Successes and Pitfalls for Research in the Clinical Trials Cooperative Groups

Felix Feng, MD

Professor of Radiation Oncology, Urology and Medicine
George and Judy Marcus Distinguished Professor
Director, Benioff Initiative for Prostate Cancer
Associate Director for Translational Research
Helen Diller Comprehensive Cancer Center
University of California at San Francisco

Chair, GU Committee, NRG Oncology

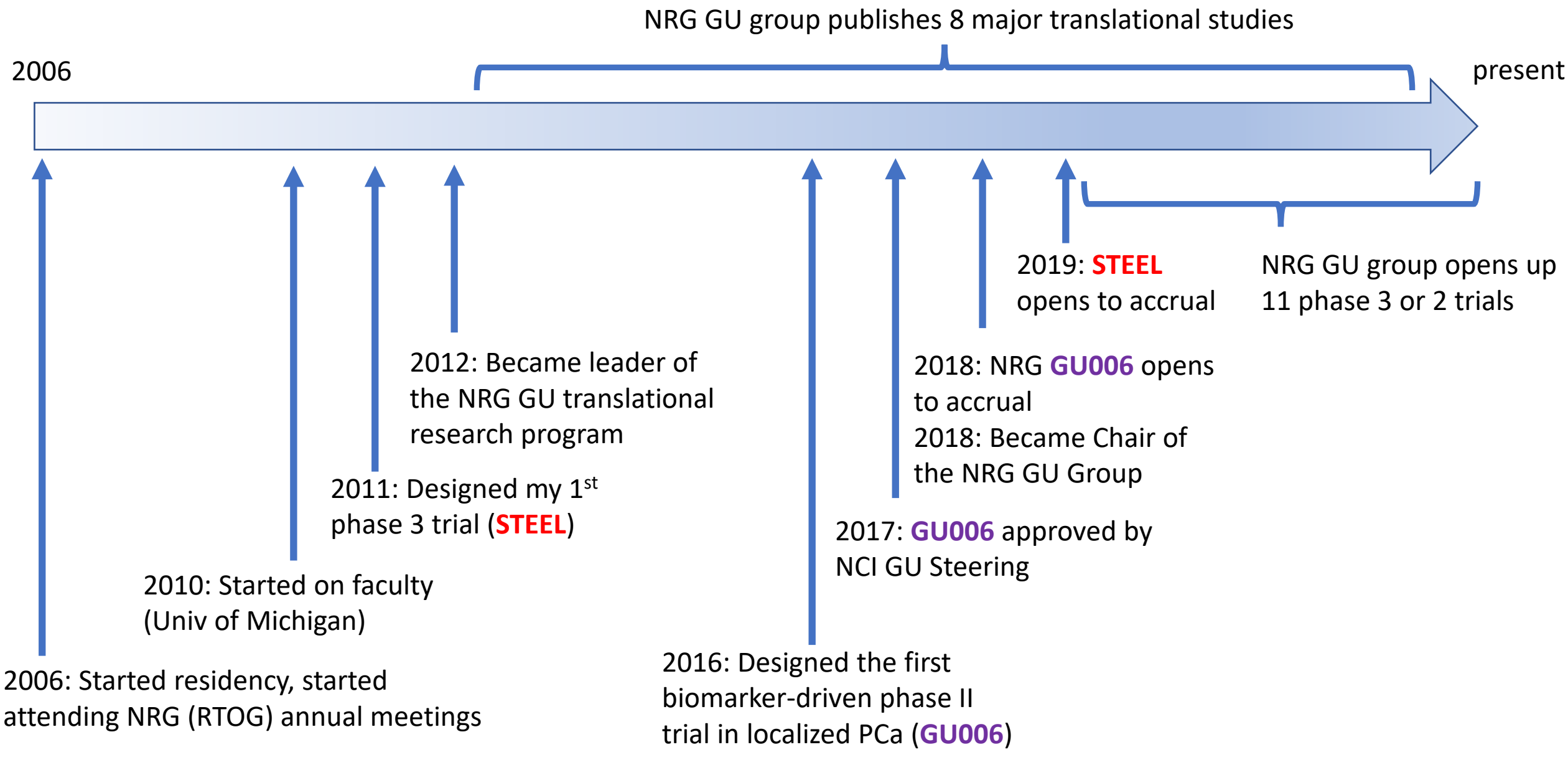
Disclosures

- I have consulted for Astellas, Bayer, Blue Earth Diagnostics, BMS, Exact Sciences, Foundation Medicine, Janssen, Myovant, Novartis, Roivant, and Varian.
- I serve on the scientific advisory board for BMS, Artera, SerImmune Diagnostics and BlueStar Genomics.

A Brief Introduction to Myself

- Physician scientist, University of California at San Francisco
- Lab focus: Using clinical and functional genomic approaches to identify targetable molecular drivers of prostate cancer
- Clinical research focus:
  - Chair, GU Cancer Committee, NRG Oncology, overseeing 6 Phase III trials and 5 Phase II trials in prostate, bladder, and kidney cancer
  - Development predictive biomarkers from phase III trials

A Brief Introduction to My Involvement in NRG Oncology



Why be involved in a cooperative group?

- **You want to do something big**
  - As a younger faculty member, it's really the only way to lead or help lead a phase III trial. (Pharma companies look for more established faculty for industry-sponsored phase III trials)
- **You can develop a cadre of collaborators nationally**
  - As opposed to ASCO and other large meetings, you can more easily develop a network of friends and mentors in your field, at cooperative group meetings
- **You want access to samples from phase III trials**
  - There are only a few avenues by which you can do translational research at a large scale. Working within a cooperative group is one of these avenues.
- **You're a glutton for punishment**
  - Be forewarned….the cooperative groups sometimes move at a glacial pace. Whatever you do in a cooperative group, it may help you get promoted to Professor in the future….but likely won't help with your promotion to Associate Professor.

The Pitfalls of Cooperative Group Research

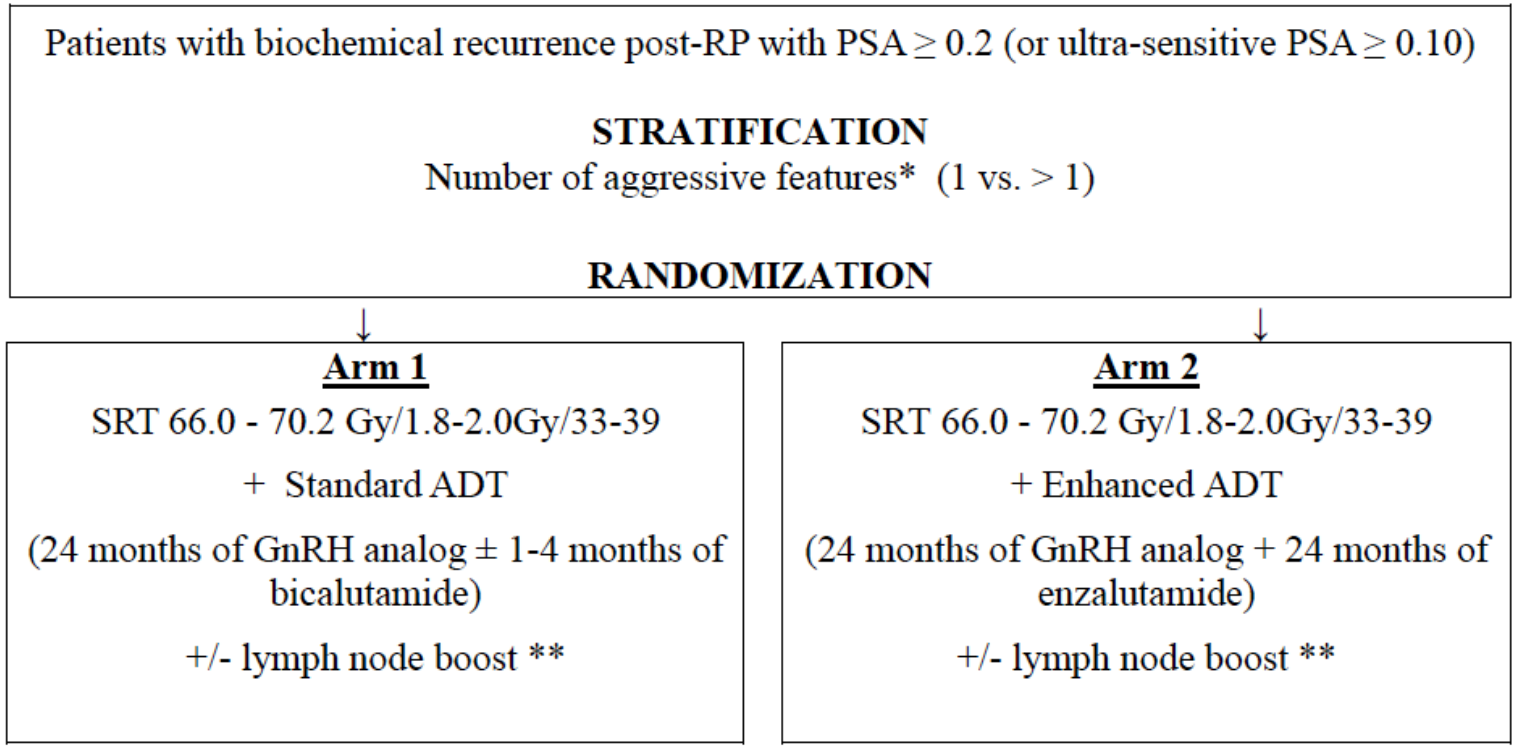
- **Things take time.**
  - You need patience and to focus on long-term goals.
- **Learn the system – and how to shepherd a trial thru to approval.**
  - Find a mentor who knows the cooperative group system!!!!!
- **Sometimes, it's not just about the science. Politics may play a role.**
  - Rely on your mentors to keep you out of too much trouble!
- **You need multiple approvals to go from concept to accruing trial.**
  - See point #1 (about patience). You will likely need buy-in from the leaders of your cooperative group, leaders from other cooperative groups and from the NCI, and the partnering pharma company.

*A Randomized Phase II Trial of **S**alvage Radiot**h**erapy with Standard vs **E**nhanced Androgen Deprivation Therapy (with **E**nza**l**utamide) in Patients with Post-Prostatectomy PSA Recurrences with Aggressive Disease Features*
RTOG 3506

Edwin Posadas, Hiram Gay, Ying Xiao, Todd Morgan, James Yu,
Stephanie Pugh, Felix Feng

An RTOG Foundation collaboration with Pfizer/Astellas

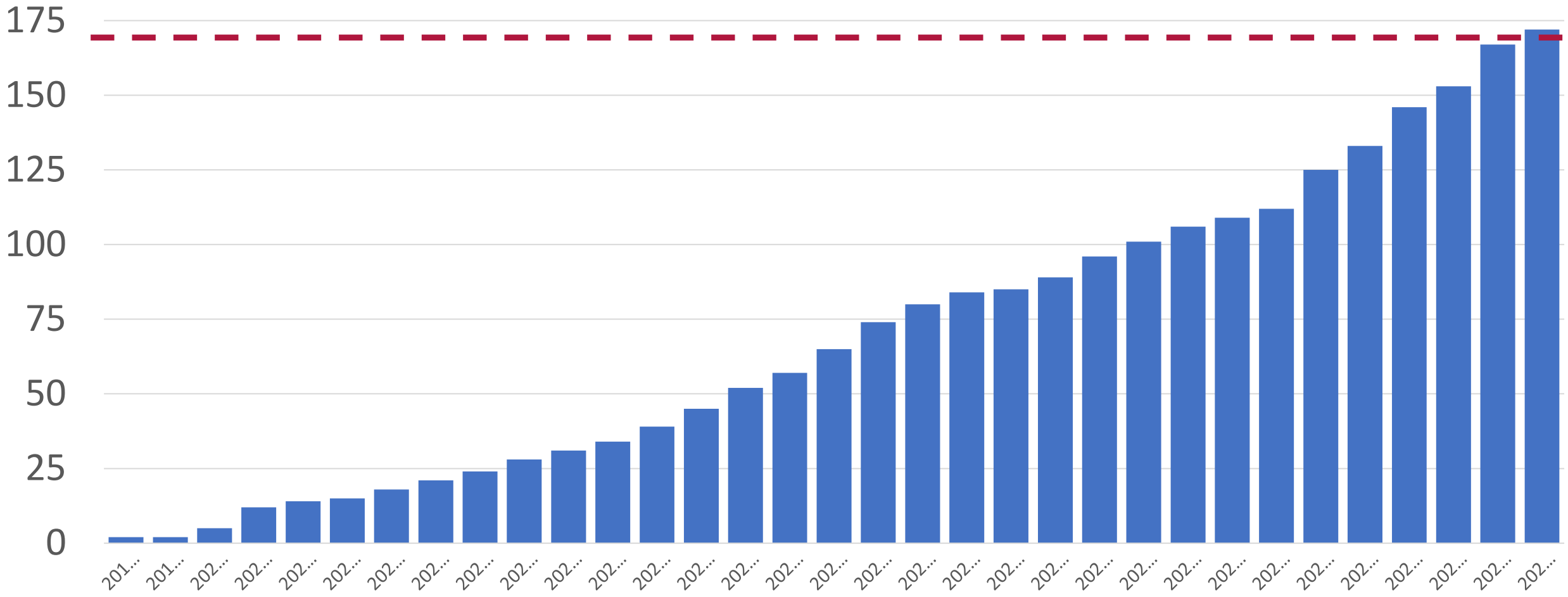
Schema



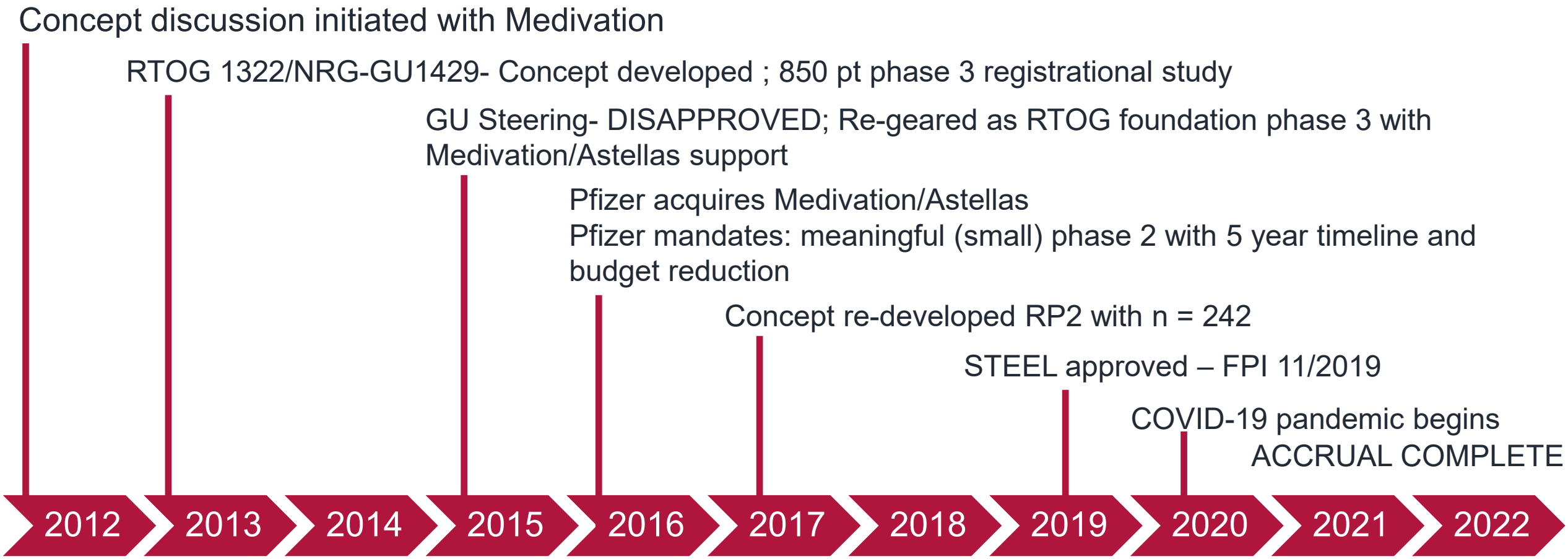
High risk features (1+ required):

- Gleason score of 8-10
- Seminal vesicle invasion (SVI)
- Locoregional node involvement at radical prostatectomy (pN1)
- Persistently elevated PSA post-RP (PEPP) defined as PSA > 0.1 ng/mL after radical prostatectomy
- PSA ≥0.7 ng/mL

RTOG 3506 (STEEL) Accrual update



Timeline


Concept discussion initiated with Medivation
RTOG 1322/NRG-GU1429- Concept developed ; 850 pt phase 3 registrational study
GU Steering- DISAPPROVED; Re-geared as RTOG foundation phase 3 with Medivation/Astellas support
Pfizer acquires Medivation/Astellas
Pfizer mandates: meaningful (small) phase 2 with 5 year timeline and budget reduction
Concept re-developed RP2 with n = 242
STEEL approved – FPI 11/2019
COVID-19 pandemic begins
ACCRUAL COMPLETE
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022

2010

PROSTATE CANCER FOUNDATION
The Republic of Tea

Felix Feng, MD

University of Michigan, Ann Arbor

2010 Republic of Tea PCF Young Investigator

- *BS, Biological Sciences, Stanford University*
- *MD, Medicine, Washington University School of Medicine*

Following medical school, Dr. Feng began a residency in radiology but switched to radiation oncology—motivated by his desire to work more directly with patients and their families, while continuing his academic pursuits.

"While radiation therapy is one of the primary modalities in the treatment of prostate cancer, there is, in my opinion, a dearth of biologically-based approaches for improving prostate radiotherapy. I was drawn to prostate cancer research by my desire to improve the field of radiotherapy and ultimately enhance patients' lives."

Felix Feng, MD

PROSTATE CANCER FOUNDATION

Edwin Posadas, MD

Cedars-Sinai Medical Center

2010 Stewart Rahr PCF Young Investigator

- *BSE, Biomedical and Chemical Engineering, Johns Hopkins University School of Medicine*
- *MD, Medicine, Johns Hopkins University School of Medicine*

Dr. Posadas is a Knight of Magisterial Grace in the Order of Malta—an organization dedicated to the service of the sick in the name of the Catholic Church.

"It has been inspiring to know that every morning the work that I pursue in the laboratory and the clinic may benefit patients in a deep and meaningful way."

Edwin Posadas, MD

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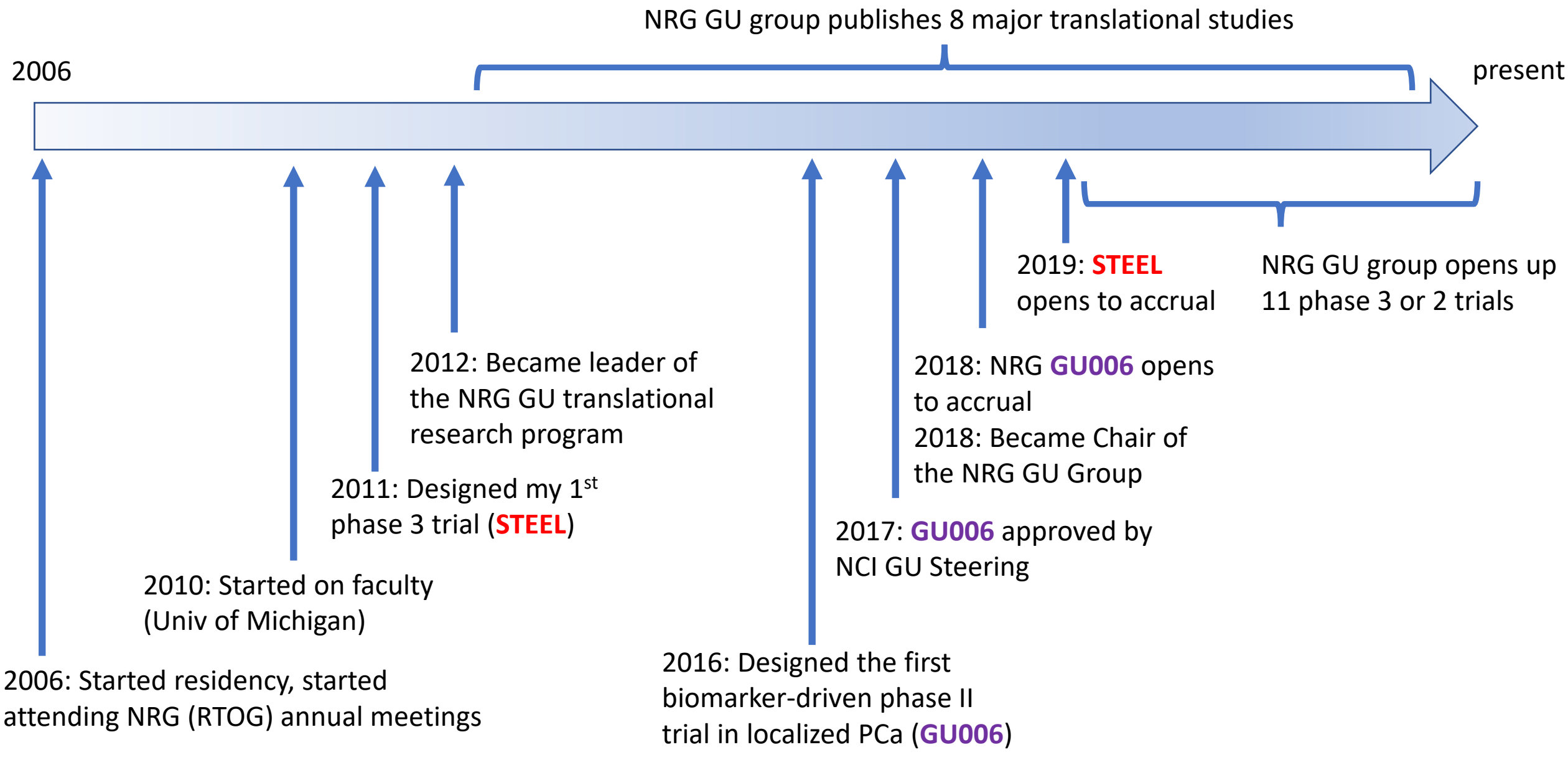
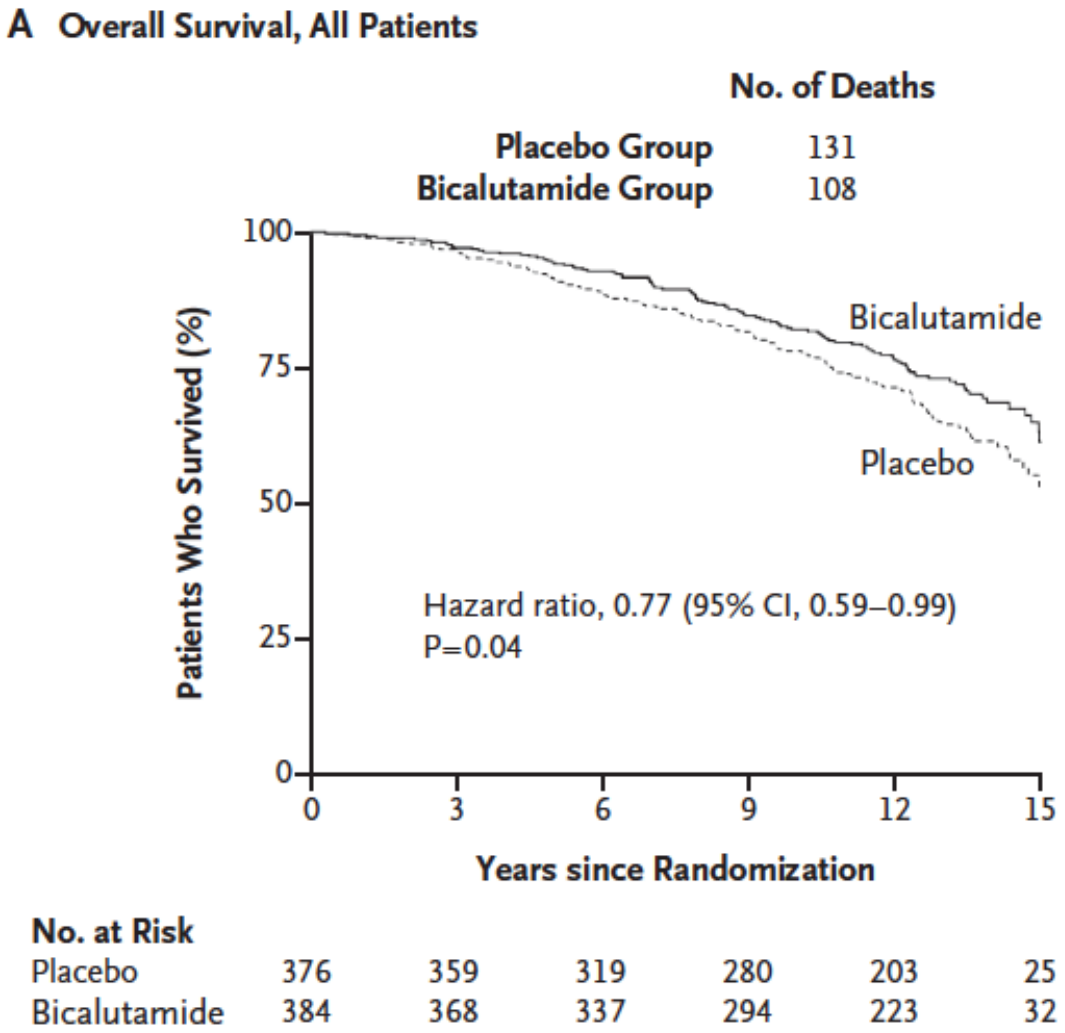


RTOG 9601: A Phase III trial of Salvage RT +/- anti-androgen therapy in post-RP pts with PSA recurrence



RTOG 9601: A Phase III trial of Salvage RT +/- anti-androgen therapy in post-RP pts with PSA recurrence

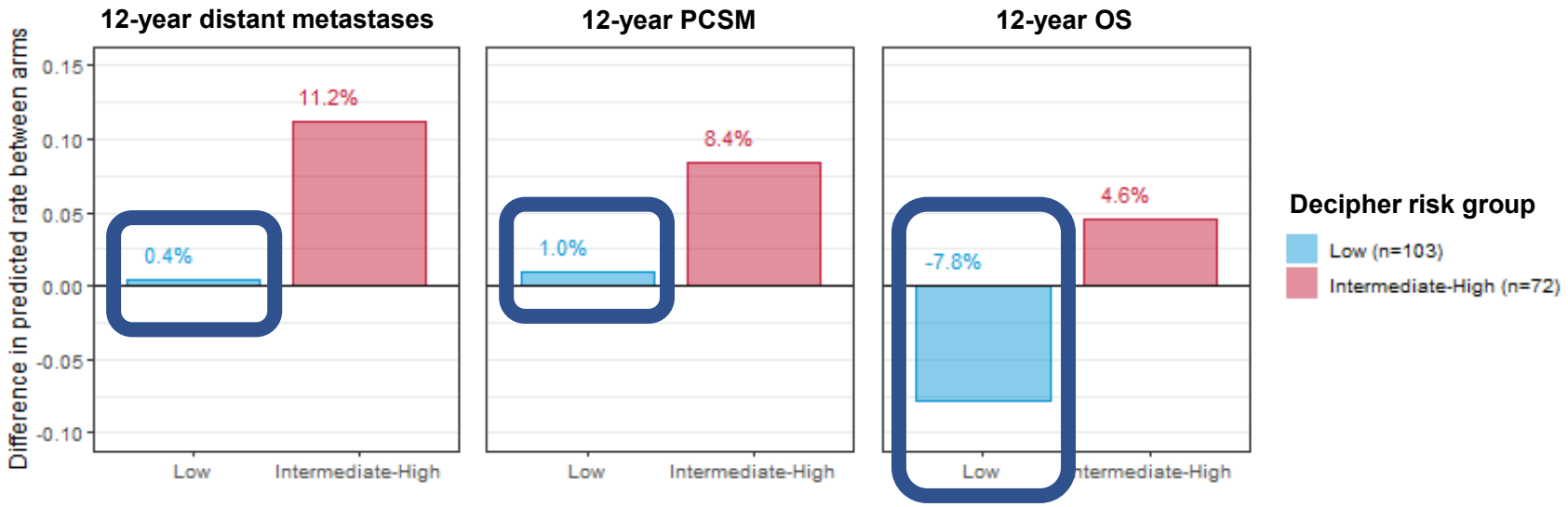
JAMA Oncology | Original Investigation

Validation of a 22-Gene Genomic Classifier in Patients With Recurrent Prostate Cancer

An Ancillary Study of the NRG/RTOG 9601 Randomized Clinical Trial

Felix Y. Feng, MD; Huei-Chung Huang, MA; Daniel E. Spratt, MD; Shuang (George) Zhao, MD; Howard M. Sandler, MD; Jeffry P. Simko, MD, PhD; Elai Davicioni, PhD; Paul L. Nguyen, MD; Alan Pollack, MD, PhD; Jason A. Efstathiou, MD, PhD; Adam P. Dicker, MD, PhD; Tamara Todorovic, MSc; Jennifer Margrave, BSc; Yang (Seagle) Liu, PhD; Bashar Dabbas, MD; Darby J. S. Thompson, PhD; Rajdeep Das, MD, PhD; James J. Dignam, PhD; Christopher Sweeney, MD; Gerhardt Attard, PhD; Jean-Paul Bahary, MD; Himanshu R. Lukka, MD; William A. Hall, MD; Thomas M. Pisansky, MD; Amit B. Shah, MD; Stephanie L. Pugh, PhD; William U. Shipley, MD; Phuoc T. Tran, MD, PhD

- I first had the idea of running Decipher on RTOG 9601 in 2012
- Had to wait until 2017, when the primary results of the trial were published, to submit an application for samples
- My application was rejected twice over 2 years, because the TRP application process was new and the NCI was trying to figure out the review criteria.
- Once approved (2020), we were able to present at ASCO GU and publish in JAMA Oncology in 2021



Feng et al, *JAMA Oncology* 2021

The Pros of Cooperative Group Research

- **Cooperative groups allow you to make advances that transform the field. Phase III trials:**
  - Are expensive (i.e., $10k-20k per patient). If you get a trial approved, the NCI funds the entire cost of the trial.
  - Require a ton of infrastructure. Where else (outside of an industry-sponsored trial) would you access to the infrastructure (resources, staff, regulatory oversight, data collection, biostats support) to run a phase III trial?
  - Require a ton of accruals. How else would you be able to accrue so many patients?
- **You develop a national reputation if you run a cooperative group trial.**
  - This national reputation leads to speaking invitations at national meetings, invitations to the steering committees of ISTs and advisory boards, etc
- **The more you know about the cooperative group system, the easier it becomes to implement your research vision.**
  - Your first few forays into the cooperative group system may be painful, but things get easier with experience.

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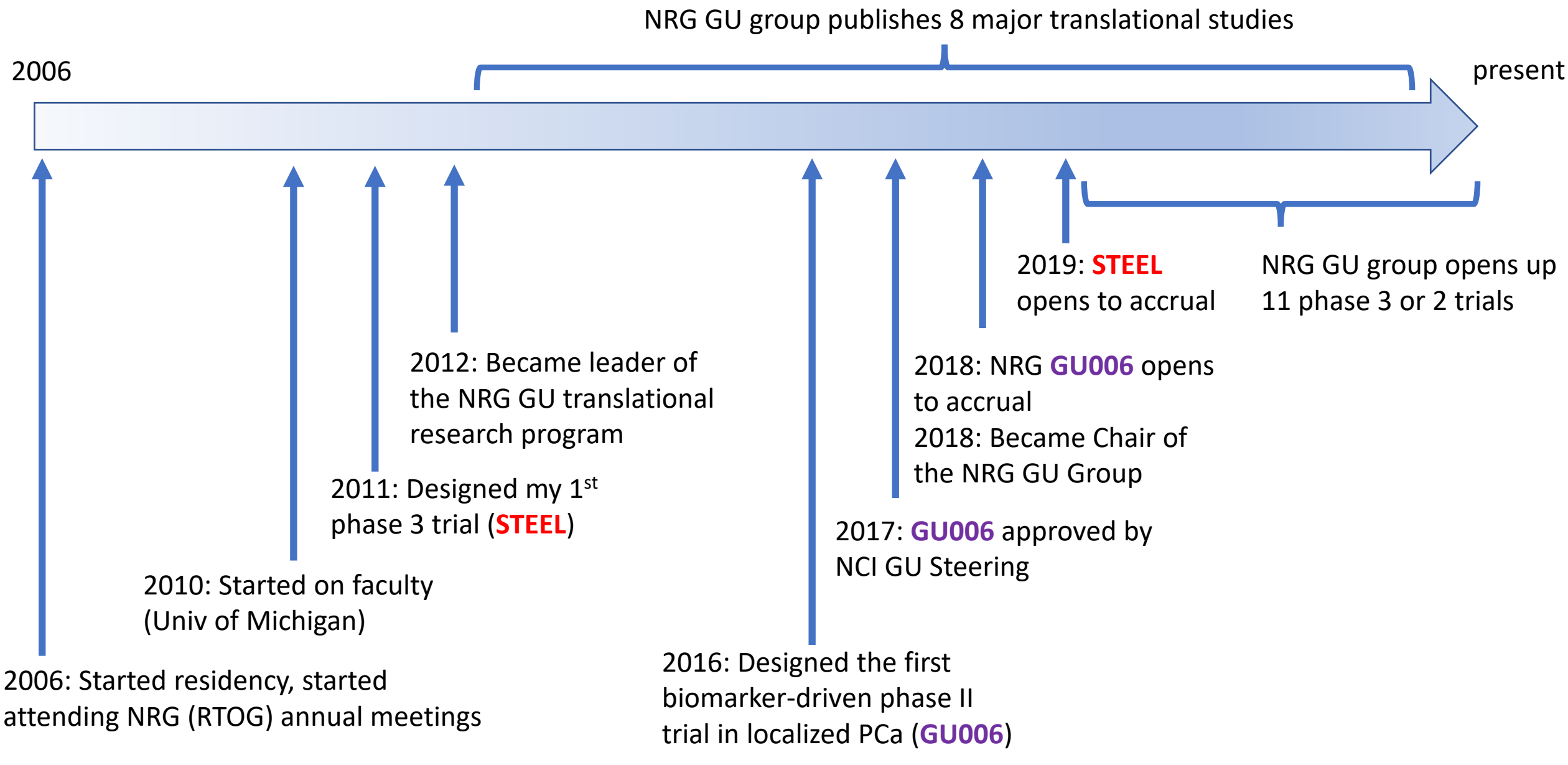


NRG GU006 SCHEMA

STEP 1
REGISTRATION

Submission of tissue for Decipher analysis

Note: Decipher analysis results must be completed before Step 2 randomization can occur.

If Decipher results have already been obtained, in lieu of tissue, results must be submitted to GenomeDX for validation.

STEP 2 REGISTRATION

STRATIFY

Surgical Margins
Positive vs.
Negative

Pre-SRT PSA
<0.5 ng/mL vs.
≥0.5-1.0 ng/mL

PAM50 Molecular Subtype (per Decipher analysis)
Luminal B vs.
(Luminal A/Basal/Unknown)

RANDOMIZE

Arm 1 (Blinded)*
External Beam Radiation:
64.8 to 70.2, 1.8 Gy/36-39 fractions

Plus

Blinded placebo daily for 6 months (~180 days) to start on Day 1 of radiation therapy (+/- 2 weeks)

Arm 2 (Blinded)*
External Beam Radiation:
64.8 to 70.2, 1.8 Gy/36-39 fractions
Plus

Blinded apalutamide daily for 6 months (~180 days) to start on Day 1 of radiation therapy (+/- 2 weeks)

NRG ONCOLOGY™

TIMELINE

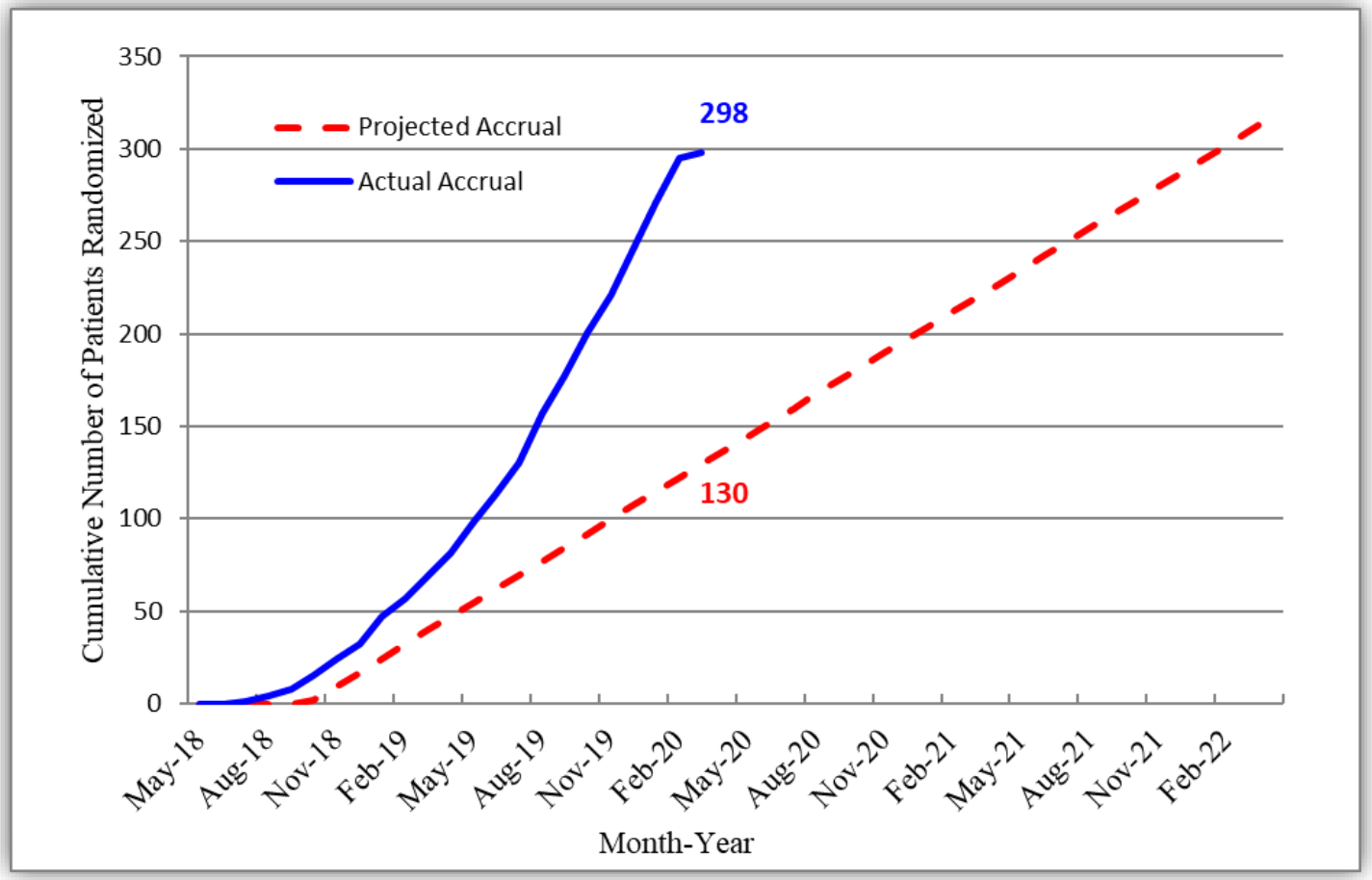
- **Fully activated: May 2018**
- **First accrual: September 2018**
- **Last accrual: February 2020**

- **Accrual duration:** 17 months to accrual all 300 patients
  - Finished 24 months ahead of schedule
  - 58% of the expected accrual time saved

- **Planned enrollment per month**: 6 patients
  - Surpassed 6 per month after 1st month of accrual
  - Averaged 25 accruals the later months = >4 times projected rate of accrual

NRG ONCOLOGY™

ACCRUAL



NRG ONCOLOGY™

LEARNING LESSONS

We can successfully (and safely) use next gen ARSI with RT in cooperative group trials

- First time successfully completed

We can successfully prospectively run and stratify by genomic biomarkers in prostate cancer in cooperative group trials

-First time successfully completed

Listen to the community.

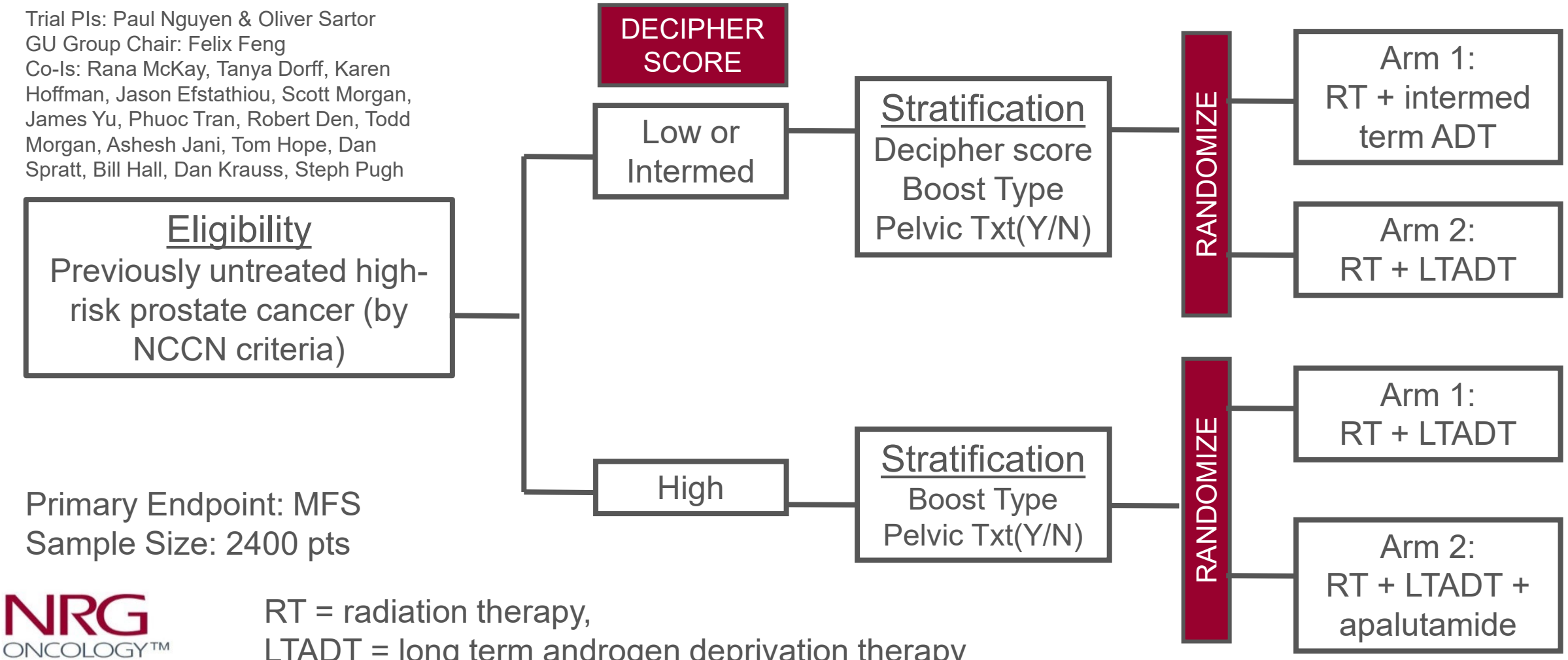
-The majority of people in clinical practice do NOT want to give ADT with early SRT.

-We need to design trials that reflect practice that will accrue.

NRG ONCOLOGY™

NRG GU009: Parallel Phase III Randomized Trials for High Risk Prostate Cancer Testing Treatment De-Intensification for Men with Lower Genomic Risk and Treatment Intensification for Men with Higher Genomic Risk (PREDICT-RT)

Trial PIs: Paul Nguyen & Oliver Sartor
GU Group Chair: Felix Feng
Co-Is: Rana McKay, Tanya Dorff, Karen Hoffman, Jason Efstathiou, Scott Morgan, James Yu, Phuoc Tran, Robert Den, Todd Morgan, Ashesh Jani, Tom Hope, Dan Spratt, Bill Hall, Dan Krauss, Steph Pugh



Primary Endpoint: MFS
Sample Size: 2400 pts

NRG ONCOLOGY™

RT = radiation therapy,
LTADT = long term androgen deprivation therapy

NRG GU010: Genomic-Risk Stratified Unfavorable Intermediate Risk Prostate Cancer: De-intensification and Intensification Clinical Trial (GUIDANCE)

Trial PIs: Alejandro Berlin & Neil Desai
Robert Den
Co-Is: Dana Rathkopf, Alicia Morgans, Ted Karrison, Brian Baumann, Zach Zumsteg, Pete Rossi, Todd Morgan, Will Lowrance, Ron Chen, Mohamed El-Shaikh, Dan Spratt

Eligibility
Previously untreated unfavorable intermediate-risk prostate cancer (by NCCN criteria)

DECIPHER SCORE

- Low → **Stratification** RT Type → RANDOMIZE
  - Arm 1: RT alone
  - Arm 2: RT + STADT
- Intermed or High → **Stratification** Decipher score, RT(Pel vs Pros), Brachy (Y or N) → RANDOMIZE
  - Arm 1: RT + STADT
  - Arm 2: RT + STADT + darolutamide

Primary Endpoints:
Intensification Trial: MFS
De-Intensification: MFS & QOL

NRG ONCOLOGY™

RT = radiation therapy,
STADT = short term androgen deprivation therapy

Additional Pros of Cooperative Group Research

- **Cooperative groups allow you to make advances that transform the field.**
  - Even outside of running prospective trials, you can make impactful advances using samples or data collected from previous trials.
- **Cooperative group trials are associated with the investigator (as opposed to the institution).**
  - If you move from one institution to another, your cooperative group research follows you.
- **The more you know about the cooperative group system, the easier it becomes to implement your research vision.**
  - Your first few forays into the cooperative group system may be painful, but things get easier with experience.

PRINCIPLES OF RISK STRATIFICATION

Table 1. Initial Risk Stratification for Clinically Localized Disease

Category	Tool	Predictive	Prognostic	Endpoint Trained For[a]	Level of Evidence for Validation[b]
Clinical	NCCN	No	Yes	See note[c]	1
	STAR-CAP[2]	No	Yes	PCSM	3
	CAPRA[11,d]	No	Yes	BCR	3
	MSKCC[12]	No	Yes	BCR and PCSM[f]	3
AI	ArteraAI Prostate (category 2B)[5,e]	No	Yes	BCR, DM, PCSM[g]	1
Gene Expression Testing	Decipher[13]	No	Yes	DM	1
	Prolaris[14]	No	Yes	See note[h]	3
	Oncotype[15]	No	Yes	Adverse pathology	3
Germline	HRR	No	Uncertain	See note[i]	4

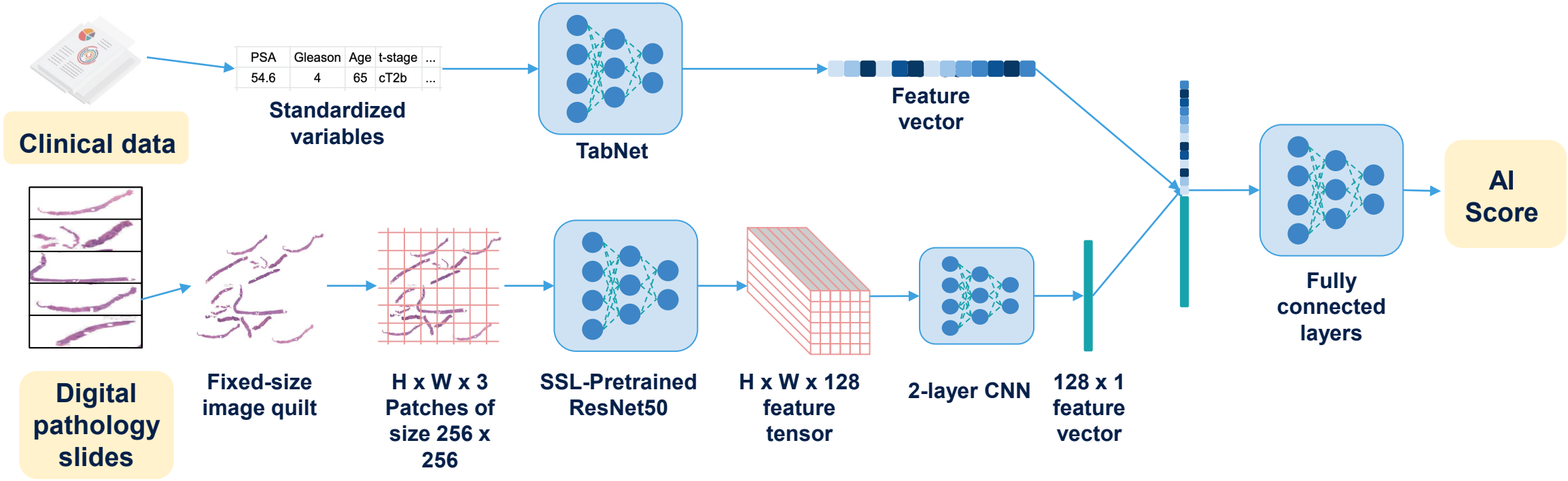
BCR, biochemical recurrence; DM, distant metastases; PCSM, prostate cancer-specific mortality

[a] "Endpoint trained for" specifically relates to what the biomarker or model was designed and optimized to predict. This is distinct from endpoints for which the biomarker has been shown to be prognostic in validation.

[b] Levels of evidence for biomarkers in this section are based on modified Simon et al criteria:[10]

1: Validation in the context of multiple clinical trials with consistent results. Randomized trials are necessary for predictive biomarkers for validation.
2: Validation in multiple independent prospective registry/observational cohorts with consistent results.
3: Validation in multiple independent retrospective studies with consistent results.
4: Validation in a single retrospective study, or multiple independent retrospective studies with inconsistent results.

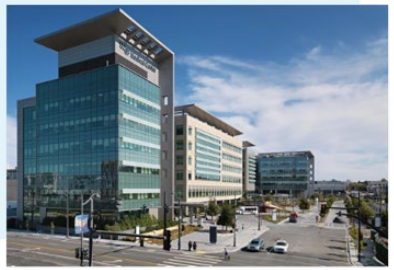
Development of a Multi-Modal Artificial Intelligence (MMAI) Tool Prognostic of Prostate Cancer Outcomes



Learns from clinical and histopathology data <u>without slide annotations</u>. This lowers the barrier for usage and allows for scalability

Esteva, Mohamad, et al, (Nature Digital Medicine 2022)

Clinical Trials Data Used to Train and Develop Multi-Modal AI (MMAI) Prognostic Biomarker



UCSF NRG ONCOLOGY

5654 patients
16204 slides

Localized disease

Radiation therapy

Pretreatment tissue biopsies

Variables	Total	RTOG-9202	RTOG-9408	RTOG-9413	RTOG-9910	RTOG-0126
Numbers of Patients	(N=5654)	(N=1180)	(N=1719)	(N=695)	(N=976)	(N=1084)
Age						
Median (IQR)	70 (66 - 74)	70 (66 - 74)	71 (66 - 74)	70 (65 - 74)	71 (66 - 74)	71 (65 - 74)
Race						
White	4503	1004	1312	481	769	937
African American	932	147	334	173	166	112
Other	37	1	10	11	6	9
No. of Pathology Slides	16204	3188	5472	2104	3075	2365
Baseline PSA (ng/mL)						
Median (IQR)	10 (6.6 - 17)	20 (11 - 40)	8.1 (5.8 - 12)	23 (13 - 35)	11 (6.8 - 15)	7.6 (5.4 - 11)
Gleason						
<7	2082	405	1048	196	271	162
7	2651	352	473	308	596	922
8-10	716	257	159	191	109	0
Risk Group						
Low	584	0	577	0	7	0
Intermediate	3060	205	944	116	711	1084
High	1925	937	159	579	250	0
Primary Endpoint	-	DFS	OS	PFS	PCSM	OS
Median follow-up (yrs)	11.4	17.4	15.1	13.7	9.3	13.2
No. Patients Died	3404	944	1154	504	297	505

NRG ONCOLOGY

Accurate clinical and long-term outcome data

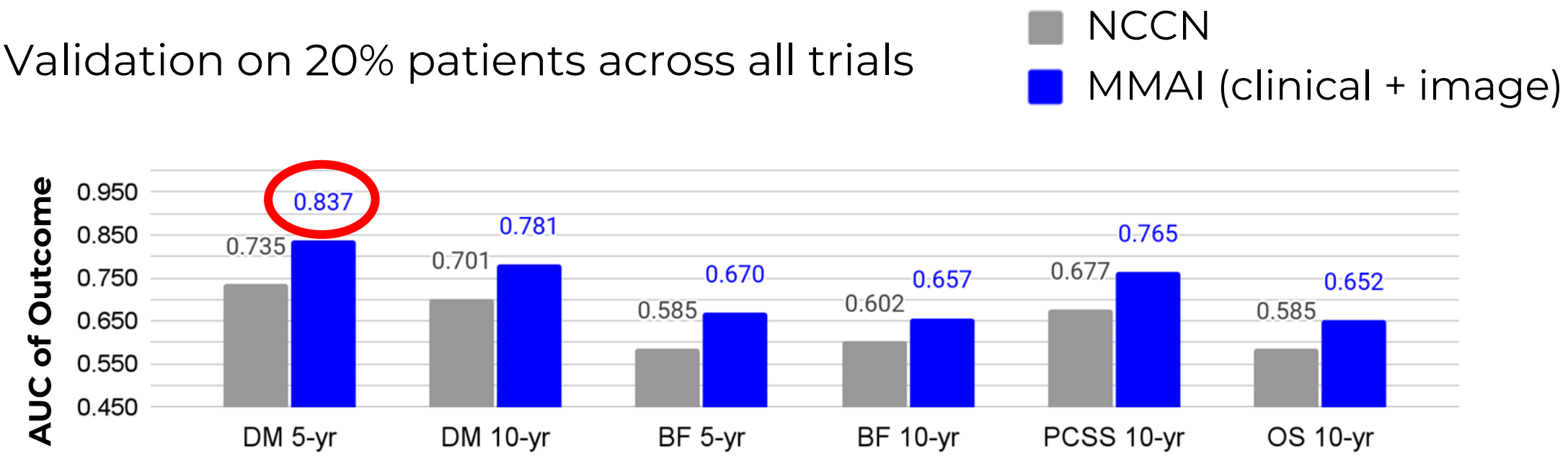
Esteva, Mohamad, et al, (Nature Digital Medicine 2022)

Prognostic AI Biomarker

Can we identify patients who have more aggressive vs less aggressive disease?

MMAI Prognostic Tool Outperforms Standard Risk Stratification Tool

Validation on 20% patients across all trials

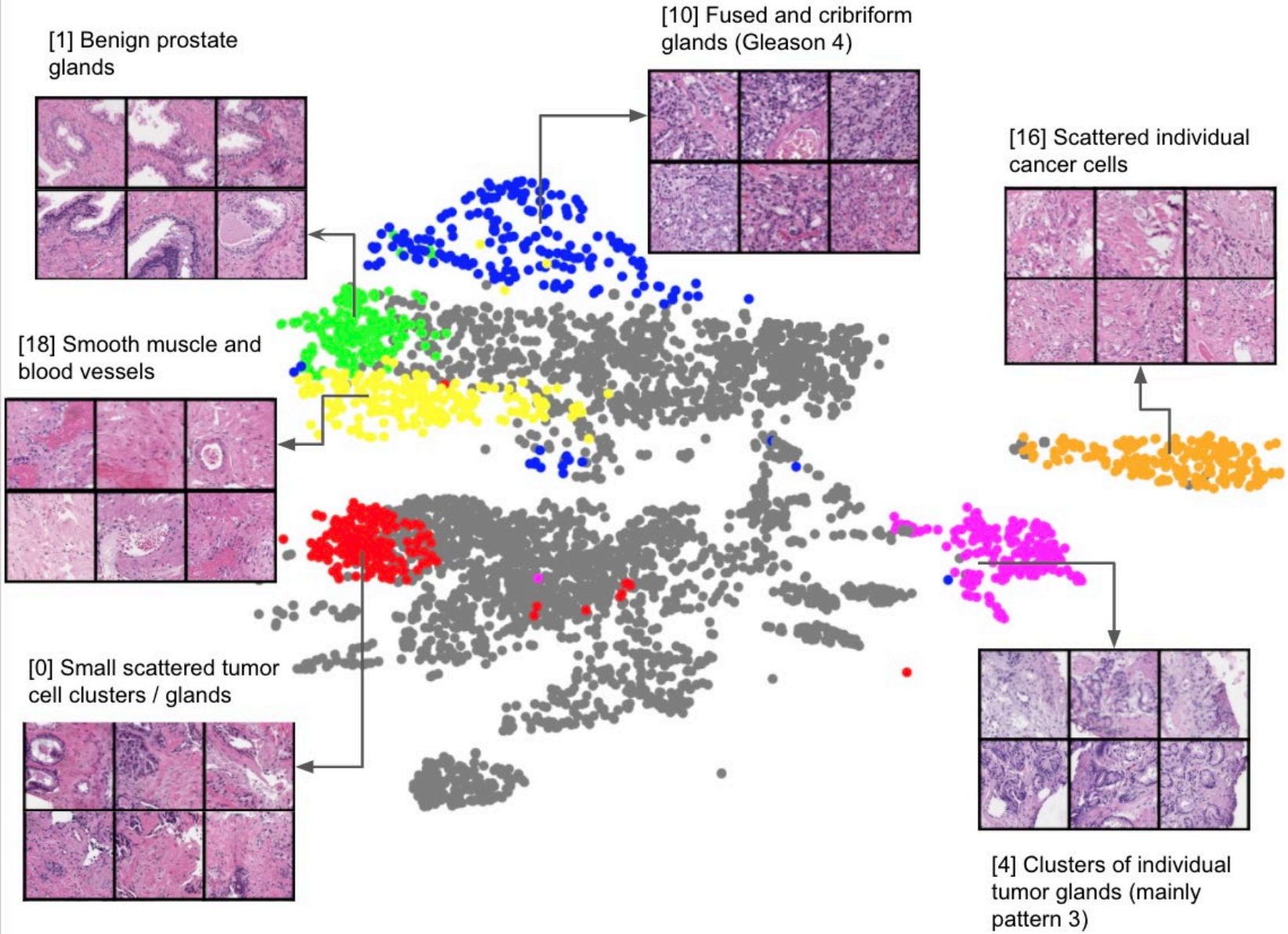


MMAI model outperforms NCCN for all endpoints

NRG ONCOLOGY

Esteva, Mohamad, et al,
(Nature Digital Medicine 2022)

Self-Supervised Learning Image Features



NRG ONCOLOGY

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Most cancer biomarker studies have focused on **prognostic** biomarkers that provide information on outcomes *independent of the treatment received*

A **predictive** biomarker specifically identifies response or resistance to a particular therapy – but not all treatments.

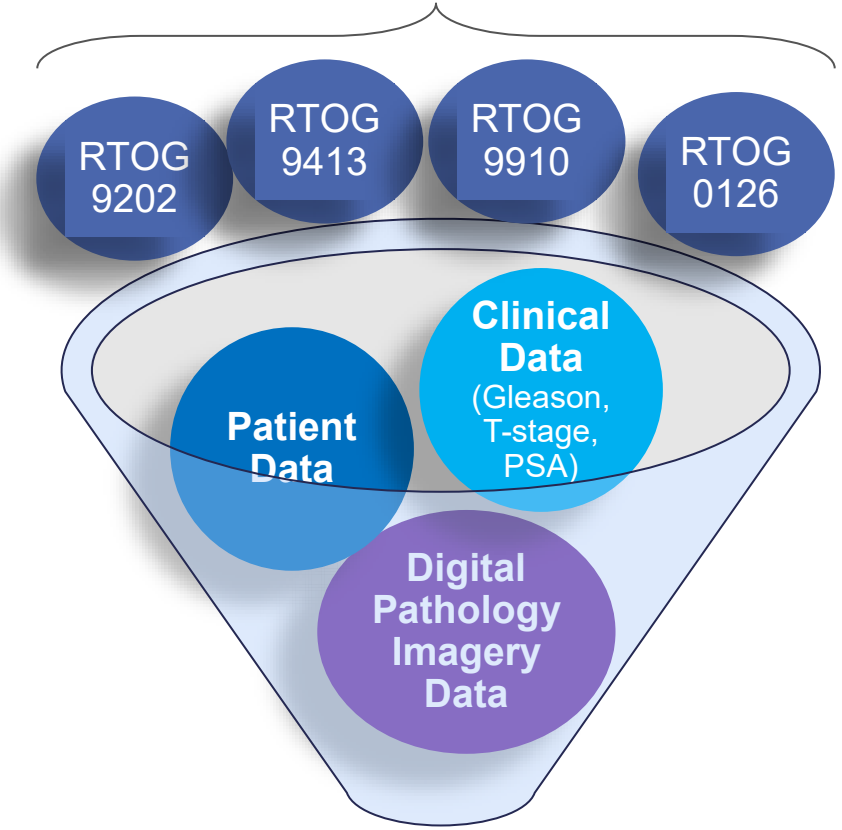
UCSF

Predictive AI Biomarker

Who will benefit from additional hormone therapy?
Who won’t?

Development of Multi-Modal AI (MMAI) Predictive Biomarker

NRG Biobank



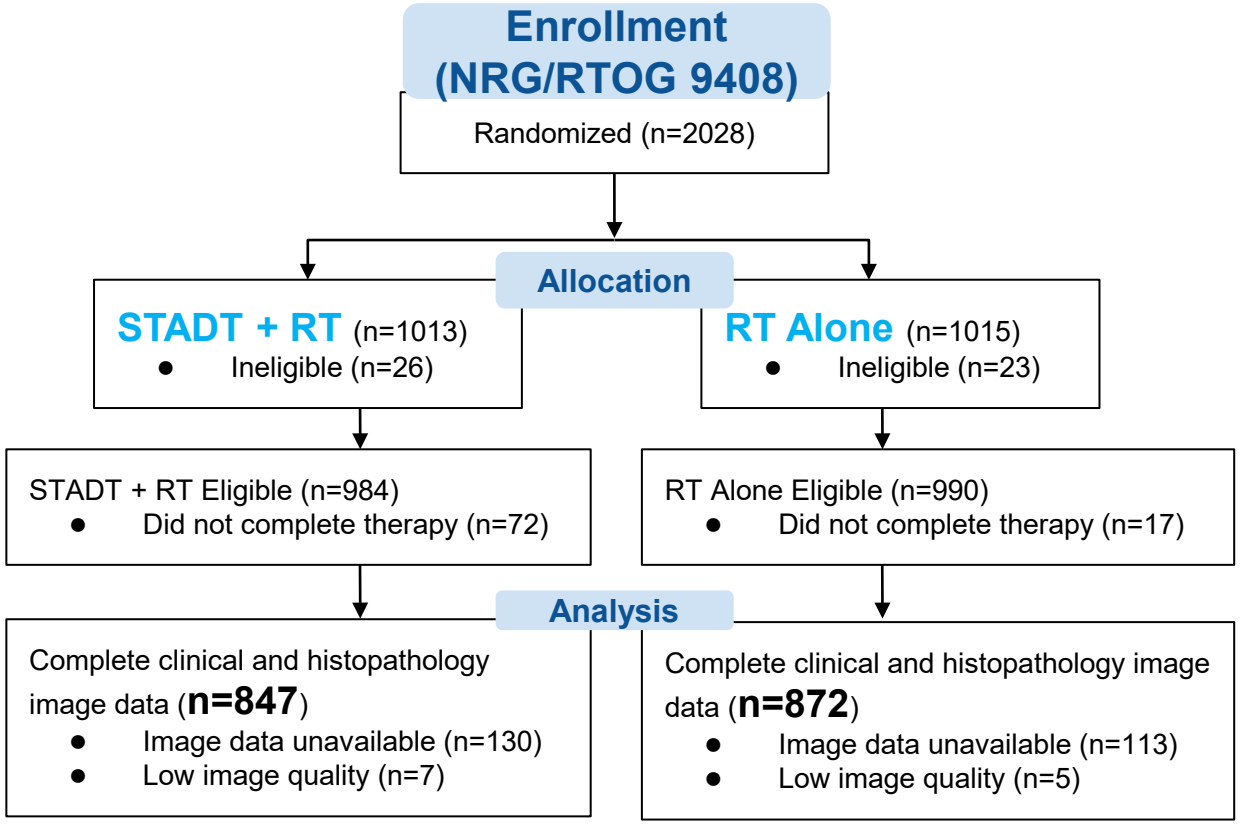
Training set (n=3,935)

Distant Metastasis

AI to Predict ADT Response

Locked model

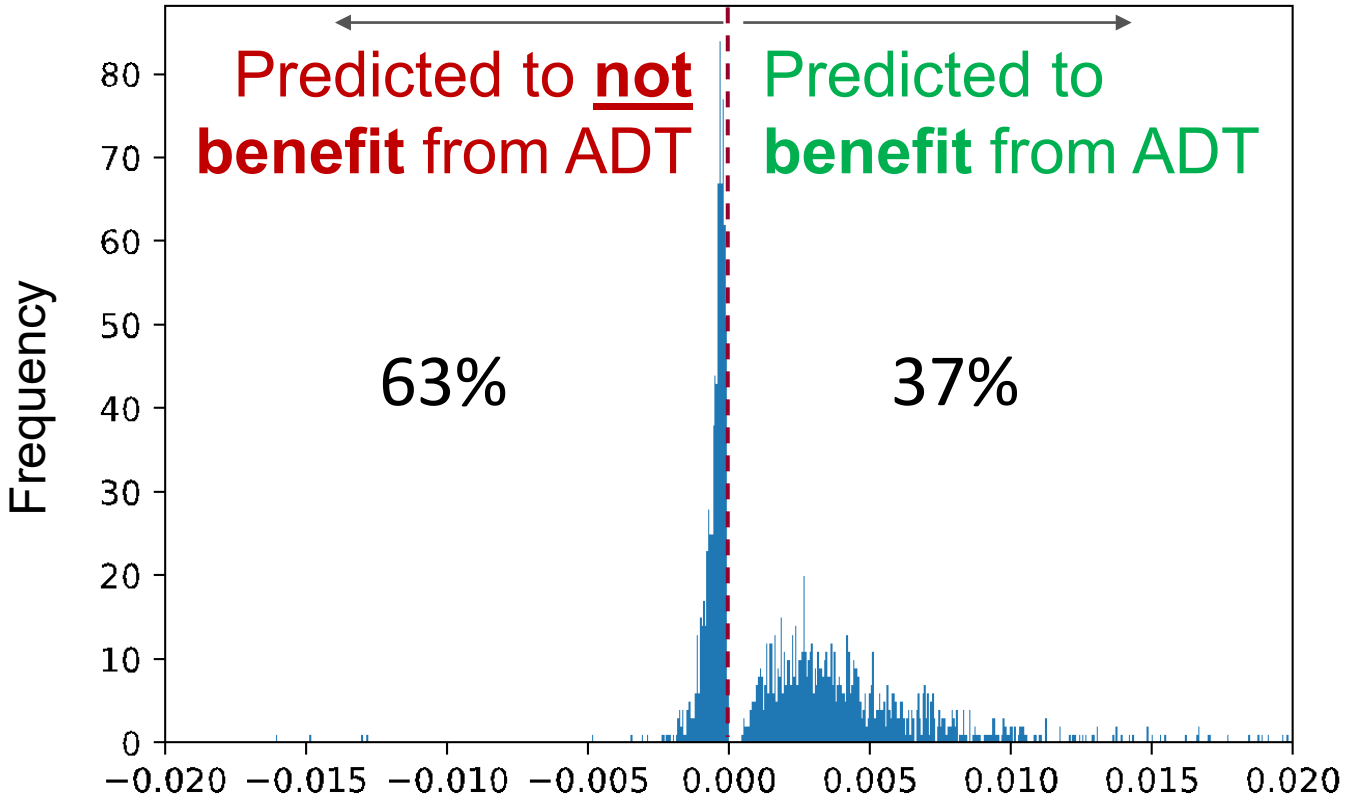
Validation



Analysis of biomarker-treatment interaction

The Multi-Modal AI (MMAI) Model Predicts that the Majority of Patients with Intermediate Risk Disease do not Benefit from ADT

Validation Set
(n=1,719)

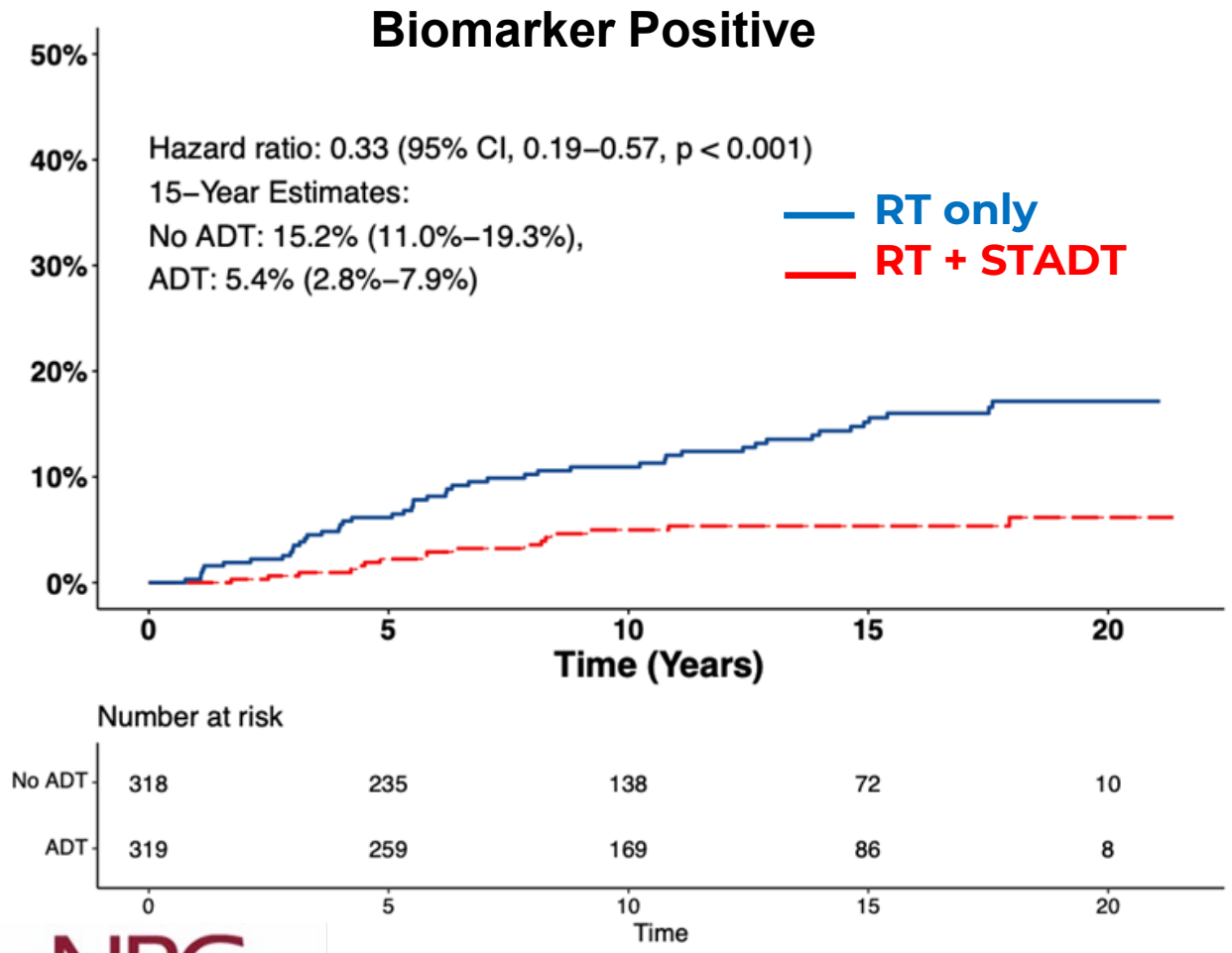


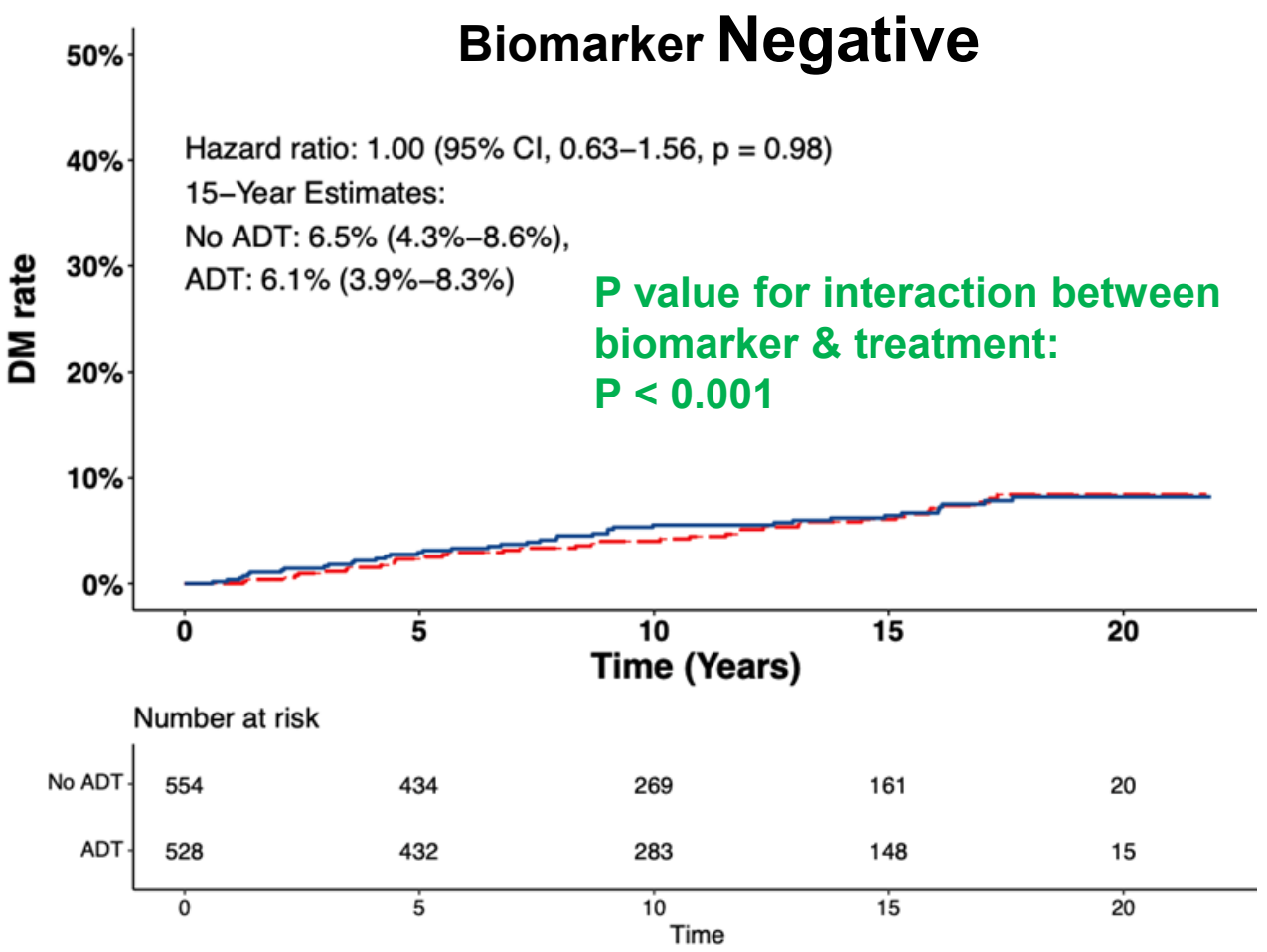
Difference in Model Scores for
ADT vs no ADT on 5-yr DM

NRG ONCOLOGY

Spratt et al, ASCO GU 2022

MMAI Predictive Model Successfully Identifies Which Patients are More Likely to Benefit from the Addition of ADT to Radiation





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	MSKCC[12]	No	Yes	BCR and PCSM[f]	3
AI	ArteraAI Prostate (category 2B)[5,e]	No	Yes	BCR, DM, PCSM[g]	1
Gene Expression Testing	Decipher[13]	No	Yes	DM	1
	Prolaris[14]	No	Yes	See note[h]	3
	Oncotype[15]	No	Yes	Adverse pathology	3
Germline	HRR	No	Uncertain	See note[i]	4

BCR, biochemical recurrence; DM, distant metastases; PCSM, prostate cancer-specific mortality

[a] "Endpoint trained for" specifically relates to what the biomarker or model was designed and optimized to predict. This is distinct from endpoints for which the biomarker has been shown to be prognostic in validation.

[b] Levels of evidence for biomarkers in this section are based on modified Simon et al criteria:[10]

1: Validation in the context of multiple clinical trials with consistent results. Randomized trials are necessary for predictive biomarkers for validation.
2: Validation in multiple independent prospective registry/observational cohorts with consistent results.
3: Validation in multiple independent retrospective studies with consistent results.
4: Validation in a single retrospective study, or multiple independent retrospective studies with inconsistent results.

Practical Advice for Cooperative Group Research

- **Find good mentors.**
  - It's easier to learn from someone else's mistakes than from your own…..
- **Be persistent.**
  - The people who succeed are those who keep trying.
- **Be strategic.**
  - Try to do something different than everyone else (and this can include joining groups where there aren't as many med oncs, if you're a med onc)
- **Get a toehold first**
  - You can be the champion for a trial at another cooperative group. Or, you can be the early career faculty in a new trial (this varies from group to group).
- **See if you can attend the closed committee meetings as an observer.**
  - By seeing these discussions, you learn to how to enhance the success of your own concept.

Practical Advice for Cooperative Group Research

- **Connect the dots.**
  - For translational research, you don't need to run your own lab. Just connect the dots (i.e., find a company that wants samples, and work to craft a translational research project). Or, find a basic research partner (like Michael Haffner in Pathology or Gavin Ha in computational science) who can help support your research interests.
- **Do not rely on just cooperative group research in your academic portfolio.**
  - Remember – the seeds that you plant in the cooperative group may not bear fruit until much later. Balance your research portfolio to include both institutional and coop group research.
- **Be present.**
  - Good things happen to those who are routinely at cooperative group meetings. You'll find collaborations that you weren't looking for.