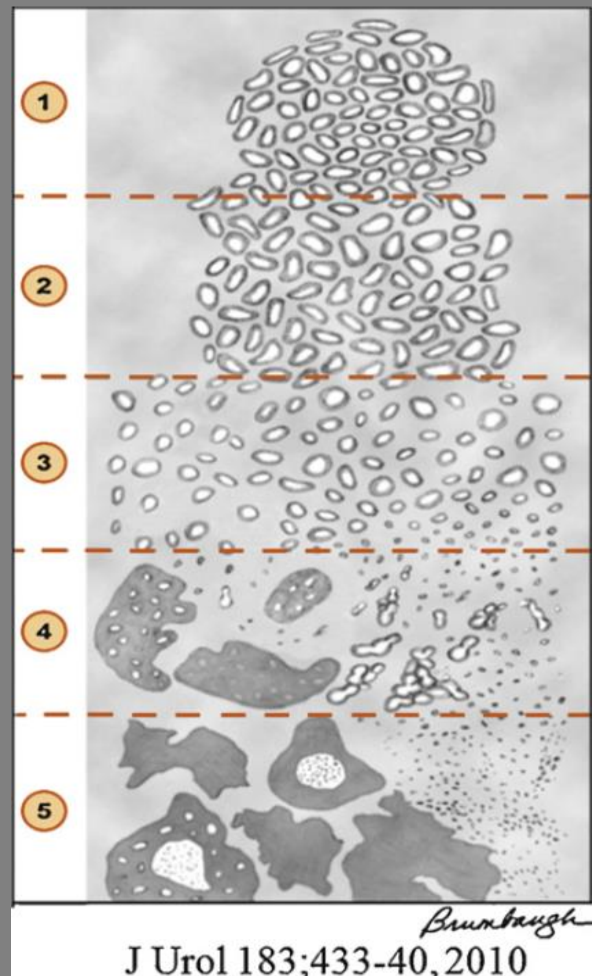
PROSTATE CANCER ANALYSIS: GLEASON TUMOR GRADE

<u>Fusion</u>

Increasing Architectural complexity

Coalescent Sheets

Decreasing Stromal Touch



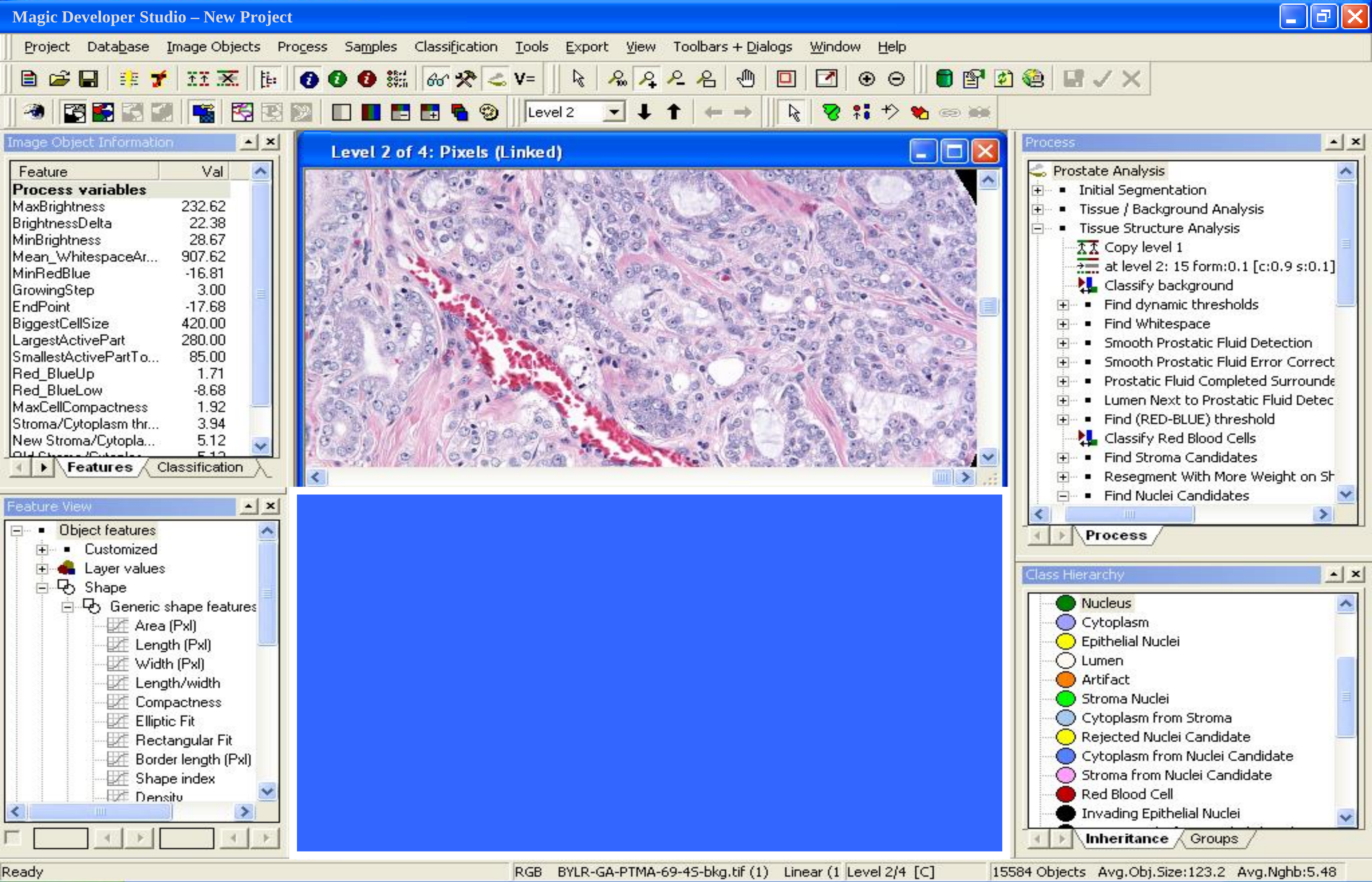
Decreasing Lumen Touch

<u>Fragmentation</u>

Increasing Glandular & Cellular Dispersion

Single Cells

Axes of Variation and the SL Product ($S^T \cdot L^T$)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MinBrightness 28.67
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EndPoint -17.68
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LargestActivePart 280.00
SmallestActivePartTo... 85.00
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Classify Red Blood Cells
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Epithelial Nuclei
Lumen
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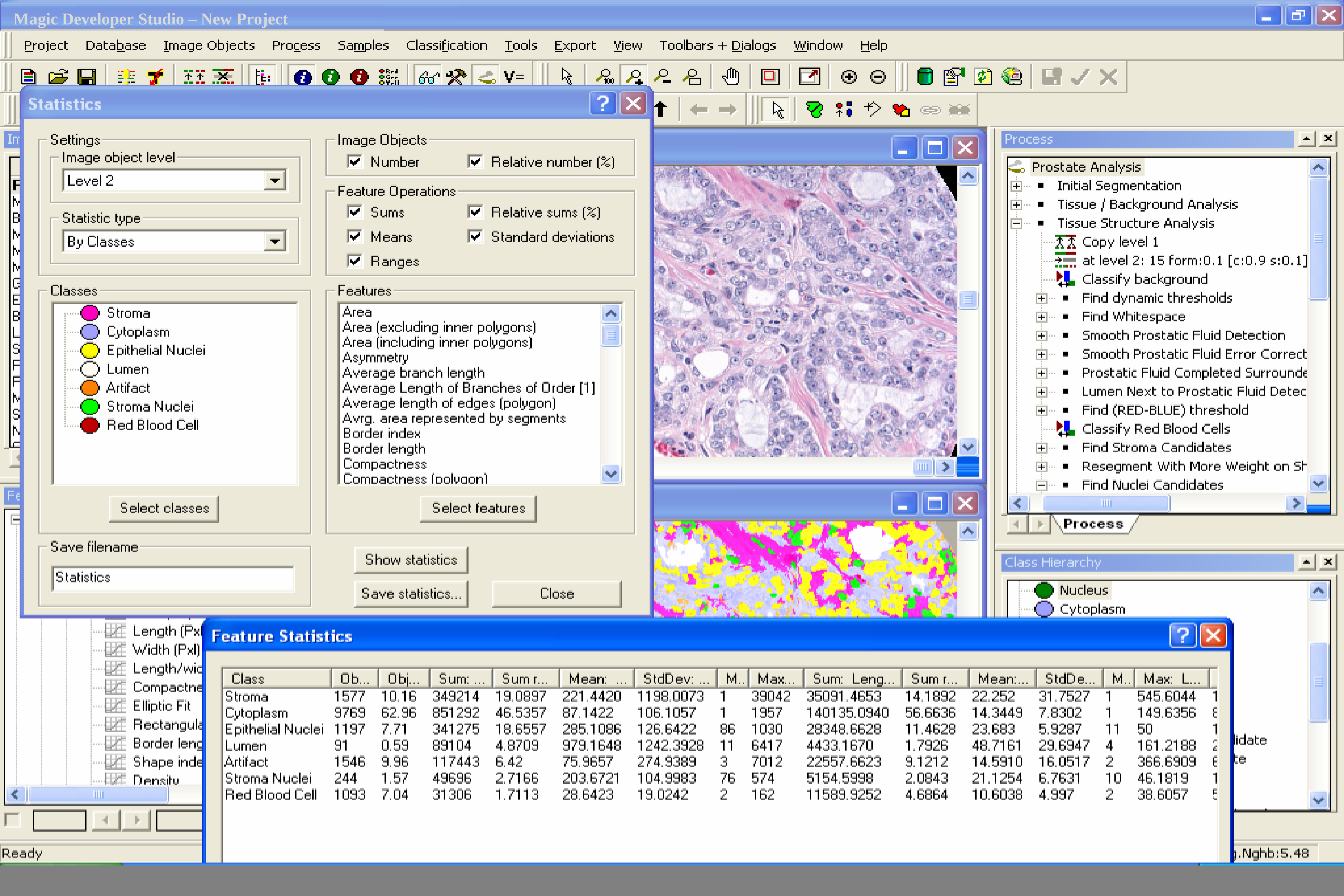
Magic Developer Studio – New Project
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Area (including inner polygons)
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Compactness (polygon)
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Tissue Structure Analysis
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Classify background
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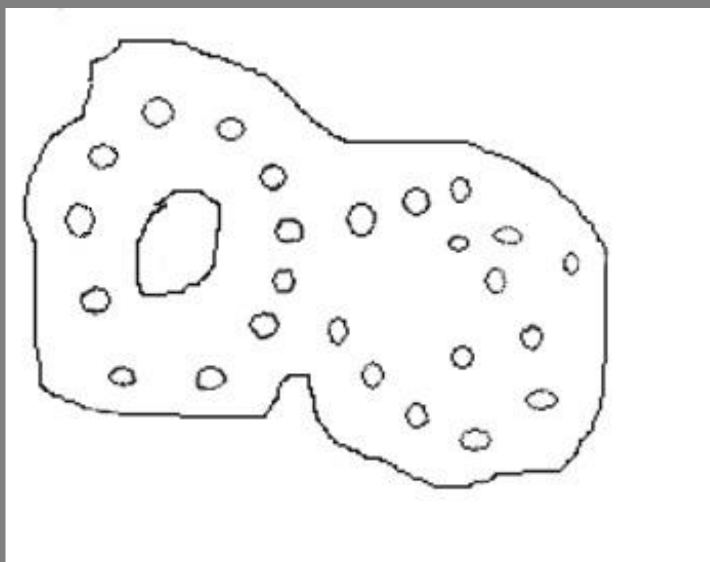
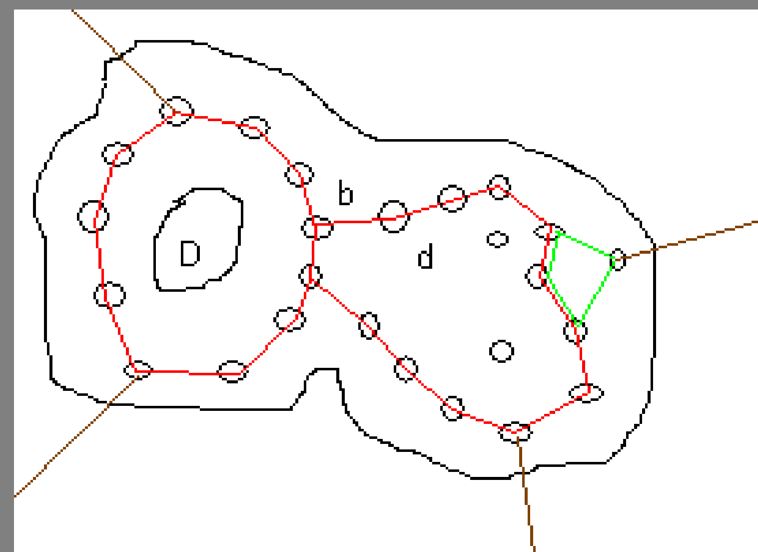
Class | Ob... | Obj... | Sum: ... | Sum r... | Mean: ... | StdDev: ... | M... | Max... | Sum: Leng... | Sum r... | Mean:... | StdDe... | M... | Max: L...
Stroma 1577 10.16 349214 19.0897 221.4420 1198.0073 1 39042 35091.4653 14.1892 22.252 31.7527 1 545.6044
Cytoplasm 9769 62.96 851292 46.5357 87.1422 106.1057 1 1957 140135.0940 56.6636 14.3449 7.8302 1 149.6356
Epithelial Nuclei 1197 7.71 341275 18.6557 285.1086 126.6422 86 1030 28348.6628 11.4628 23.683 5.9287 11 50
Lumen 91 0.59 89104 4.8709 979.1648 1242.3928 11 6417 4433.1670 1.7926 48.7161 29.6947 4 161.2188
Artifact 1546 9.96 117443 6.42 75.9657 274.9389 3 7012 22557.6623 9.1212 14.5910 16.0517 2 366.6909
Stroma Nuclei 244 1.57 49696 2.7166 203.6721 104.9983 76 574 5154.5998 2.0843 21.1254 6.7631 10 46.1819
Red Blood Cell 1093 7.04 31306 1.7113 28.6423 19.0242 2 162 11589.9252 4.6864 10.6038 4.997 2 38.6057
Ready
.Nghb:5.48

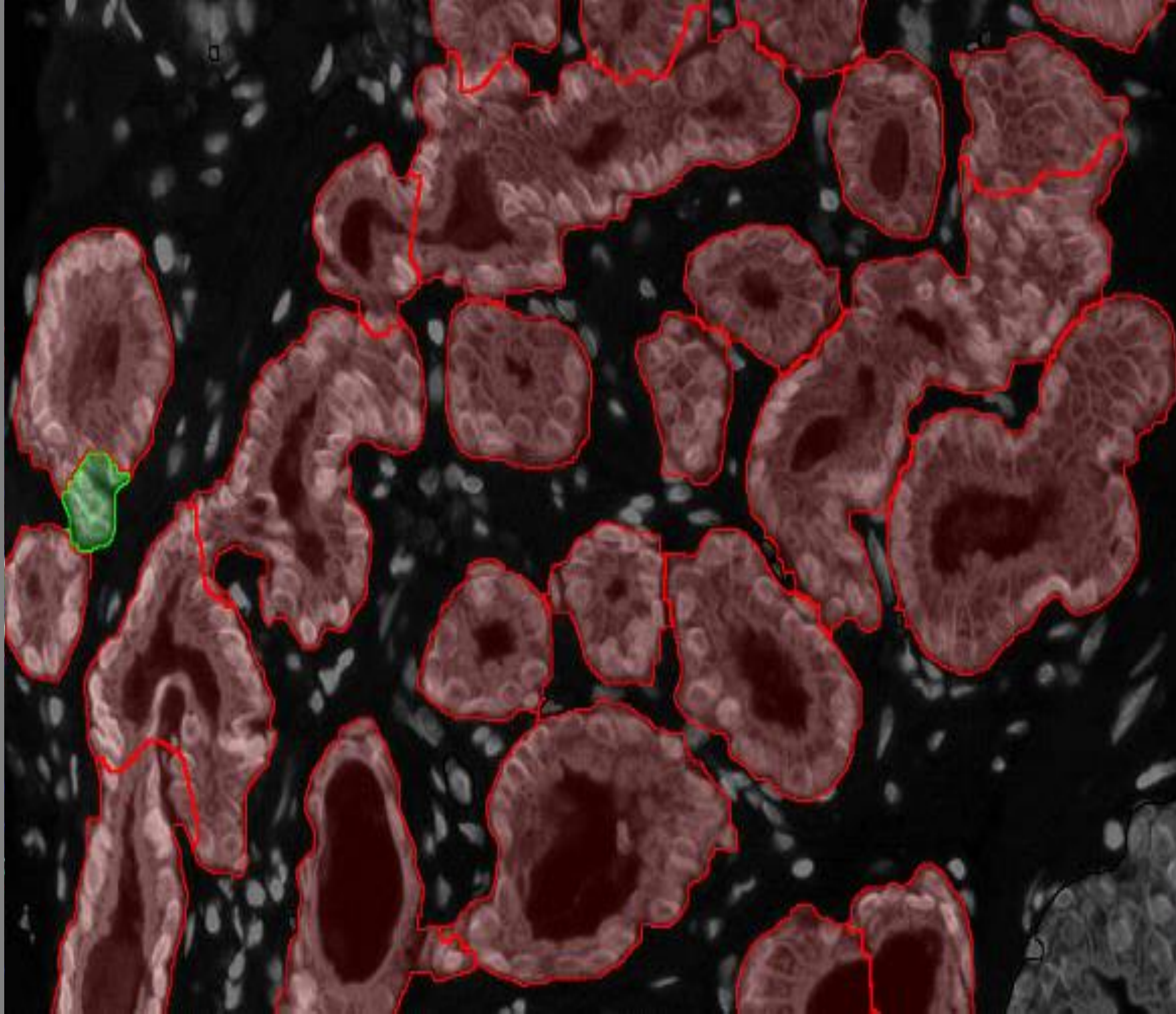
MORPHOMETRIC AND AUTOMATED GLEASON GRADING GLANDULAR RING STRUCTURES

- Prostate cancer grading is based on morphological assessment of glandular differentiation (Gleason Grade).
- Gleason Grade notoriously lacks interobserver reproducibility.
- Glandular structures can be converted mathematically to “ring” structures
- Technical definition: A graph theory and “voronoi” diagram based algorithm for identifying gland rings as a basis for quantitating architectural structure, specifically degree of glandular differentiation.

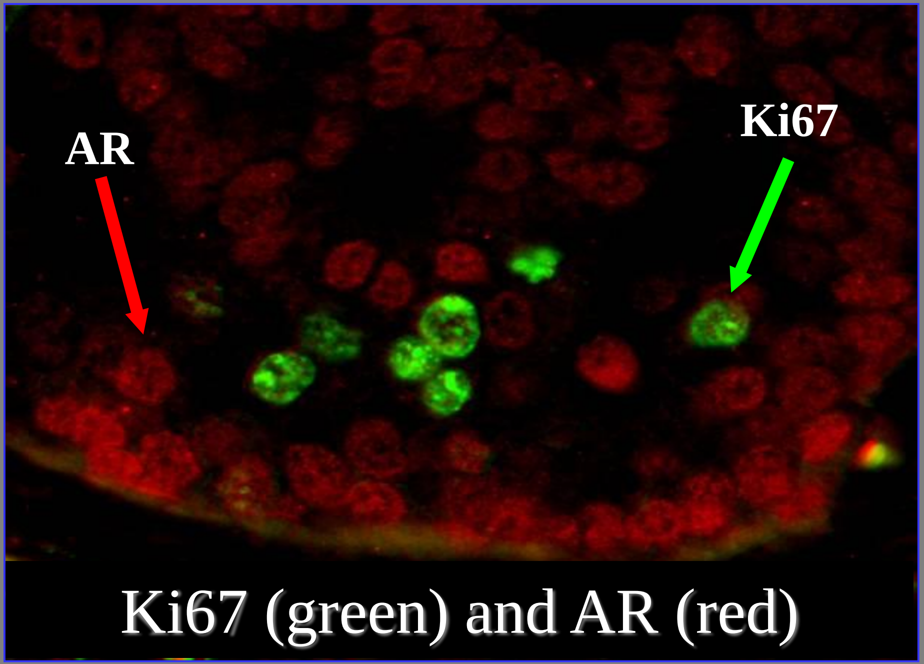




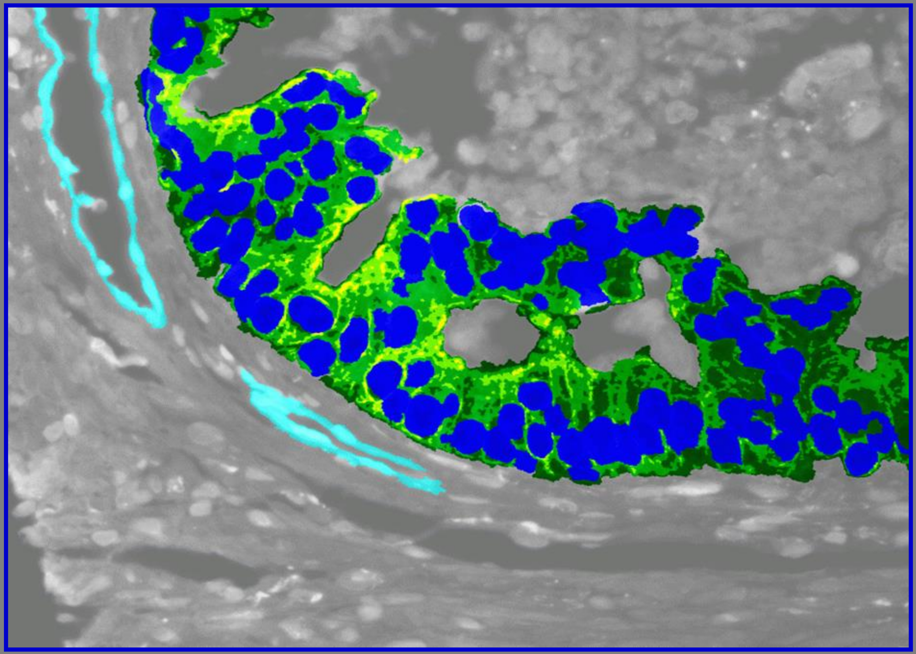
Continuous Grading (e.g., 2.4+2.8 = 5.2)



PROTEIN MULTIPLEXING AT MICROANATOMICAL DETAIL



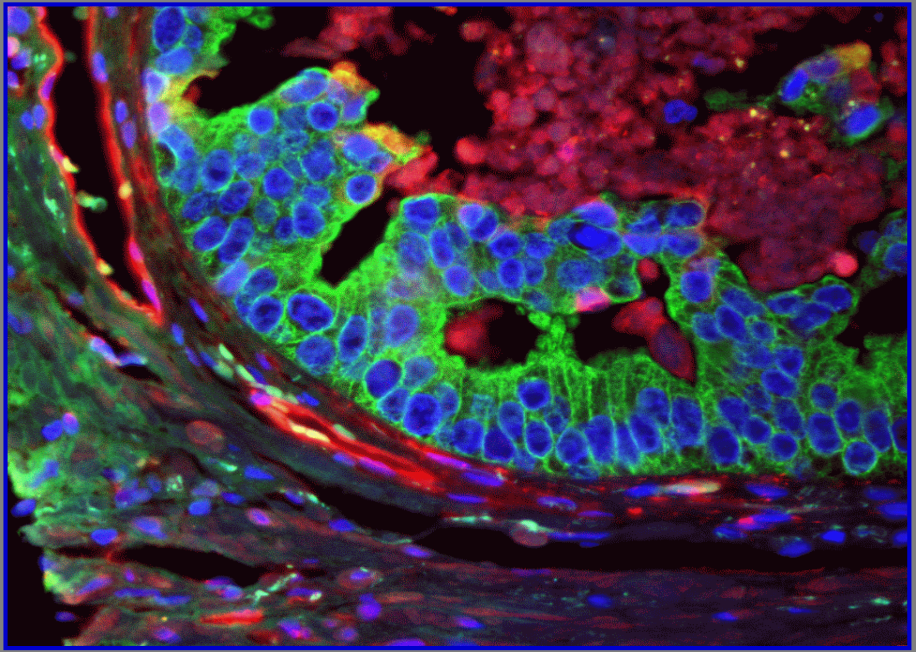
MULTIPLEXED IMAGE



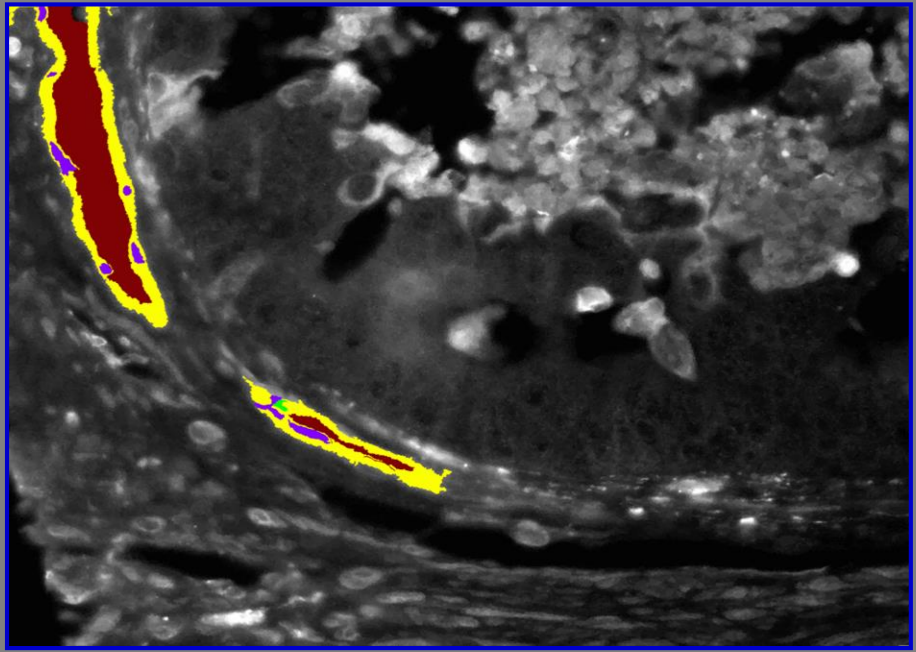
EXTRACTED FEATURE

NUMBER OF EPITHELIAL CELLS (DAPI+ CK18)
AVERAGE SIGNAL INTENSITY IN THE CYTOPLASM

PROTEIN MULTIPLEXING AT MICROANATOMICAL DETAIL



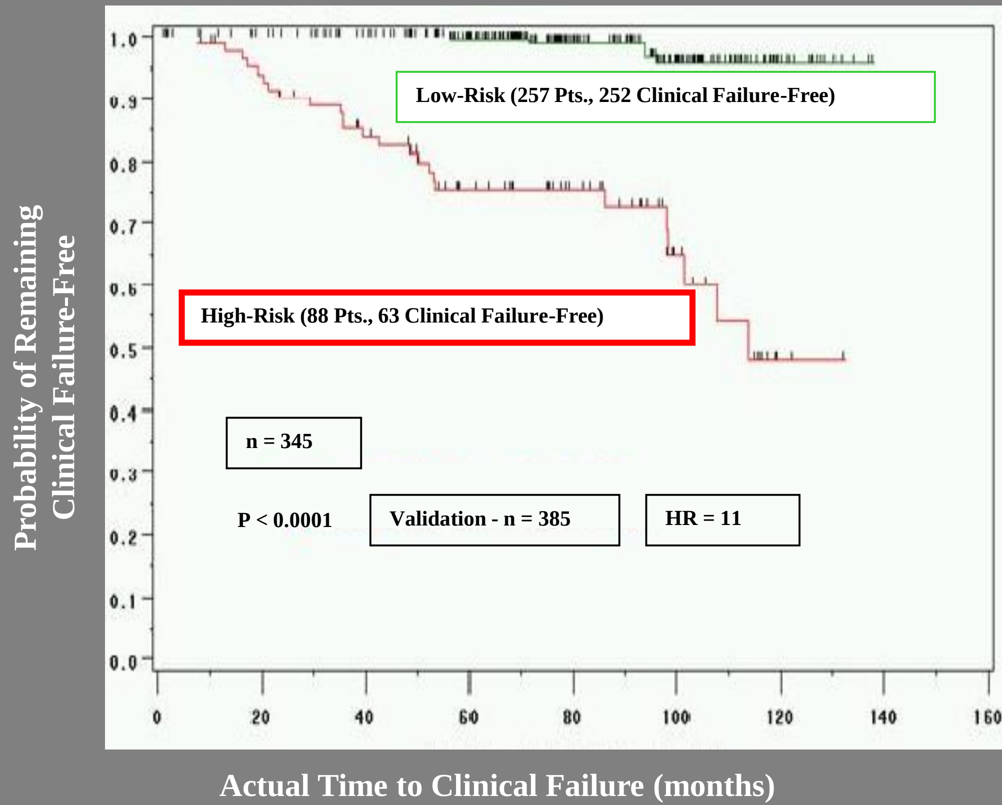
MULTIPLEXED IMAGE



EXTRACTED FEATURE

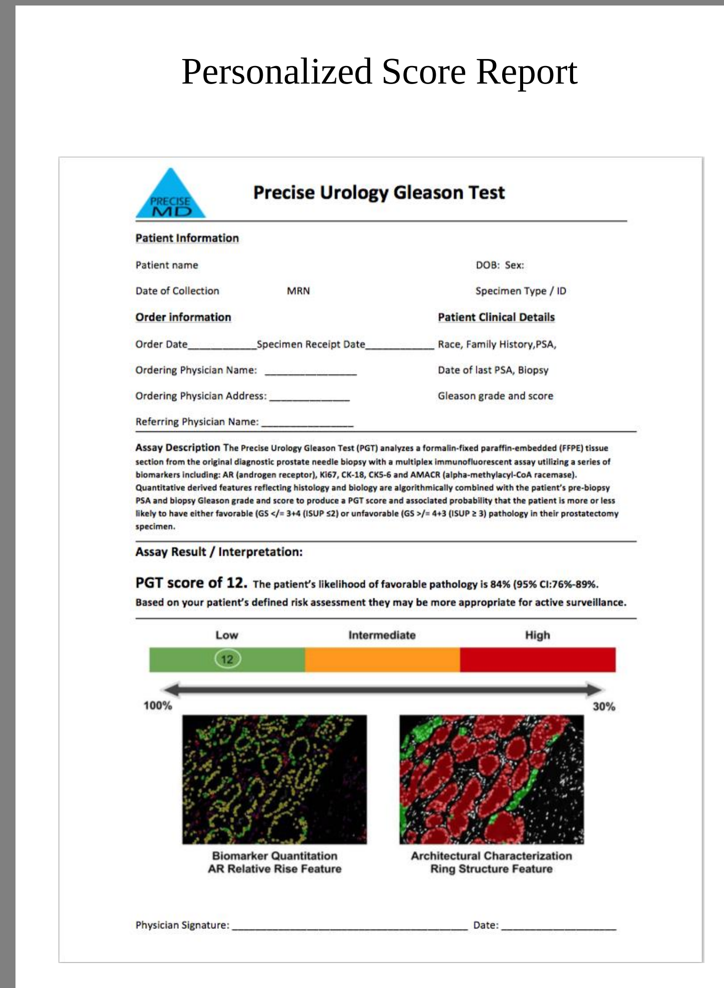
NUMBER OF LABELED VESSELS (CD34)
TOTAL VESSEL AREA, PERIMETER, LENGTH, WIDTH
MICROVESSEL AREA (MVD)

INTEGRATION OF CLINICAL AND MOLECULAR VARIABLES RENDERS PRECISE DIAGNOSIS AND PROGNOSIS



PREDICTIVE ACCURACY: 92% - SPECIFICITY: 91%; SENSITIVITY: 90%

(More than 10,000 prostate cancer cases analyzed to date)



Personalized Score Report

Precise Urology Gleason Test

Patient Information

Patient name DOB: Sex:

Date of Collection MRN Specimen Type / ID

Order information | **Patient Clinical Details**

Order Date____________Specimen Receipt Date____________ Race, Family History,PSA,

Ordering Physician Name: ________________ Date of last PSA, Biopsy

Ordering Physician Address: ______________ Gleason grade and score

Referring Physician Name: ________________

Assay Description The Precise Urology Gleason Test (PGT) analyzes a formalin-fixed paraffin-embedded (FFPE) tissue section from the original diagnostic prostate needle biopsy with a multiplex immunofluorescent assay utilizing a series of biomarkers including: AR (androgen receptor), Ki67, CK-18, CK5-6 and AMACR (alpha-methylacyl-CoA racemase). Quantitative derived features reflecting histology and biology are algorithmically combined with the patient's pre-biopsy PSA and biopsy Gleason grade and score to produce a PGT score and associated probability that the patient is more or less likely to have either favorable (GS </= 3+4 (ISUP ≤2) or unfavorable (GS >/= 4+3 (ISUP ≥ 3) pathology in their prostatectomy specimen.

Assay Result / Interpretation:

PGT score of 12. The patient's likelihood of favorable pathology is 84% (95% CI:76%-89%. Based on your patient's defined risk assessment they may be more appropriate for active surveillance.

Low Intermediate High

12

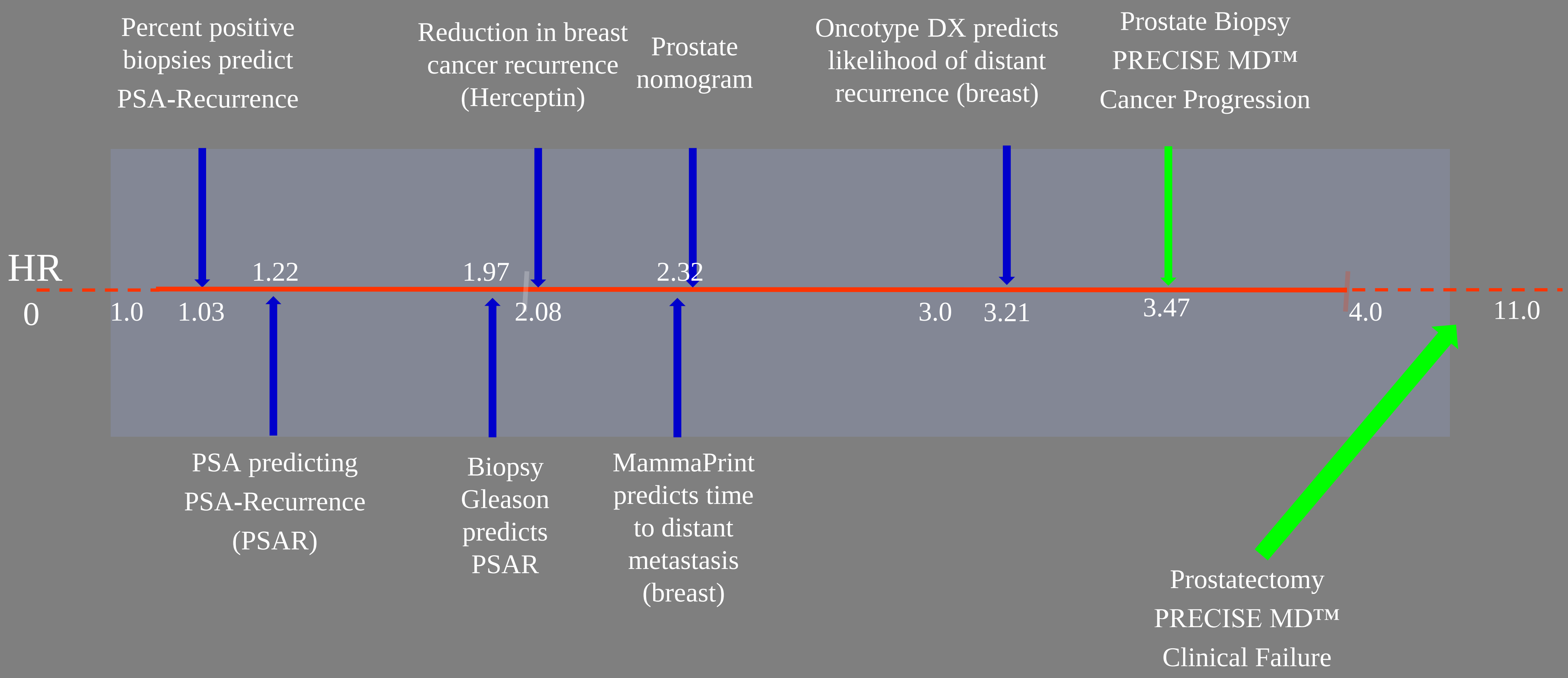
100% 30%

Biomarker Quantitation
AR Relative Rise Feature

Architectural Characterization
Ring Structure Feature

Physician Signature: ______________________________ Date: ________________

INTEGRATION OF CLINICAL AND MOLECULAR VARIABLES RENDERS PRECISE DIAGNOSIS AND PROGNOSIS



NCI-Hazard Ration (HR) (definition): A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. For example, a hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one means that survival was better in one of the groups.

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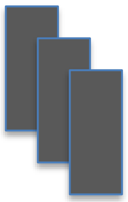
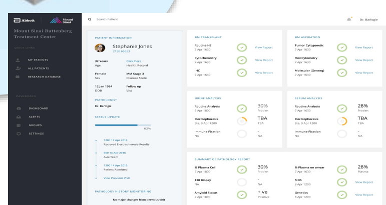


DATA INPUTS

- EHR/EMR
- Laboratory LIS Result
  - Clinical Pathology
  - Anatomic Pathology
  - Molecular Pathology
  - Next Generation Sequencing
  - External Labs (e.g., media)
- Clinical Annotations/Outcomes
- Image Storage (up to 90 days)
- Image Back-up (low cost)

Digital Sign Outs



Pathology/Consoles Dashboards

Proprietary Database/Tests

CLINICAL SERVICES

CONTINUED EDUCATION AND INNOVATION

- Clinical Applications of Digital Pathology
- New Developments in Clinical Laboratory Medicine
- Clinical Informatics: A Novel Area Board Certification

GRADUATE MEDICAL EDUCATION

- Pathology & Cell/Molecular Biology Courses
  - Medical Students
  - PhD Students
- Self Assessment Modules

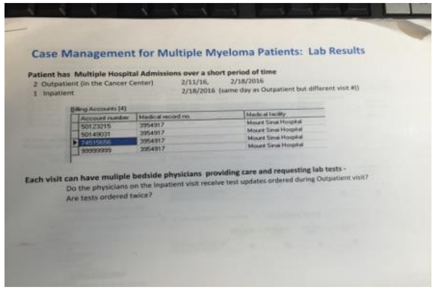
POST-GRADUATE EDUCATION

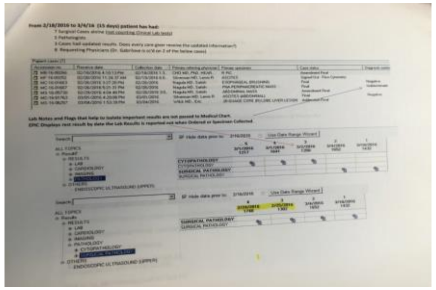
- Residency/Fellowship Training Modules
- Post-Doctoral Training Modules

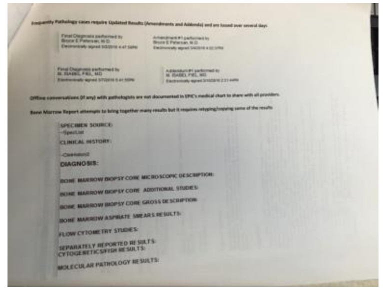
EDUCATIONAL DIMENSIONS

THE NEED FOR COMPREHENSIVE PLATFORMS
TEST REPORTING (MULTIPLE MYELOMA AS EXAMPLE)

<u>FRACTIONATED and MANUAL DATA FLOW</u>





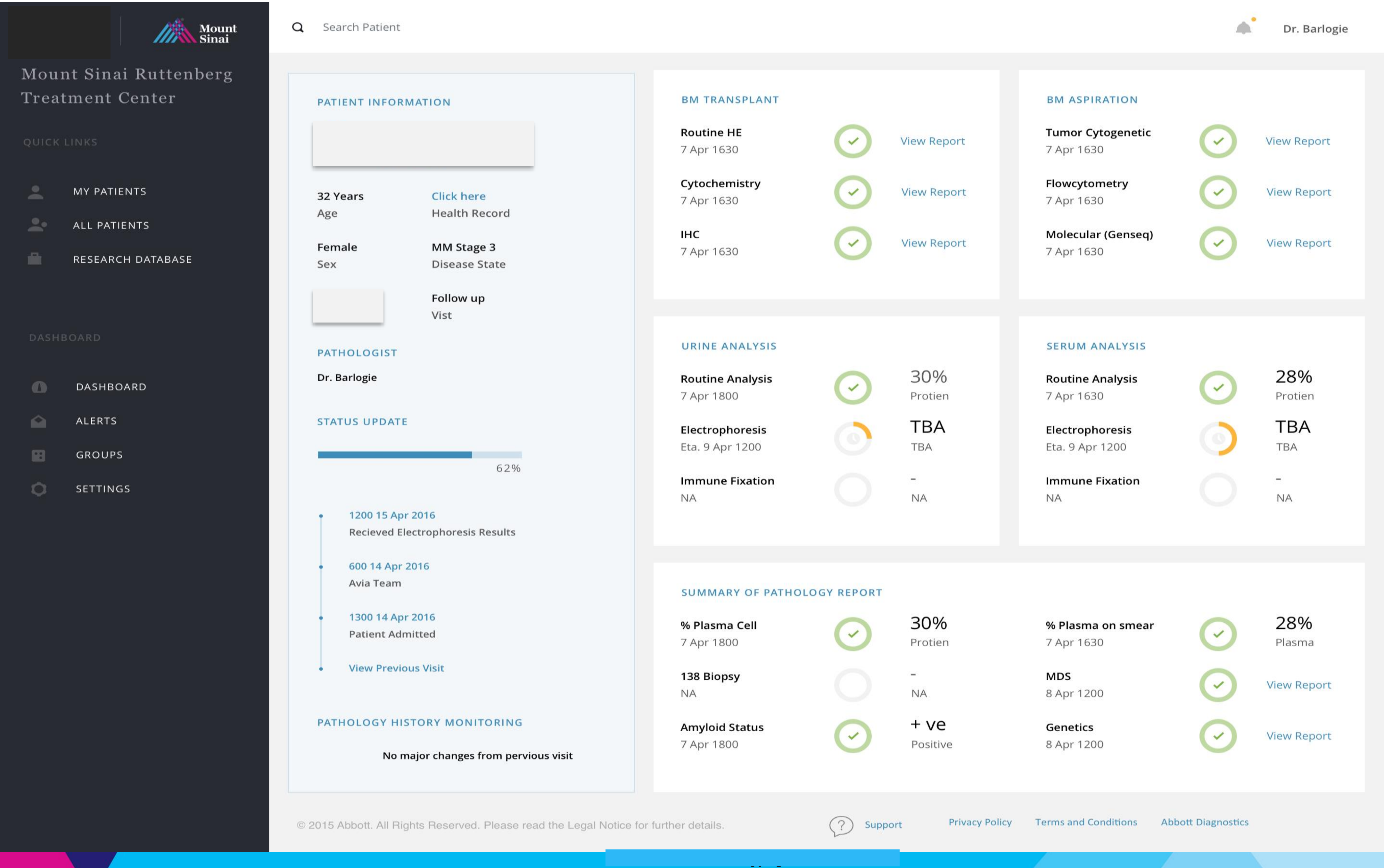


The MM clinic manually aggregates **<u>+20 Clinical Results</u>** per case for the oncologist to review in 15-20 minute

<u>CHALLENGES:</u>

- Data residing in different systems and formats.
- Long TAT (1 to 3 wks).
- Significant manual process (risks of diagnostic errors).
- Every Hospital develops internal procedures that are not standarized and are not harmonized.

MULTIPLE MYELOMA PATHOLOGY DASHBOARD



THE NEED FOR COMPREHENSIVE PLATFORMS

PATHOLOGY DASHBOARDS

1. Consolidation of all Pathology Results.
2. Real-time Updates on Pathology Results.
3. Streamlined Access to stored Pathology Results.

DIRECT BENEFITS:

Reduced TAT and reporting times.
Improve Documentation/Reporting.
Translate Data into Knowledge.

INDIRECT BENEFITS:

Improves Patient Management/Outcomes.
Improves Physician Satisfaction.
Increased Accountable Care.

To assist Personalized Treatments and Improved Outcomes

INTEGRATION OF DIAGNOSTIC SERVICES:
MAXIMIZING EFFECTIVENESS, IMPROVING OUTCOMES, AND MITIGATING RISK