2nd Annual Southern California Genitourinary Cancer Research Forum

Key Updates in Testicular Cancer

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Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Discuss changing demographic of testicular cancer, including in underrepresented minorities.*
- *Discuss overcoming barriers to care.*

Testicular cancer

- Most life years lost for nonpediatric cancers
- Most common cancer in men between 18-45
- 10,000 new cases/year
- 460 deaths/year

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Outline

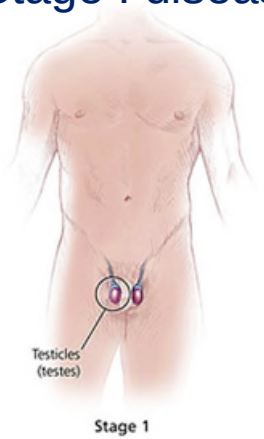
Clinical Updates

Introduction to microRNAs for GCT diagnostics

Clinical trials across the GCT spectrum

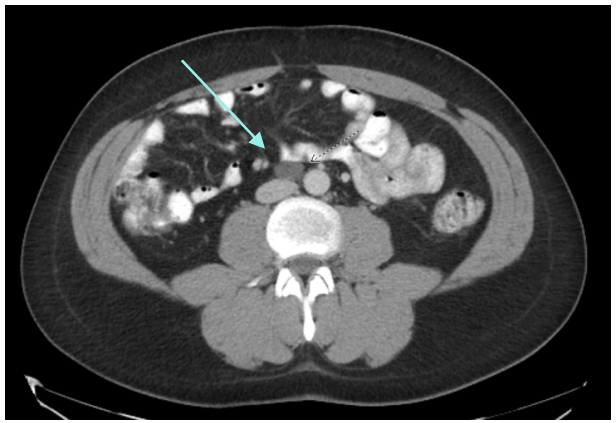
Pre-orchiectomy

Stage I disease

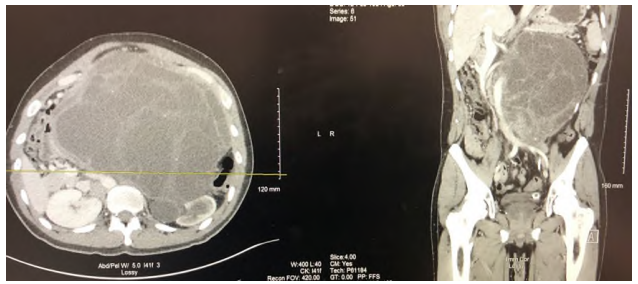


Stage 1

Stage II disease



Post-chemotherapy



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Primary RPLND for seminoma metastatic to RP

Phase 2 Single-arm Trial of Primary Retroperitoneal Lymph Node Dissection in Patients with Seminomatous Testicular Germ Cell Tumors with Clinical Stage IIA/B (PRIMETEST)

Andreas Hiester[a,†], Yue Che[a,†], Achim Lusch[a,b], Oliver Kuþ[c,d], Günter Niegisch[a], Anja Lorch[a,e], Christian Arsov[a,f], Peter Albers[a,]*

Surgery in Early Metastatic Seminoma: A Phase II Trial of Retroperitoneal Lymph Node Dissection for Testicular Seminoma With Limited Retroperitoneal Lymphadenopathy

Siamak Daneshmand, MD[1]; Clint Cary, MD[2]; Timothy Masterson, MD[2]; Lawrence Einhorn, MD[3]; Nabil Adra, MD[3]; Stephen A. Boorjian, MD[4]; Christian Kollmannsberger, MD[5]; Anne Schuckman, MD[1]; Alan So, MD[6]; Peter Black, MD[6]; Aditya Bagrodia, MD[7]; Eila Skinner, MD[8]; Mehrdad Alemozaffar, MD[9]; Timothy Brand, MD[10]; Scott Eggener, MD[11]; Phillip Pierorazio, MD[12]; Kelly Stratton, MD[13]; Lucia Nappi, MD[5]; Craig Nichols, MD[14]; Chunqiao Luo, MS[15]; Ming Li, PhD[15]; and Brian Hu, MD[16]

Retroperitoneal Lymph Node Dissection in Clinical Stage IIA/B Metastatic Seminoma: Results of the COlogne Trial of Retroperitoneal Lymphadenectomy In Metastatic Seminoma (COTRIMS)

Axel Heidenreich[a,b,], Pia Paffenholz[a], Florian Hartmann[a], Felix Seelemeyer[a], David Pfister[a]*

American Urological Association

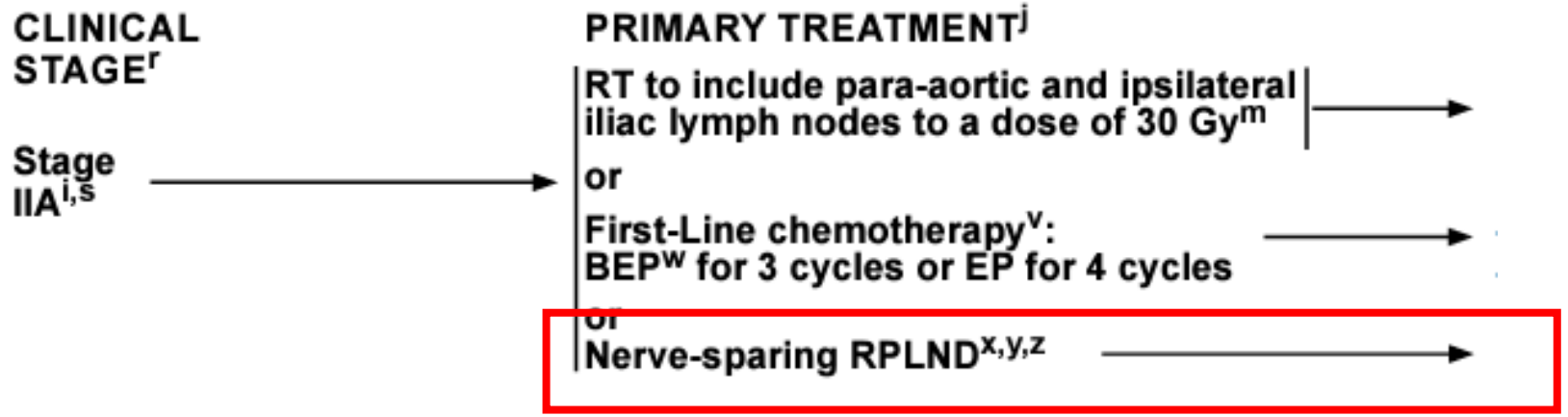
27a. For patients with stage IIA or IIB seminoma with a lymph node ≤3cm, clinicians should recommend RT or multi-agent cisplatin-based chemotherapy based on shared decision-making. *(Moderate Recommendation; Evidence Level: Grade B)*

27b. For patients with stage IIA or IIB seminoma with a lymph node ≤3cm who wish to avoid the long-term toxicities associated with chemotherapy or radiation therapy, RPLND may be offered as an appropriate and effective treatment option. *(Moderate Recommendation; Evidence Level: Grade B)*

27c. For patients with IIB seminoma with a lymph node >3 cm, chemotherapy is recommended. *(Moderate Recommendation; Evidence Level: Grade B)*

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Testicular Cancer - Pure Seminoma



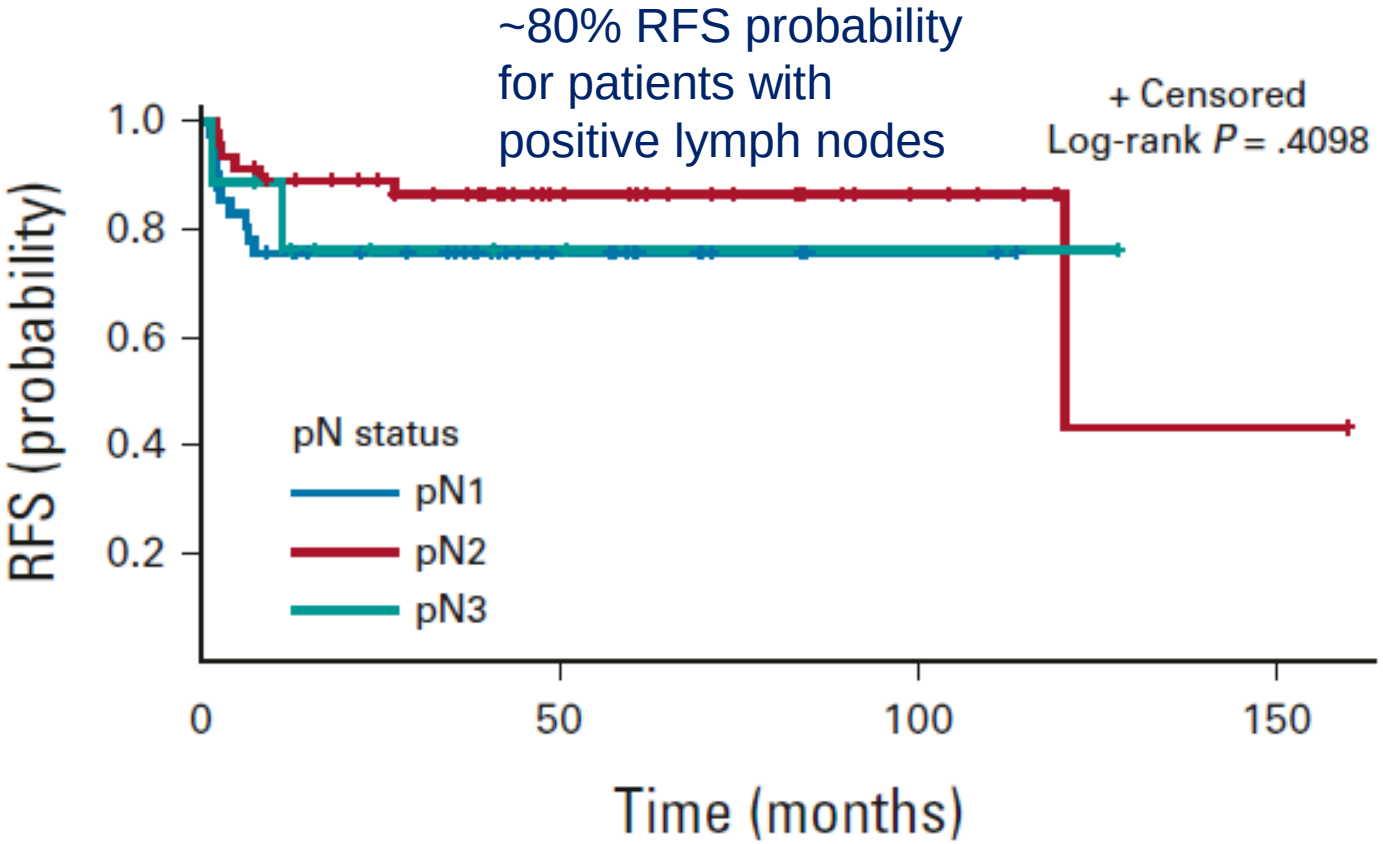
*pRPLND not included in EAU guidelines at this time

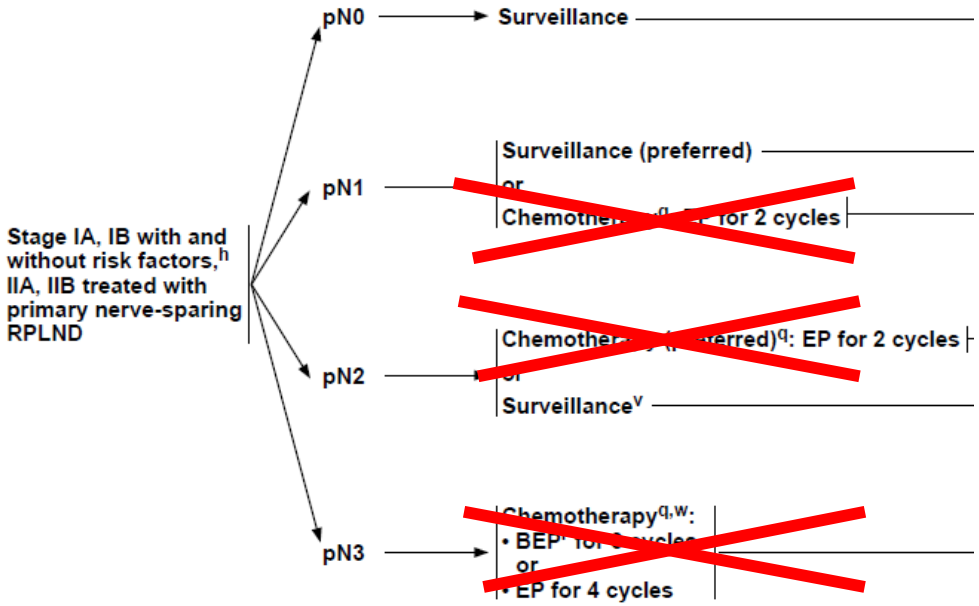
Stage II Nonseminoma

Primary Retroperitoneal Lymph Node Dissection for Patients With Pathologic Stage II Nonseminomatous Germ Cell Tumor—N1, N2, and N3 Disease: Is Adjuvant Chemotherapy Necessary?

Isamu Tachibana, MD[1]; Sean Q. Kern, MD[1]; Antoin Douglawi, MD[1]; Yan Tong, MS[2]; Mohammad Mahmoud, MD[1]; Timothy A. Masterson, MD[1]; Nabil Adra, MD[3]; Richard S. Foster, MD[1]; Lawrence H. Einhorn, MD[3]; and Clint Cary, MD, MPH[1]

~80% RFS probability for patients with positive lymph nodes






Micro RNAs
(miRNA)

Current GCT serum markers are underwhelming

- **Conventional tumor markers lack specificity:**
  - **AFP: HCC, liver disease, familial**
  - **hCG: bladder, renal, gastric, lung, marijuana, cross-reactivity with LH**
  - **LDH: any clinical setting with rapid cell turnover**

Table 1 | **Serum AFP and hCG levels in GCTs**[22]

GCT histological subtype	AFP	hCG
Yolk sac tumour	++	-
Seminoma	-	±
Embryonal carcinoma	±	±
Choriocarcinoma	-	++
Teratoma	±	-

AFP, α-fetoprotein; GCT, germ cell tumour; hCG, human chorionic gonadotrophin. ++, strongly positive levels; ±, levels may be negative or moderately positive; –, negative levels.

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Histology: miR-371a-3p vs conventional markers

Parameter Studied	AFP	hCG	miR-371a-3p
Seminoma	<3%	18-31%	87%
Non-seminoma	60-70%	53%	94%
Embryonal carcinoma	40%	25%	>90%
Yolk sac tumor	>95%	<5%	>90%
Choriocarcinoma	<5%	>95%	>90%
Teratoma	-	-	<5%
Mixed GCT	Variable	Variable	~90%
Extragonadal	Variable	Variable	>90%
Non-GCT	12%	14%	6%
Half-life after orchiectomy	5-7 days	1.5-3 days	12 hours
Decrease during/after chemotherapy	+	+	+

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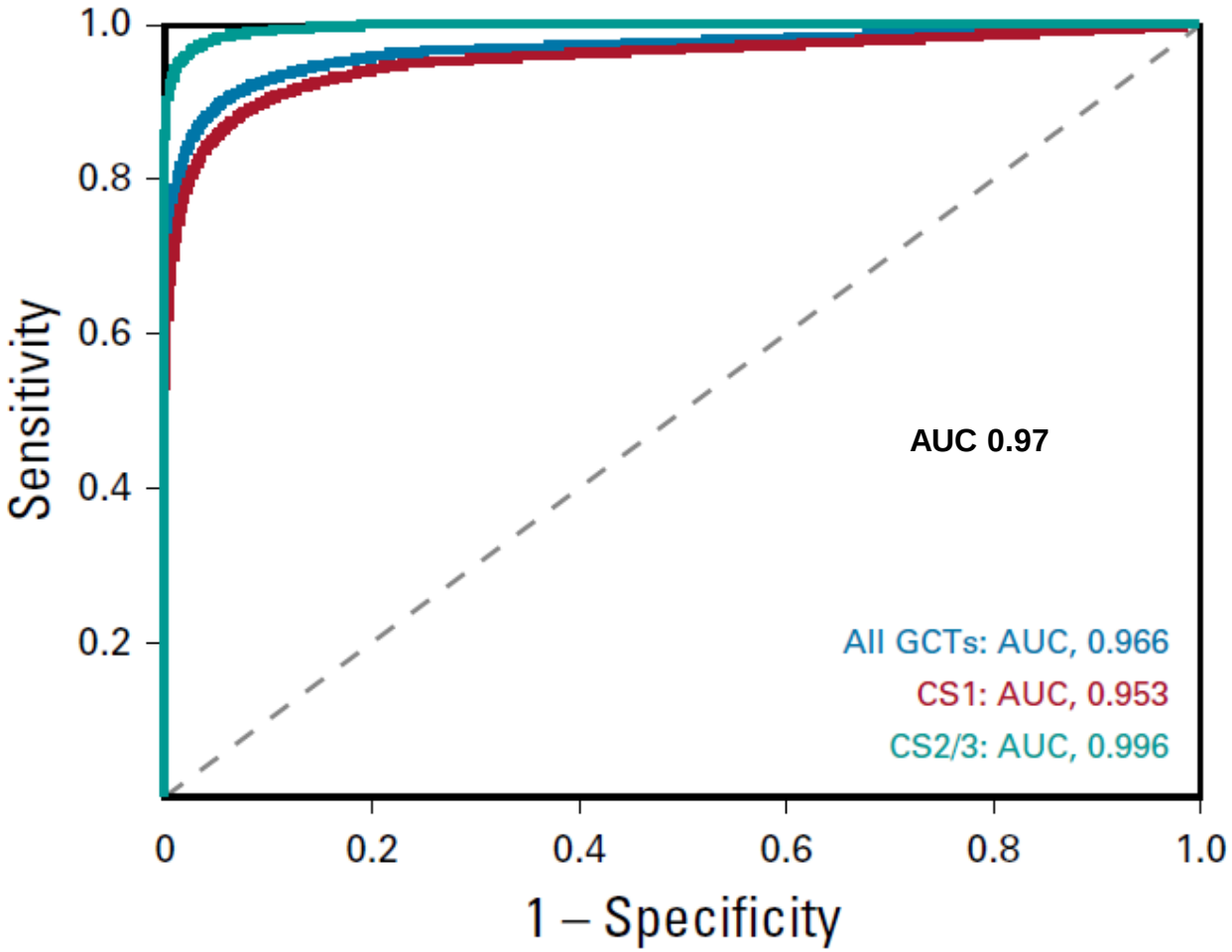
Pre-orchiectomy: Serum miR-371a-3p at diagnosis in malignant GCTs



n=874; 616 malignant GCT *vs.* 258 controls

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Dieckmann *et al*, *Journal Clinical Oncology*, 2019

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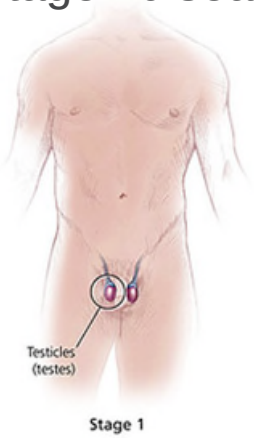
Circulating miR-371a-3p across the disease spectrum

Pre-orchiectomy

Dieckmann *et al*, *Journal Clinical Oncology,* 2019

Badia, Lafin, Bagrodia et al, Journal of Urology, 2021

Stage I disease

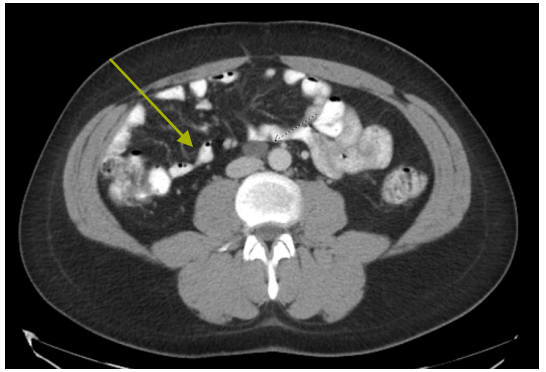


Stage 1

Lobo, Hamilton et al European Urology Oncology 2022

Fankauser et al, Britic Jounral of Cancer, 2022

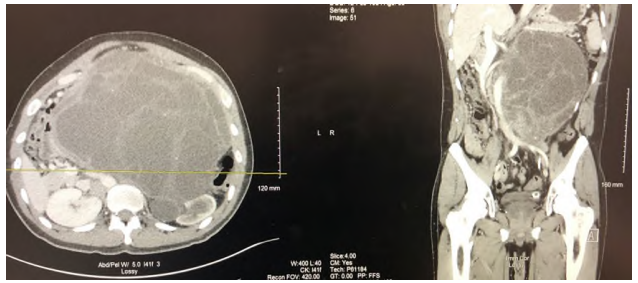
Stage II disease



Lafin et al, Scientific Reports 2023

Heidenreich et al, European Urology Oncology, 2022

Post-chemotherapy



Viable GCT

Hamilton et al Journal of urology, 2019

Teratoma

Lafin et al, European Urology Open Science, 2021

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Next Steps

- **Incorporate miRNAs into clinical trials**
  Provide miRNA testing in a CLIA certified laboratory

Clinical trials

AGCT 1531: A Phase III Study of Active Surveillance for Adult and Pediatric Patients with Germ Cell Tumors

- Inclusion Criteria:
  - Stage IA/B: Seminoma/NSGCT
    - TanyN0M0S0
  - Any age

International Sites for AGCT1531

S1823:A PROSPECTIVE OBSERVATIONAL COHORT STUDY TO ASSESS miRNA 371 FOR OUTCOME PREDICTION IN PATIENTS WITH NEWLY DIAGNOSED GERM CELL TUMORS

- Inclusion Criteria:
  - Stage I-IIA: Seminoma/NSGCT

S1823: Eligibility and primary endpoints

- **Primary Endpoints:**
- To establish PPV of miR371 in predicting active GCT
- To establish lead time (if any) of miRNA 371 expression vs conventional STMs/imaging to detect recurrence

AGCT 1531 and S1823

- **Study objectives:**
  - **Describe performance characteristics of miR-371a-3p for early stage GCT**
- **Complementary Trials:**
  - **Plan for assay cross validation in the future**
- **Can co-register patients to both**
- **Contacts:**
  - **AGCT: Furqan Shaikh furqan.shaikh@sickkids.ca**
  - **SWOG: Craig Nichols craig@tccommons.org**

miR-371a-3p based clinical trial: EA8221

ORCHIECTOMY

serum miR371

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OBSERVATION

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RPLND

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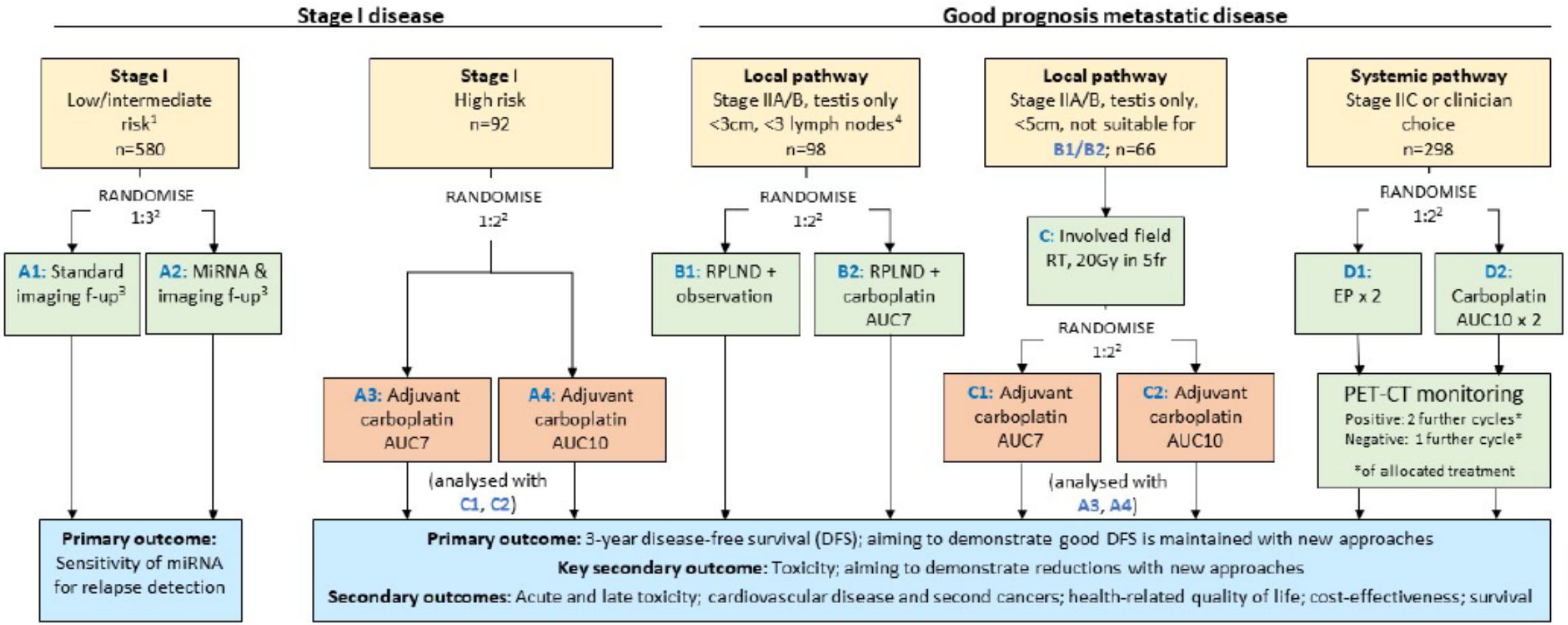
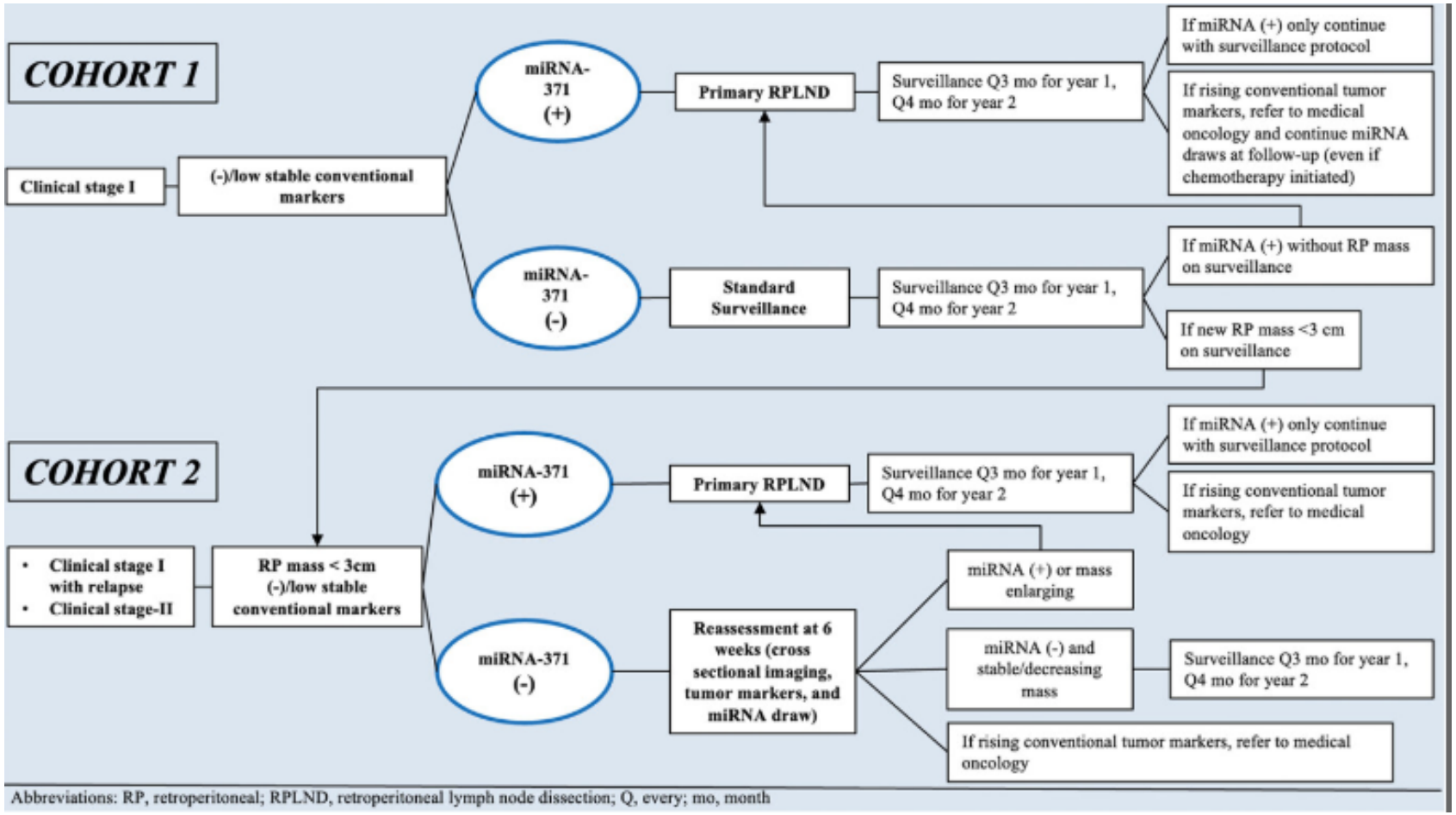
Surveillance arm: miR - patients

- **Patients negative miR371 levels will be observed per AUA guidelines**
- **Patients with positive miR371 will receive high quality RPLND**

Optimal therapy in Seminoma Trial (OTIS)



MAGESTIC CLINICAL TRIAL



PRESTIGE HRQOL in stage II GCT

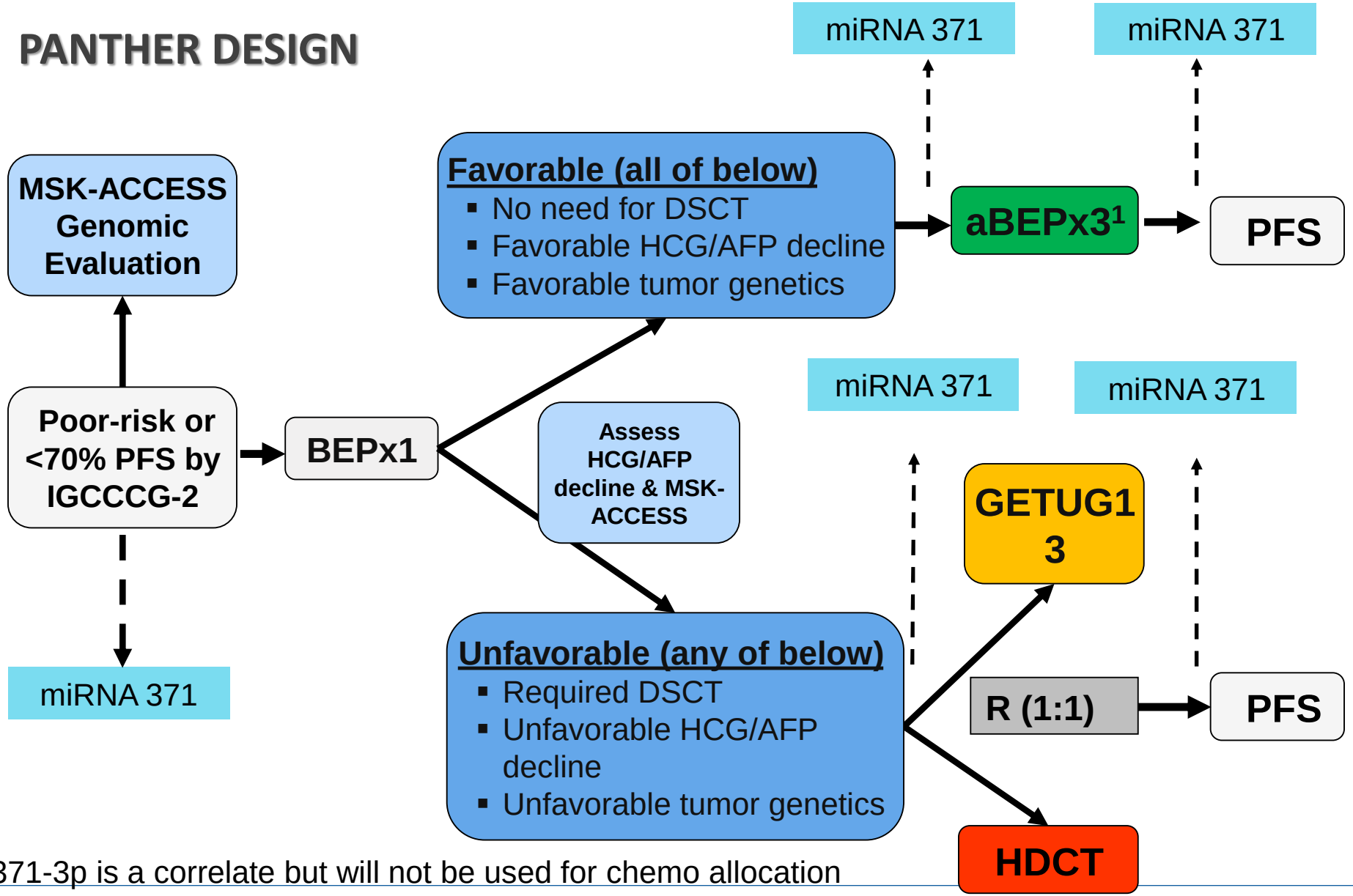
- EORTC QLQ-C30
- EORTC QLQ-TC26
- Brief Male Sexual Function Inventory and specific questions focusing on retrograde ejaculation and fertility

Alysouf / Daneshmand (MAGESTIC trial, JU 2024); Conduit et al (PRESTIGE)

PANTHER

Phase III Randomized trial of Adaptive Dose Intense Treatment for High risk Germ Cell Tumors

PANTHER DESIGN



*miRNA 371-3p is a correlate but will not be used for chemo allocation

Abbreviations: STM, serum tumor markers; DSCT, disease-stabilizing chemotherapy; aBEP, accelerated BEP; GETUG13 = T-BEPx1 + BIPx2

Relapse/refractory GCT

- Claudin 6 exciting new target with multiple inhibitory strategies including CAR-T, ADCs, and bispecific antibodies
- Hypomethylating agents, GPC3 targeting, and dual VEGFR and c-Met inibitoirs

Alysouf / Daneshmand (MAGESTIC trial, JU 2024); Conduit et al (PRESTIGE)

Moving microRNA testing into the clinic

Clinical Implementation

- Congress passed Clinical Laboratory Improvement Amendments (CLIA) in 1988
  - establishing **authority to promulgate standards to ensure**
    - **Accuracy**
    - **reliability**
    - **timeliness of test results regardless of where or by whom the test was performed.**

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Moving towards CLIA certification

- Work flows
- Equipment
- Reagents
- Scaling
- Reproducibility

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Clinical Implementation

UTSW Research

UTSW CLIA

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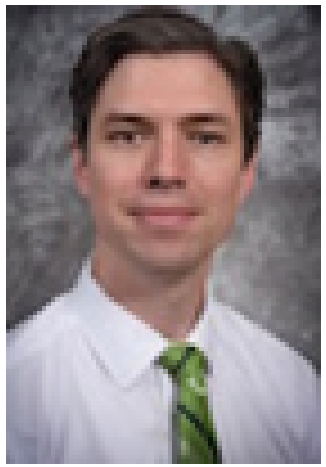
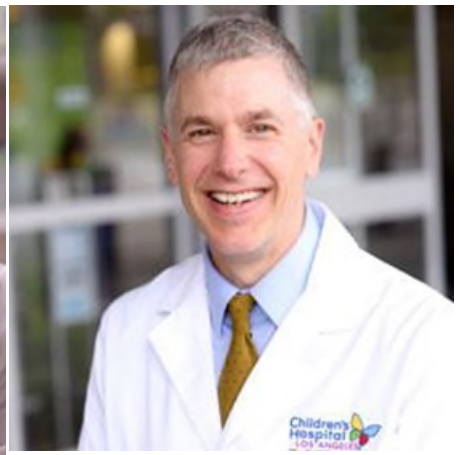
CLIA










miRNA testing CLIA available 4-2-2025 at UCSD!

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Current status

- Promising work on standardization, reproducibility, thresholding
- Large scale clinical trials (AGCT1531 and SWOG 1823)
- Clinical Implementation ongoing
- Technical refinements
  - ddPCR?
  - cfDNA?
  - Methylation profiling?

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Conclusions

- **Major strides in clinical care geared toward improved survivorship**
- **Critical clinical trials in place/in development across disease spectrum**
- **microRNAs poised to impact the way patients are diagnosed, treated, and surveyed**

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Thank you!

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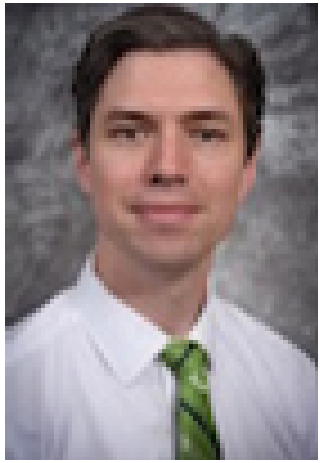
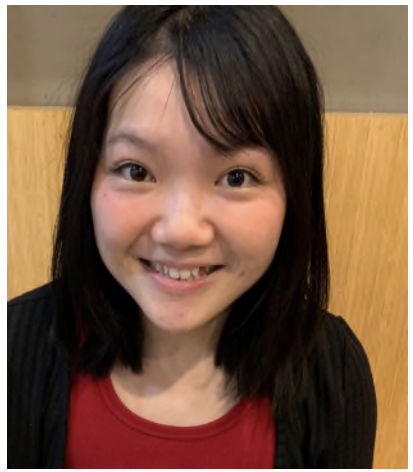
- John Lafin, PhD
- Anna Savelyeva, PhD
- Bendu Konneh, BS
- James Amatruda, MD, PhD
- Matthew Murray, MD, PhD

- Jeffrey Gaggan, MD, PhD
- Sarah Murray, MD PhD
- Lindsay Frazier, MD
- Cinzia Scarpini, PhD
- Yun Cheng, MS











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