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## MODERN PATHOLOGY

### Updating pathological predictors of metastatic testicular carcinoma

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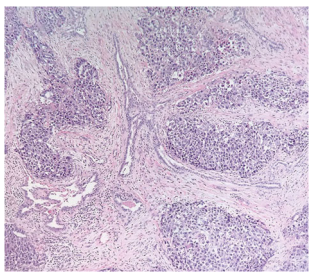

Scandura et al. set out to investigate pathological risk factors for metastatic disease in patients with testicular non-seminomatous germ cell tumors by examining these factors at presentation in 219 cases. Considering age, tumor size, hilar soft tissue, spermatic cord, and several other factors and comparing two classification methods, the group found that 69% were clinical stage I and 31% were clinical stage II/III. Tumor at spermatic cord margins was not significantly associated with higher clinical stage. The group acknowledges the possibility of intra-observer variation but note that the eighth edition of the American Joint Committee on Cancer's classifications reflects considerable effort toward standardization. A tumor size of 6 cm and an embryonal carcinoma percentage of 70% were significant features that could be replicated to match with staging, and, along with lymphovascular invasion and stromal rete testis invasion, are predictive markers of metastatic disease.

### Validation of a novel marker for breast cancer

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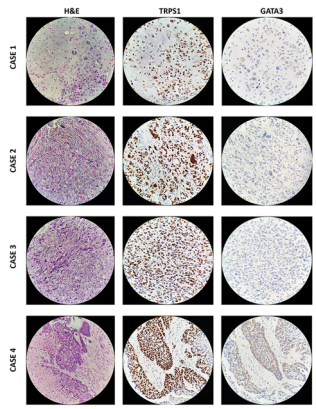
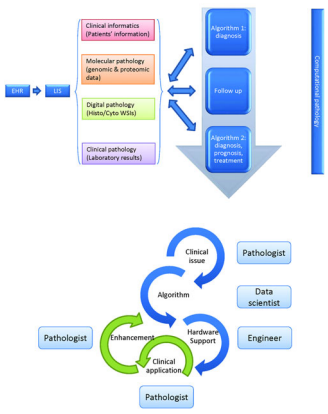



Breast cancer does not have a single specific and sensitive marker, although it can be characterized based on expression of combinations of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Using data mining from The Cancer Genome Atlas, Ai et al. identified a novel gene—trichorhinophalangeal syndrome type 1 (TRPS1)—with expression specific to breast cancer in a 31-gene array and across all four subtypes of breast carcinoma. TRPS1 expression matched the established diagnostic marker for breast cancer, GATA3, in ER+ and HER2+ breast carcinomas, and was significantly better than GATA3 in triple-negative breast cancer (86% compared with 20%). Across a panel of carcinomas from multiple organs, GATA3 was highly expressed in urothelial carcinoma and TRPS1 showed little to no expression in the other carcinoma types tested. The authors propose TRPS1 as a highly sensitive and specific marker for breast carcinoma and note that its use could improve diagnostics, especially in triple-negative breast cancer.

## LABORATORY INVESTIGATION

### Review of breakthroughs in computational pathobiology




Biology has evolved considerably in the past decade as high-throughput technologies have been developed and applied to various disciplines in the life sciences, including pathology. These technologies have generated an unprecedented amount and new types of biological data. Making sense of these (big) data sets is an emerging technological and conceptual challenge. Computational

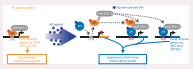
biology relies largely on computational and statistical algorithms to better understand biological processes, removing the human element and adding consistency even where it might miss nuance. In our view, it is the right way to address the aforementioned challenge. Computational biology helps us process, cleanse, annotate, analyze, and make predictions from newly generated biological data. The role of computational biology has become increasingly important as high-throughput biomedical data have been generated and shared over the past several years.

The editors of *Laboratory Investigation* have broadened the scope of the journal and commissioned experts in the fields of investigative pathology and computational biology to contribute to two special issues: "Computational Pathobiology 2020," which was published in October 2020, and the current issue, "Computational Pathobiology 2021." In these special issues we include original research and review articles that develop, modify, improve, use, or summarize computational algorithms to solve biomedical questions. These issues describe a variety of technological advances, including single-cell RNA sequencing, proteomics, deep learning, artificial intelligence, computational pathology, metabolomics, and DNA variant analyses. They also address a broad range of disease or biomedical questions: infertility, patient-derived explants, molecular toxicology, cancer, image analysis of predictive biomarkers, and tissue-quality validation. These collections are just the beginning of *Laboratory Investigation*'s focus on computational pathobiology. We believe that computational biology will lead to a drastic shift in our understanding of biomedical processes.

## nature.com/pathology

### Removing ambiguity from the role of AR

Controversy surrounding the role of androgen receptor (AR) in estrogen receptor (ER)-α-positive breast cancer limits therapeutic options for these patients. Hickey et al. demonstrated that AR activation exerts potent antitumor activity across disease contexts, including the finding that AR agonists combined with standard-of-care agents enhance therapeutic responses. Activating AR affects genomic distribution of ER and co-activators (p300, SRC-3) and directly represses ER-regulated cell cycle genes and upregulates AR target genes and tumor suppressors. The combination of an AR agonist and palbociclib exerted the greatest growth inhibition in vitro. They found that an AR activity signature could positively predict disease survival in ER-positive breast cancers, indicating that AR agonism can provide optimal therapeutic opportunity in this family of cancers, removing the ambiguity that previously obscured this finding in the literature.



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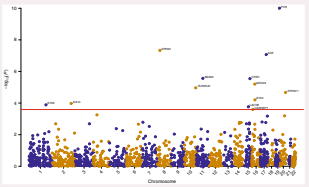
### Novel therapeutic targets for Alzheimer's disease

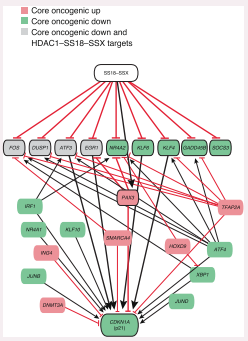
Wingo et al. investigated the ways in which established risk loci for Alzheimer's disease (AD) confer that risk, focusing in on the loci that affect brain protein abundance. Integrating the results of AD genome-wide association studies (GWAS) with human brain proteomes, they performed a proteome-wide association study (PWAS) of AD and identified 11 genes consistent with a causal role in AD via *cis*-regulated brain protein abundance. Validation was possible for 9 of 11 genes, and 8 of the 11 represent new AD-risk genes not previously identified during the GWAS study. The group validated their findings by regressing out the effect of *APOE e4*, an allele already known to be strongly associated with AD. Future mechanistic studies of these new genes are warranted to search for novel therapeutics for AD.



*Nature Genetics* 2021;53:143–146; https://doi.org/10.1038/s41588-020-00773-z

### Investigation into fusion-driven malignancy

SS18-SSX fusion is a known driver of synovial sarcoma, and the aggressive neoplasm is characterized by T-cell infiltration. Using single-cell RNA sequencing (scRNA-seq), spatial profiling, and genetic and pharmacological perturbations, Jerby-Arnon et al. sought to elucidate the interplay of the cancer and the immune system in SyS. An immune-derived niche in situ was identified and found to be predictive of poor clinical outcomes. The group investigated this malignant cell state and found the controlling fusion mutation (SS18-SSX fusion), a repression mechanism (cytokines secreted by T cells and macrophages), and a therapeutic target (combination of HDAC and CDK4/CDK6 inhibitors). The authors suggest that the design of this study can be applied to the investigation of other fusion-driven malignancies as well as provide a better understanding of the role of immune evasion and oncogenic processes.




*Nature Medicine*, published online 25 January 2021; https://doi.org/10.1038/s41591-020-01212-6

Authors: Emma Judson and Lanjing Zhang.