Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Multidisciplinary Precision Cancer Medicine

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Center for Precision Medicine

City of Hope

Disclosures

- Grant/Research Support from Abbvie, AstraZeneca, Eisai, Genvivo, Halo, and Invitae
- Co-founder with equity Brogent International LLC.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

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

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency & Implicit Bias

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:

- *Self-reported race*
- *Self-reported ethnicity*

Learning Objectives

- Explore multidisciplinary approaches to implementing genetic & genomic analyses for patient care.
- Apply evidence-based cancer risk management, prevention, and targeted therapeutics recommendations.
- Examine challenges and solutions related to diversity, equity, and inclusion in patient care.
- Recognize advances in identifying and managing individuals with hereditary GI cancer syndromes.

Precision Medicine – The Future of Cancer Care

A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

> "Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."
>
> — President Barack Obama, State of the Union Address, January 20, 2015

Collins FS and Varmus H, *NEJM*, 2015

Treating Patients, Targeting Mutations

- Drugs for diseases
- Drugs for physiology
- Drugs for genes
- Drugs for mutations

- Rapidly moving to a world of precision medicine that is so precise there are different drugs for different mutations

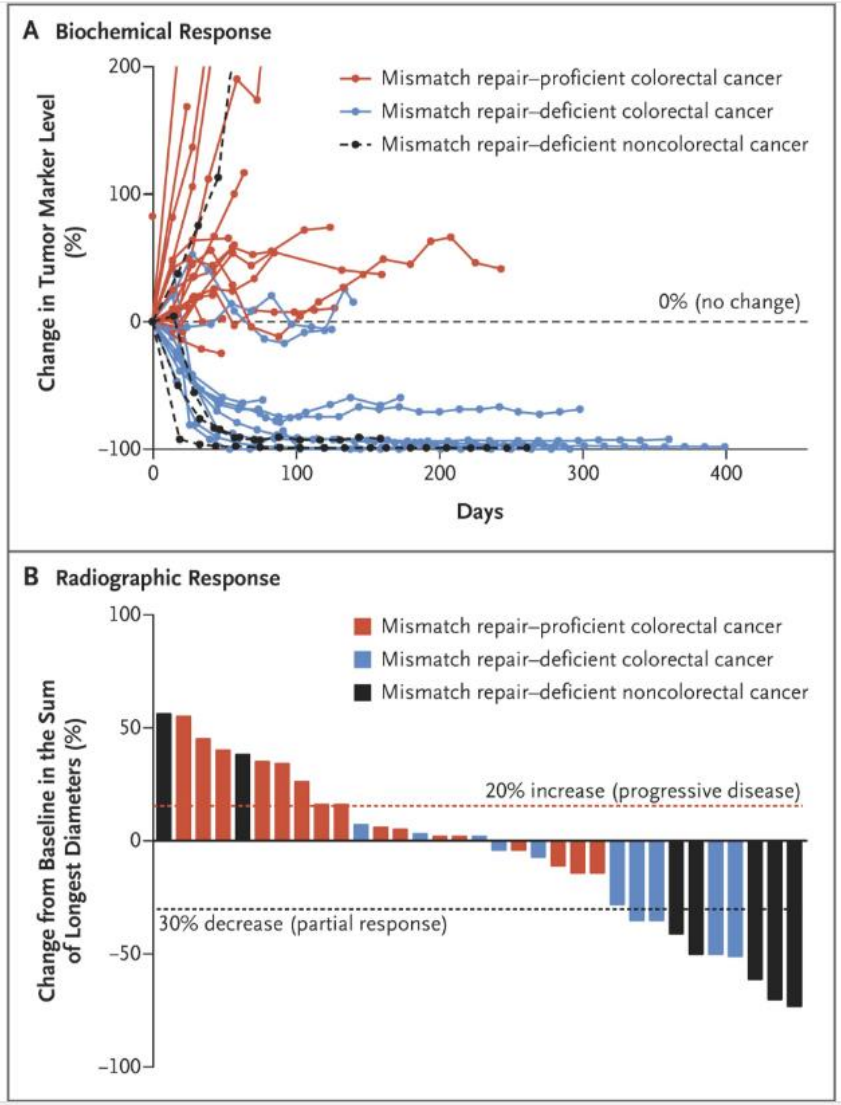
The NEW ENGLAND JOURNAL of MEDICINE

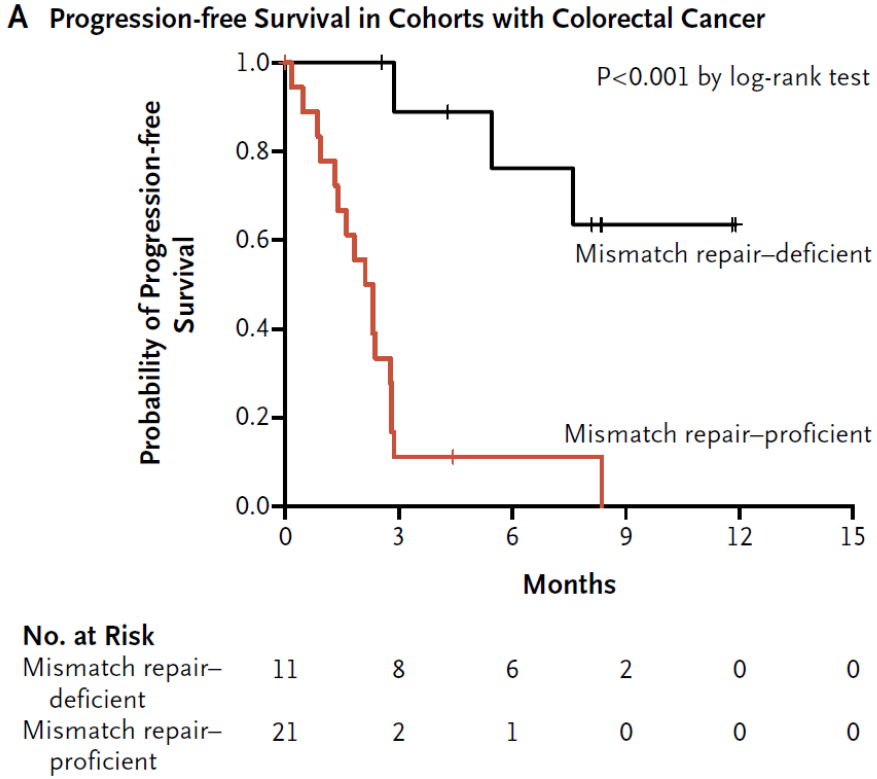
ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

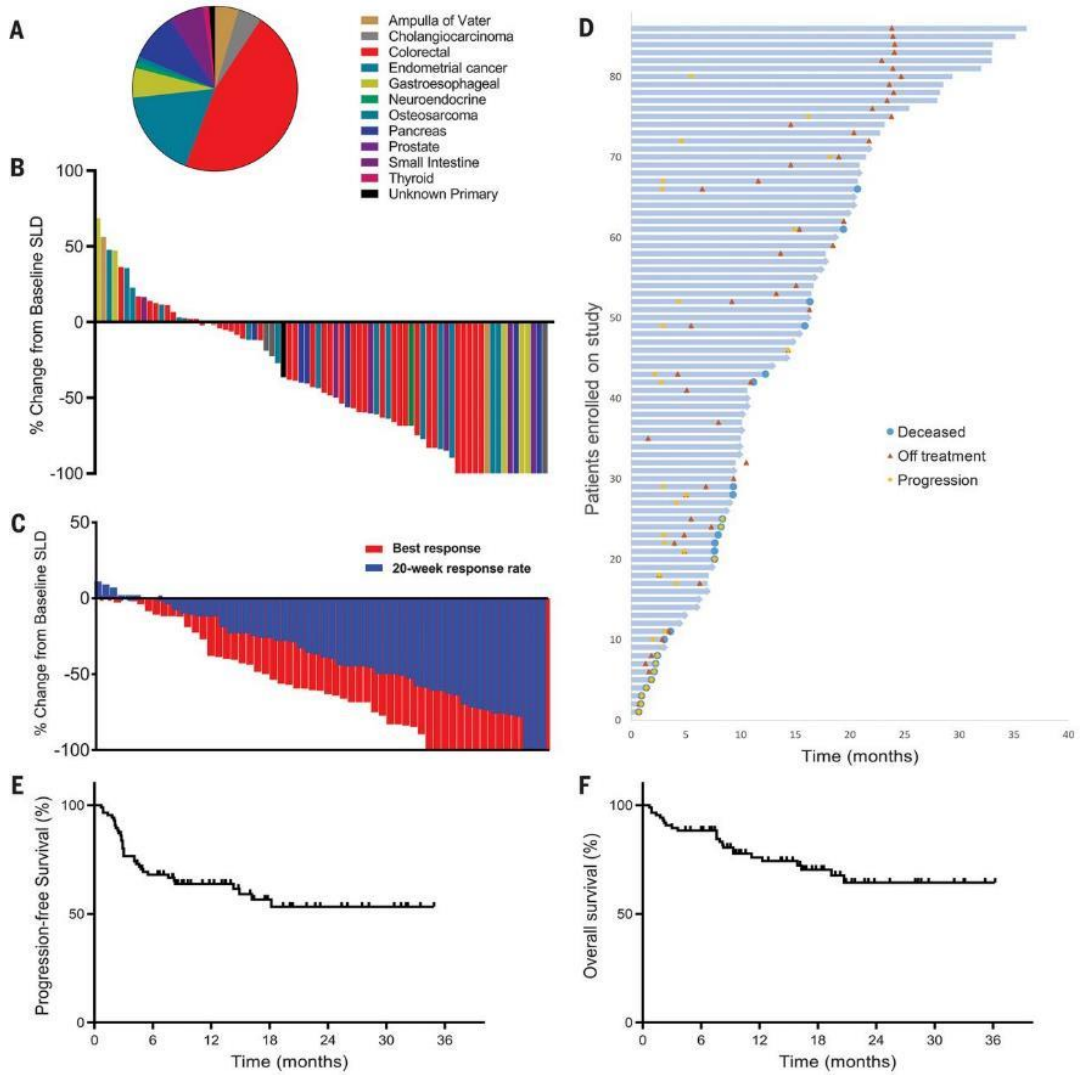
Mismatch-repair Status Predicts Clinical Benefit of Immune Checkpoint Blockade with Pembrolizumab





Le *et al*, *N Engl J Med* June 2015

Patient survival and clinical response to Pembrolizumab across 12 different tumor types with mismatch repair deficiency



Dung T. Le et al. Science 2017;357:409-413

FDA Approves Pembrolizumab for Microsatellite Instability-High and Mismatch Repair Deficient Cancers

Jason M. Broderick @jasoncology
Published: Tuesday, May 23, 2017

Richard Pazdur, MD

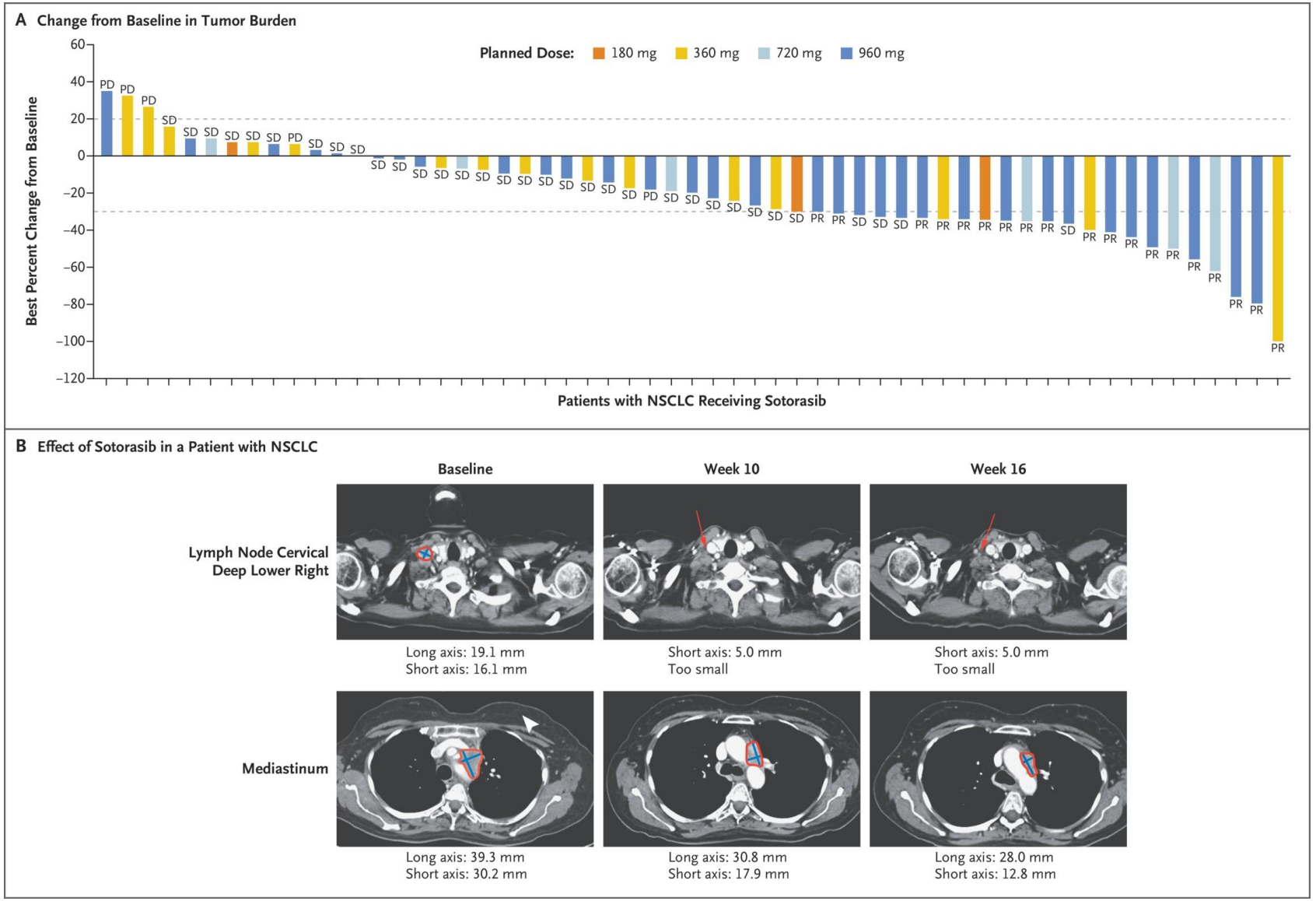
The FDA has granted an accelerated approval to pembrolizumab (Keytruda) for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed after prior treatment and who have no satisfactory alternative treatment options, as well as for patients with MSI-H or dMMR colorectal cancer following progression on a fluoropyrimidine, oxaliplatin, and irinotecan.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 24, 2020 VOL. 383 NO. 13

KRAS^{G12C} Inhibition with Sotorasib in Advanced Solid Tumors

D.S. Hong, M.G. Fakih, J.H. Strickler, J. Desai, G.A. Durm, G.I. Shapiro, G.S. Falchook, T.J. Price, A. Sacher, C.S. Denlinger, Y.-J. Bang, G.K. Dy, J.C. Krauss, Y. Kuboki, J.C. Kuo, A.L. Coveler, K. Park, T.W. Kim, F. Barlesi, P.N. Munster, S.S. Ramalingam, T.F. Burns, F. Meric-Bernstam, H. Henary, J. Ngang, G. Ngarmchamnanrith, J. Kim, B.E. Houk, J. Canon, J.R. Lipford, G. Friberg, P. Lito, R. Govindan, and B.T. Li

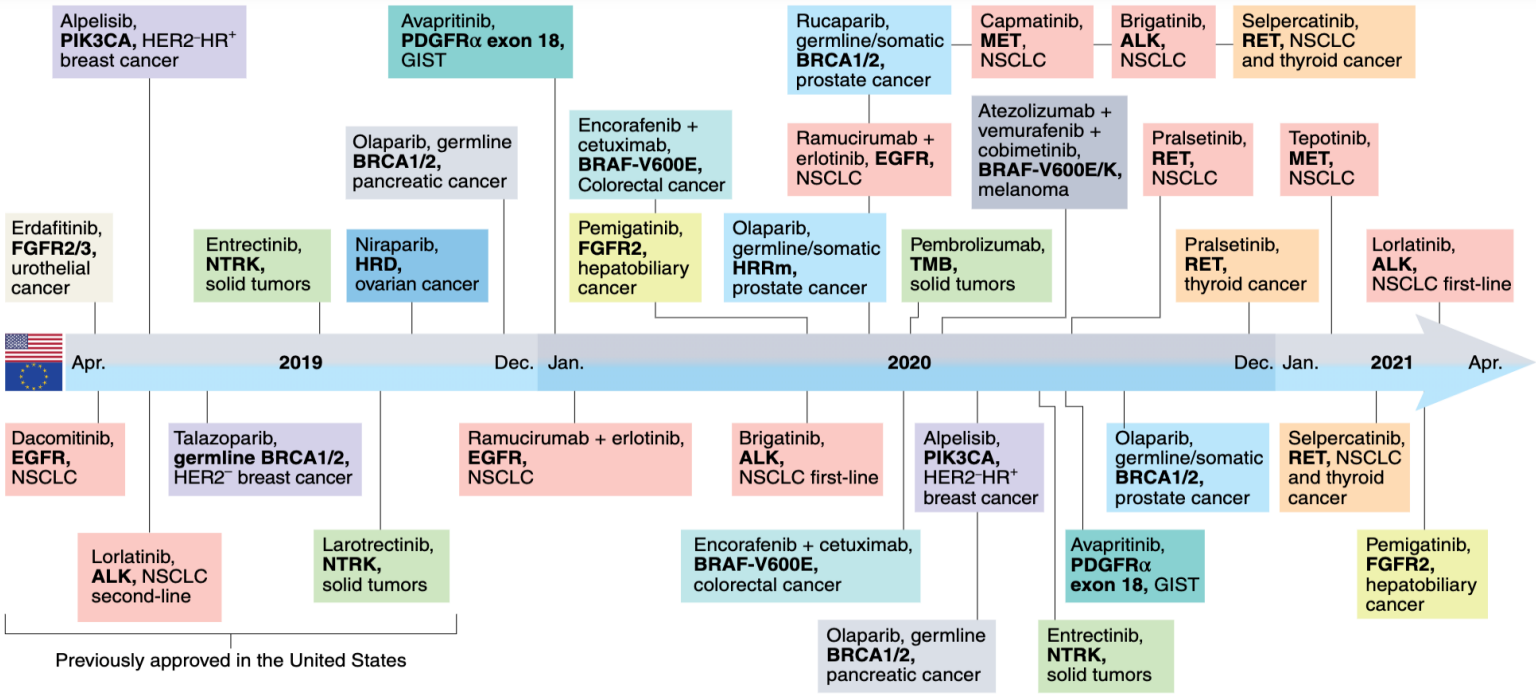


City of Hope

Hong *et al*, *NEJM*, September 24, 2020

Precision Medicine is Transforming Oncology

Unprecedented pace of new biomarker-driven drug approval



Significant gap between advances in cancer drug development & delivery of these drugs to patients

Mateo et al, Delivering precision oncology to patients with cancer, Nature Medicine, Vol 28, April 2022

Precision Medicine Vision

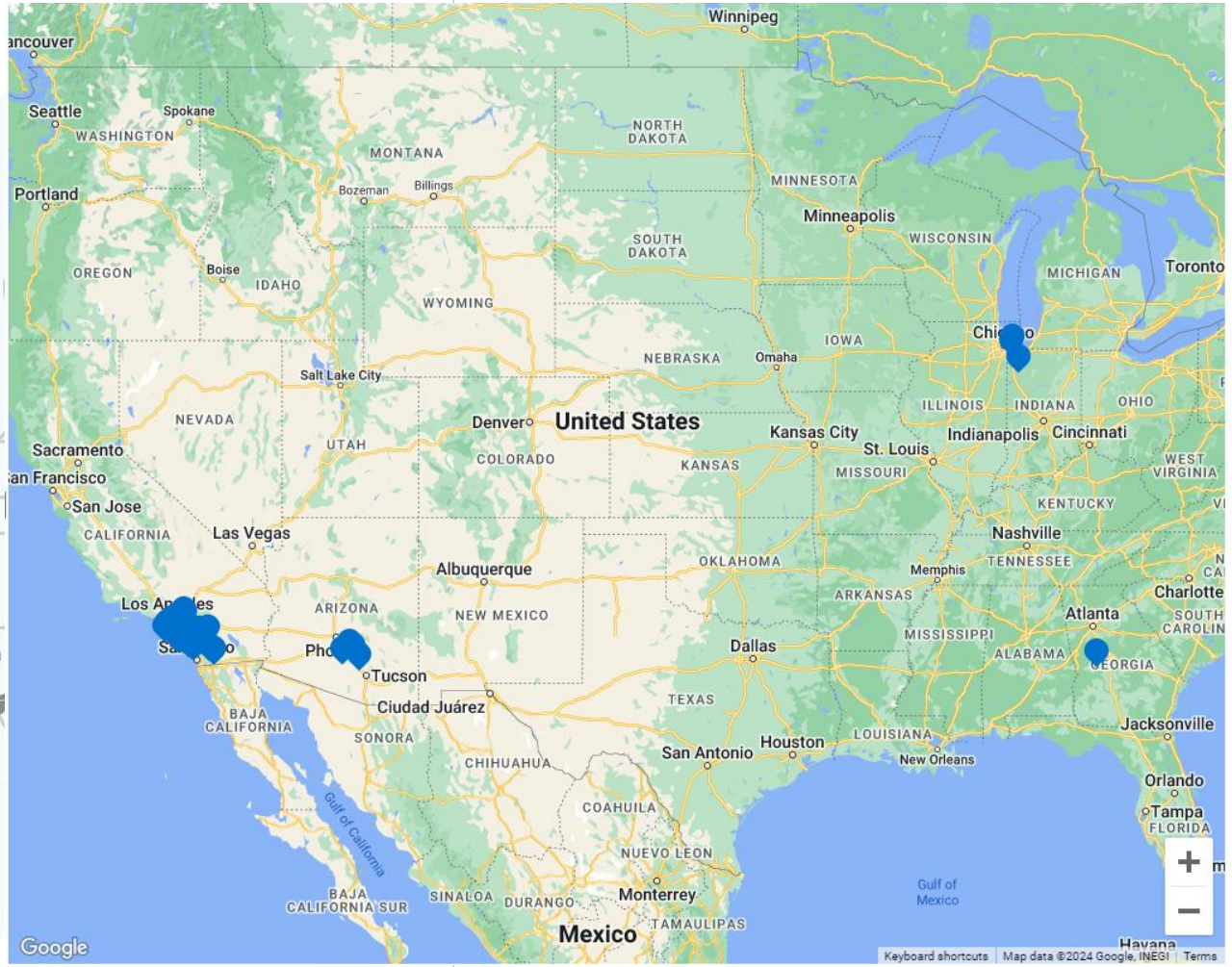
Harness genomic-driven insights, clinical expertise, and advanced analytics to pioneer personalized prevention and treatment plans to transform the outcomes and quality of life for our patients, their families, and our community

Strategy

1. IMPACT CLINICAL OUTCOMES by applying genomic insights to deliver cutting-edge care and developing new products and services that expand access to COH's precision medicine program
2. LEAD DISCOVERY OF NEW DRUGS AND DIAGNOSTICS by using genomic sequencing to accelerate treatments and therapies, and by developing NGS and diagnostic tools that advance discovery
3. UNLOCK THE POWER OF 'OMICS THROUGH DATA & ANALYTICS, through data aggregation, abstraction, and analytics, and linking "omic" and clinical data to identify optimal pathways for every person with cancer

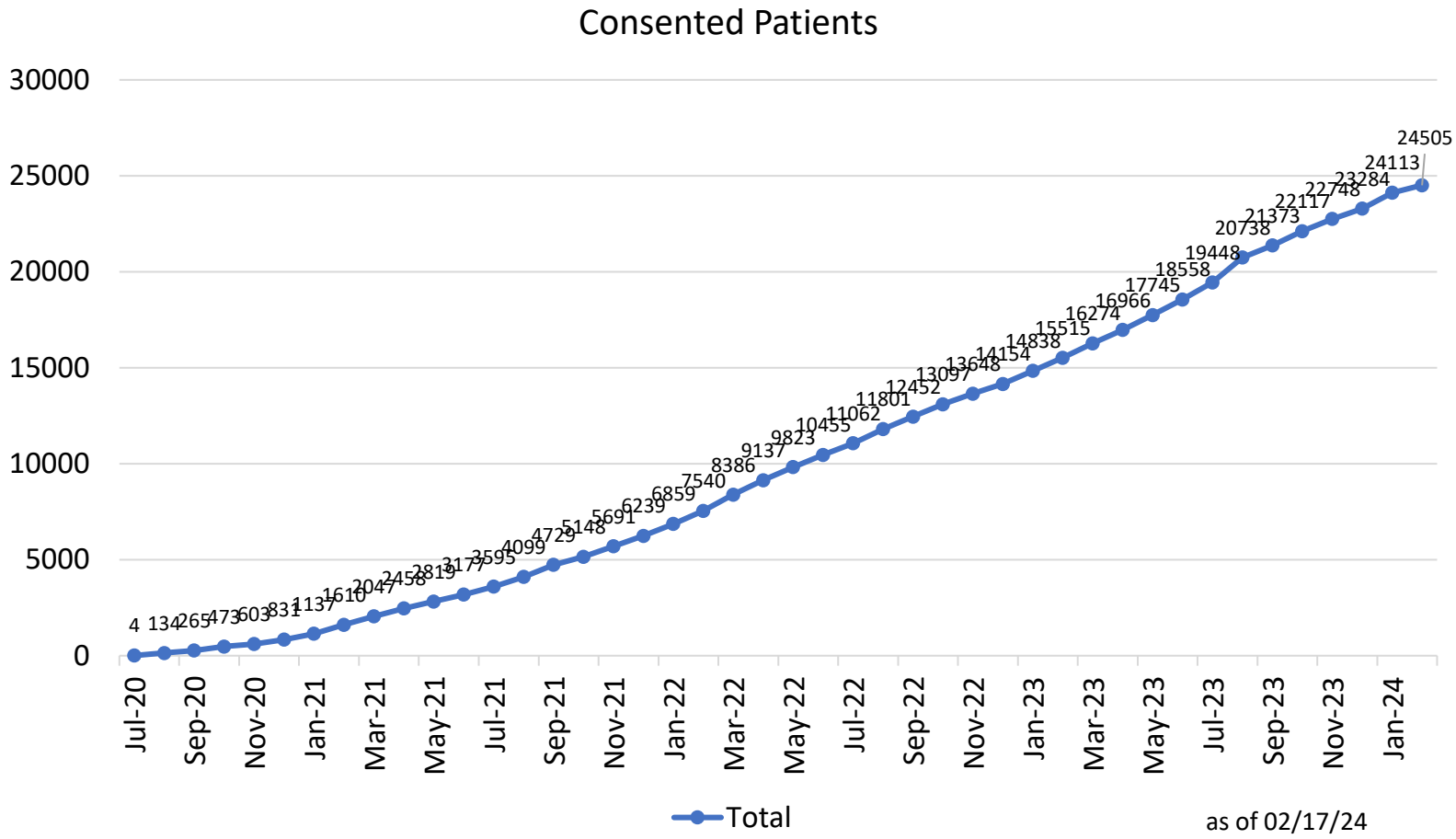
Key accelerators: enterprise-wide protocol, genomic profiling, data & clinical trials infrastructure, analytic capabilities

City of Hope Serves Southern California & Expanded USA



CityofHope.org

Impact on Clinical Care: Improving Access



Elements of Consent

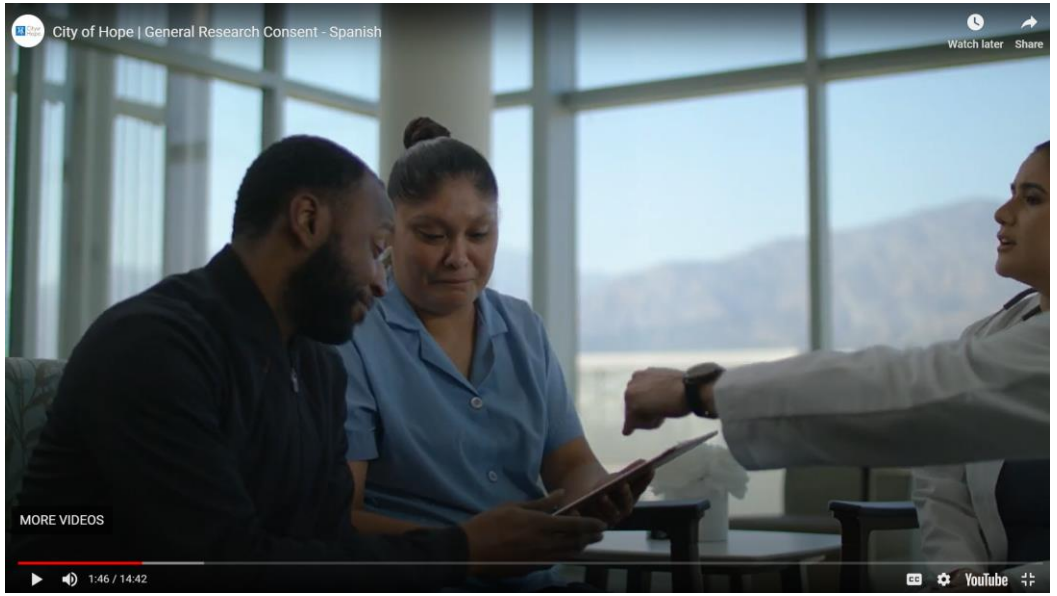
Active, opt-in
Commercial use
Somatic profiling
Germline genetic testing
Biosample sharing
Future contact

We have **gained efficiencies and optimized** processes. Implemented throughout Southern California, now expanding to Arizona, Georgia, and Illinois.

INSPIRE – Implementing Next-generation Sequencing for Precision Intervention and Risk Evaluation

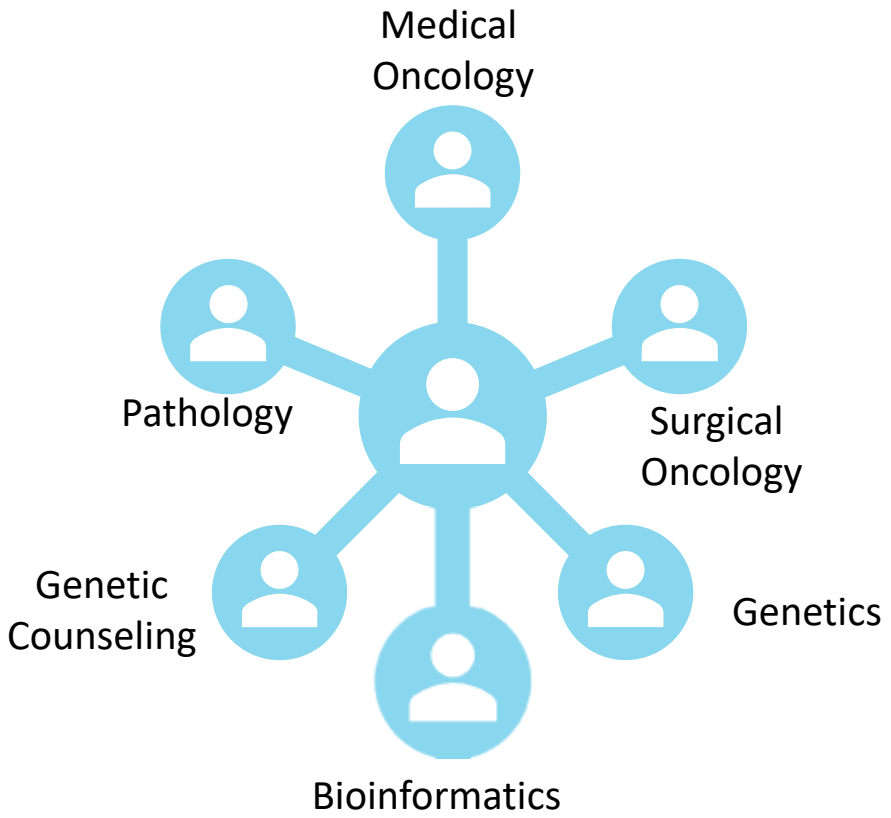
How is City of Hope expanding access to genomic profiling and genetic testing?

- *All* City of Hope patients eligible to join the Precision Medicine (INSPIRE) Study
- INSPIRE study delivered through “General Research Consent” protocol
- **No Cost** genetic testing (Germline and Somatic)
- Upfront in-clinic and teleconsenting with Docusign
- Centralized, integrated review & Tumor Board
- High-risk management



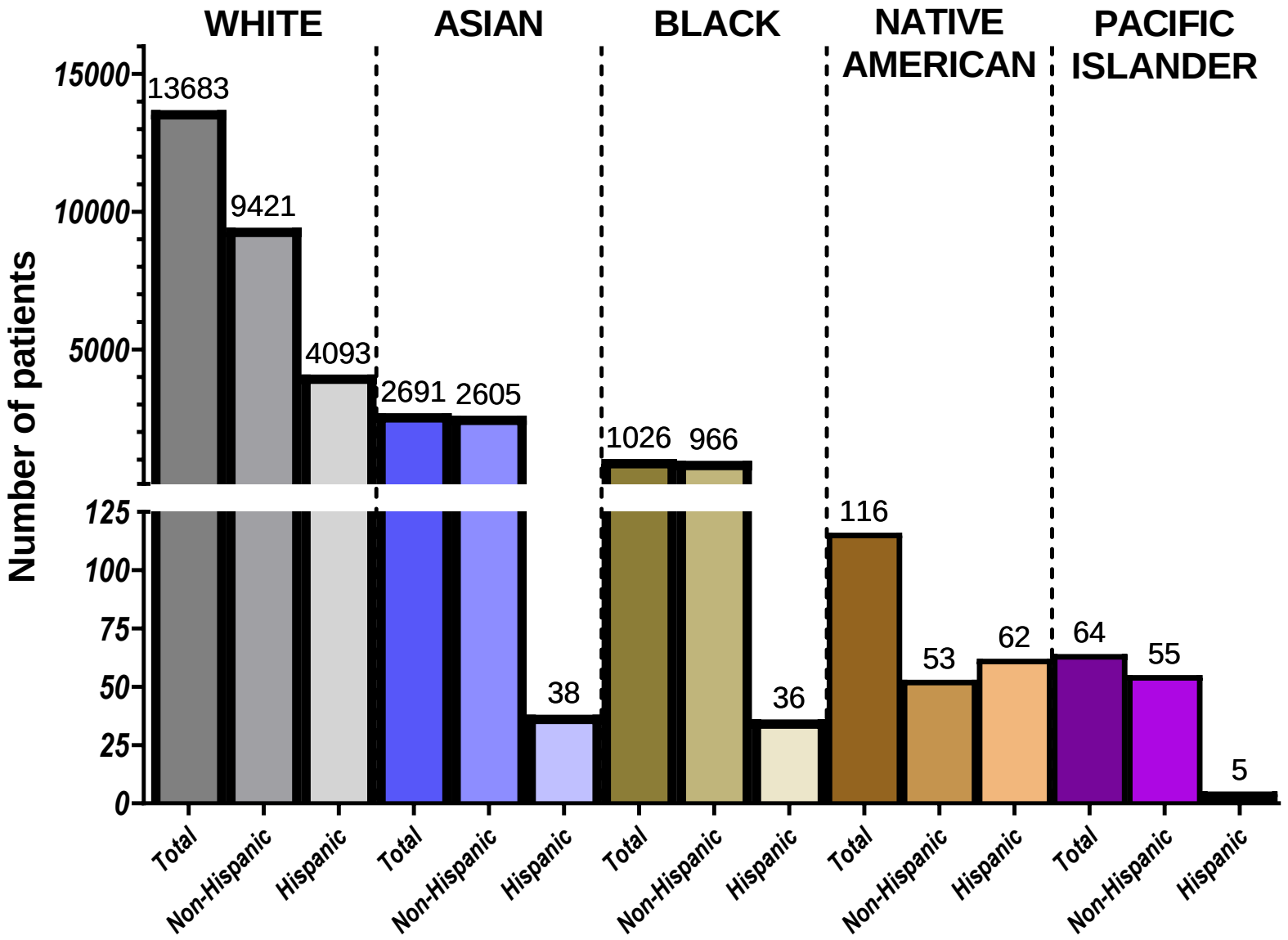
Precision Oncology Tumor Board

- Weekly multidisciplinary precision oncology tumor board
- Systematic review of all germline and somatic results
- Deep dives into challenging cases
- Request for case review



Dr. Kevin McDonnell

Self-Reported Race&Ethnicity/INSPIRE Study

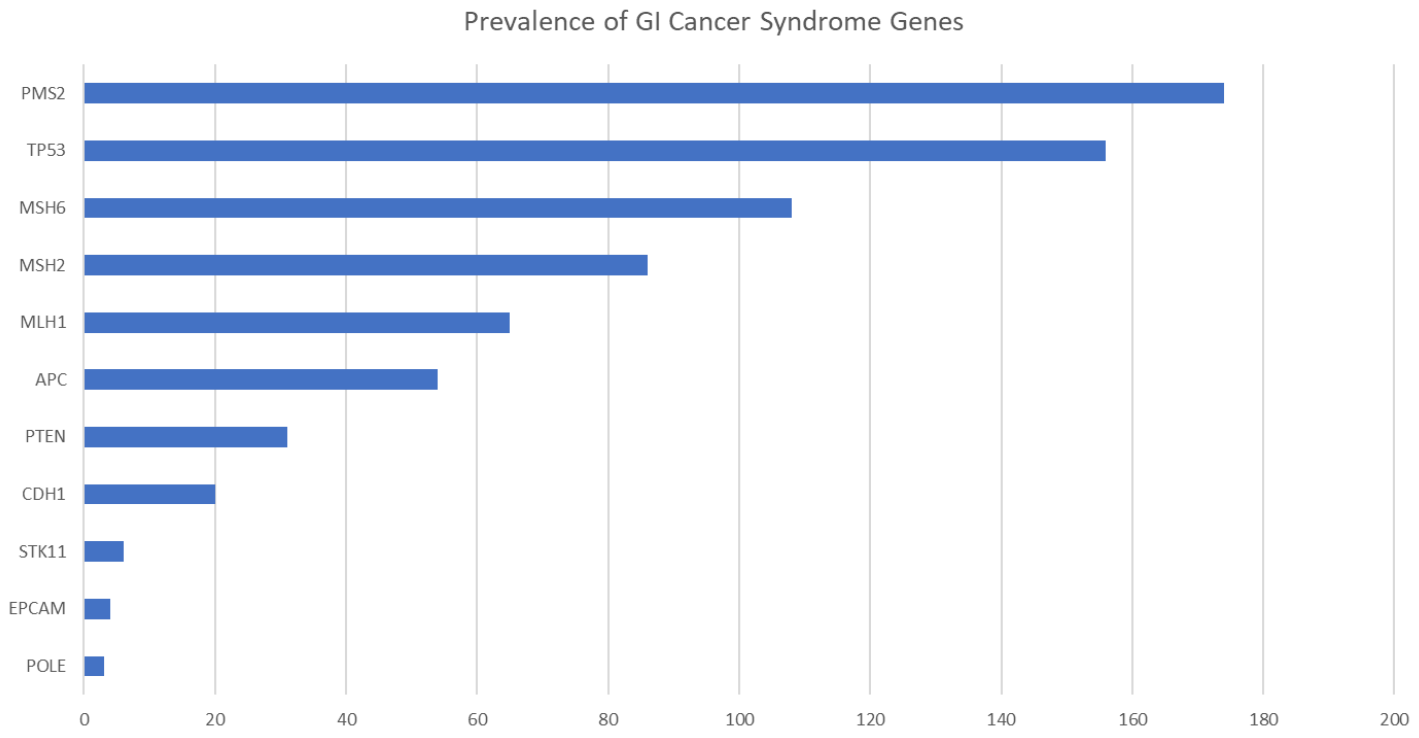


Data is presented in accordance with California Assembly Bills 1195 & 241 towards understanding the cultural diversity of our patient population and sources of potential implicit bias.

Clinical Operations: Germline

- 155 Gene Inherited Cancer Gene Panel
- 59 Gene American College of Medical Genetics (ACMG) Actionable Disorders Panel
- All CAP/CLIA grade with Invitae (2 panels) or Fulgent (1 panel)
- 10-14 day turnaround time (Fulgent), 10-21 day turnaround time (Invitae)
- 99% Opt-in

Prevalence of High-Penetrance GI Cancer Syndromes



Gene	Frequency	Prevalence
PMS2	174	0.0087
TP53	156	0.0078
MSH6	108	0.0054
MSH2	86	0.0043
MLH1	65	0.0032
APC	54	0.0027
PTEN	31	0.0015
CDH1	20	0.0010
STK11	6	0.0003
EPCAM	4	0.0002
POLE	3	0.0001
GI Total	707	0.0353
Lynch	437	0.0218
Total	**20,023**	

Lynch Syndrome identified in 2.2% of unselected patients through universal genetic testing. High penetrance cancer genetic syndromes are common (3.5%) and critical to identify.

Clinical Operations: Somatic

- Whole exome sequencing
- Whole transcriptome sequencing
- Integrated report with clinical trial options
- MSI, TMB, optional PD-L1 IHC
- Turnaround time - 14 days

Genomic Snapshot

- Analytes sequenced: DNA+RNA
- Actionable Targets: 6
- TMB: Low
- MSI: Stable
- Clinical Trials: Yes

TUMOR GENOMIC ALTERATIONS[1]

APC FBXW7 KRAS TP53

GENOMIC TARGETS	FDA-APPROVED DRUGS -for patient's cancer	FDA-APPROVED DRUGS -for another cancer	DRUGS PREDICTED NON-BENEFICIAL	POTENTIAL CLINICAL TRIALS
6	0	0	2	Yes
APC (A415fs)				Yes
APC (S1465fs)				Yes
FBXW7 (Y545C)				Yes
KRAS (G12D)			cetuximab, panitumumab	Yes
TP53 (C176R)				Yes
TP53 (R213Q)				Yes

TUMOR MUTATION BURDEN (TMB)

LOW (2 mut/Mb)	No

MICROSATELLITE STATUS (MSI)

STABLE	No

Study of MRTX1133 in Patients With Advanced Solid Tumors Harboring a KRAS G12D Mutation

ClinicalTrials.gov ID NCT05737706

Sponsor Mirati Therapeutics Inc.

Brief Summary

A Phase 1/2 study of MRTX1133 in solid tumors harboring a KRAS G12D mutation.

Detailed Description

This first-in-human clinical trial will begin with an exploration of MRTX1133 dose and regimen. As potentially viable regimens are identified, Phase 1b expansion cohorts may be implemented to ensure collection of sufficient safety and PK information, and early evidence of clinical activity are available to recommend Phase 2 regimens. In Phase 2, separate cohorts of patients by histological diagnosis and/or baseline characteristics will be evaluated for the clinical activity and efficacy of MRTX1133.

Official Title

A Phase 1/2 Multiple Expansion Cohort Trial of MRTX1133 in Patients With Advanced Solid Tumors Harboring a KRAS G12D Mutation

Conditions

Solid Tumor | Advanced Solid Tumor | Non-small Cell Lung Cancer | Colo-rectal Cancer | Pancreatic Adenocarcinoma

Study Start (Actual)

2023-03-20

Primary Completion (Estimated)

2026-08-30

Study Completion (Estimated)

2026-08-30

Enrollment (Estimated)

386

Study Type

Interventional

Phase

Phase 1
Phase 2

Colorectal Cancer Cases by Microsatellite Status and Stage at Initial Diagnosis

	Stage I	Stage II	Stage III	Stage IV	Stage Unknown	Overall
MSI High (All tumors)	1 (7.7%)	4 (8.3%)	11 (10.4%)	2 (1.5%)	1 (10%)	19 (6.2%)
MSI High (Primary)	0	3	11	2	1	17
MSI High (Non-Primary)	1	1	0	0	0	2
MSS (All tumors)	12 (92.3%)	44 (91.7%)	95 (89.6%)	128 (98.5%)	9 (90%)	288 (93.8%)
MSS (Primary)	11	36	75	94	4	220
MSS (NonPrimary)	1	8	20	34	5	68
Total Patients	13 (4.2%)	48 (15.6%)	106 (34.5%)	130 (42.3%)	10 (3.2%)	307

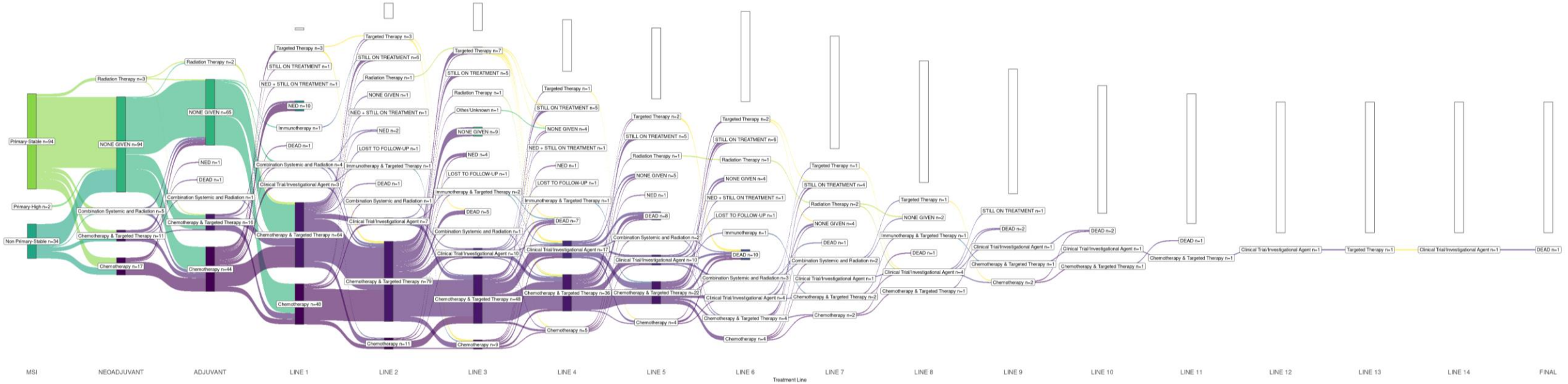
Cases with initial abstraction completed before 01/31/2024.

Treatments (received at any stage) by Stage at Initial Dx

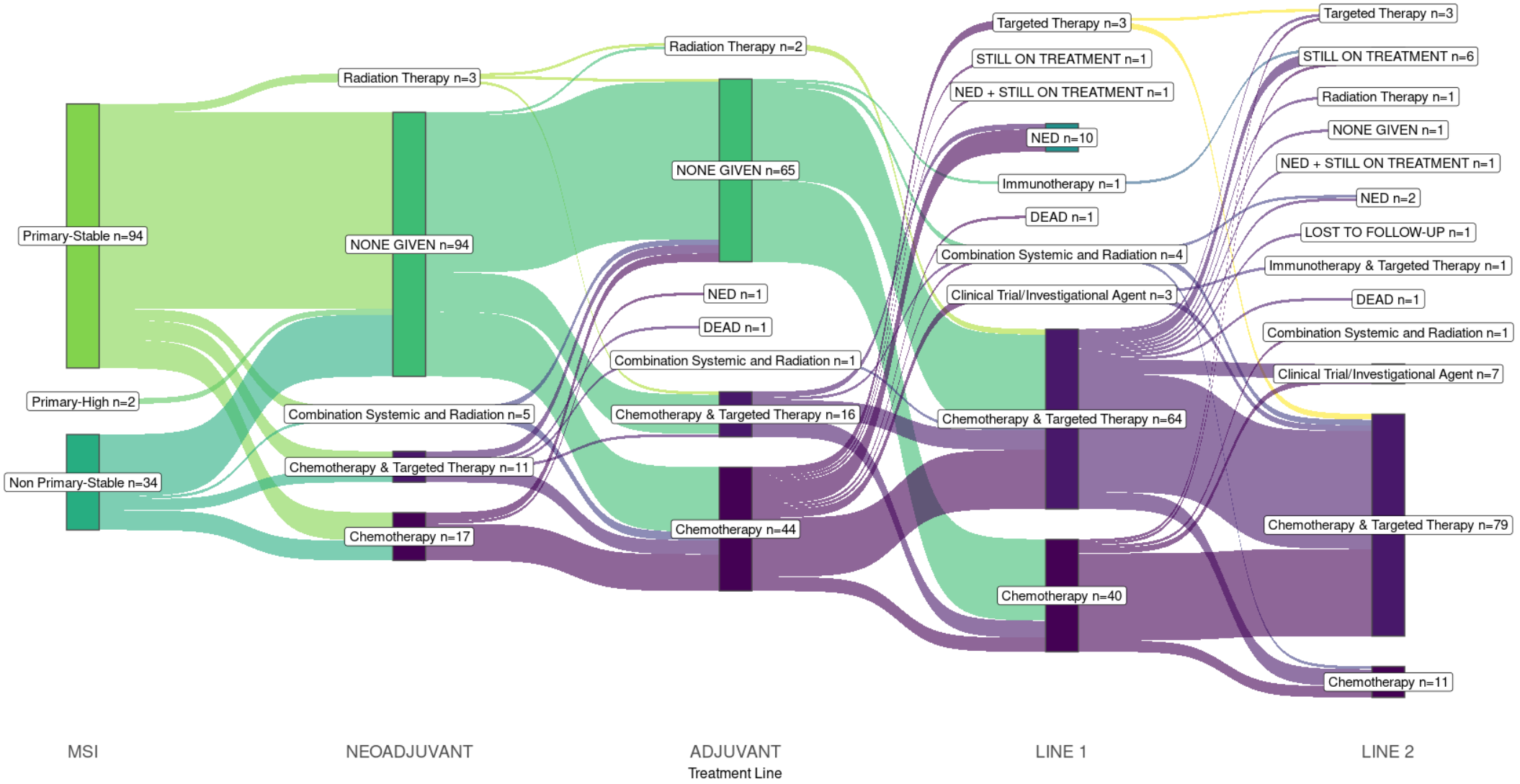
	Stage I	Stage II	Stage III	Stage IV	Stage Unknown	Overall
Number of CRC patients	13	48	106	130	10	307
Prop. CRC patients who received:						
No Systemic Treatment	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)		3 (1%)
Any Systemic Treatment	13 (100%)	47 (97.9%)	106 (100%)	130 (100%)		304 (99%)
Clinical Trial/Investigational Agent	1 (7.7%)	7 (14.6%)	17 (16%)	43 (33.1%)		68 (22.1%)
Immunotherapy	2 (15.4%)	0 (0%)	5 (4.7%)	2 (1.5%)		9 (2.9%)
Targeted Therapy	0 (0%)	5 (10.4%)	11 (10.4%)	17 (13.1%)		34 (11.1%)
Combination Immuno- and Targeted Therapy	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)
Combination Chemo- and Targeted Therapy	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)
Chemo/Chemoradiation Therapy	8 (61.5%)	32 (66.7%)	95 (89.6%)	96 (73.8%)		237 (77.2%)

Sankey Plot showing Treatment Trajectory for Stage IV CRC Patients

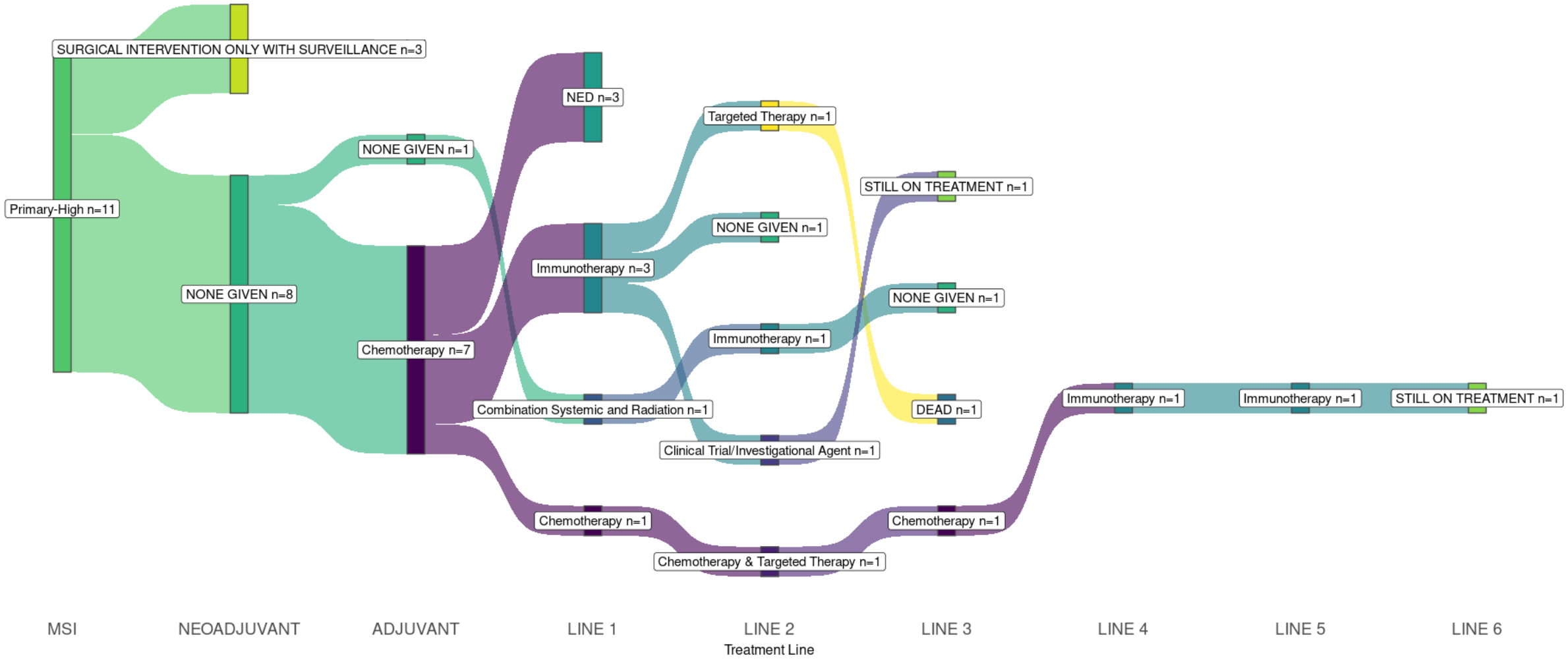
Jenny Lu, BS



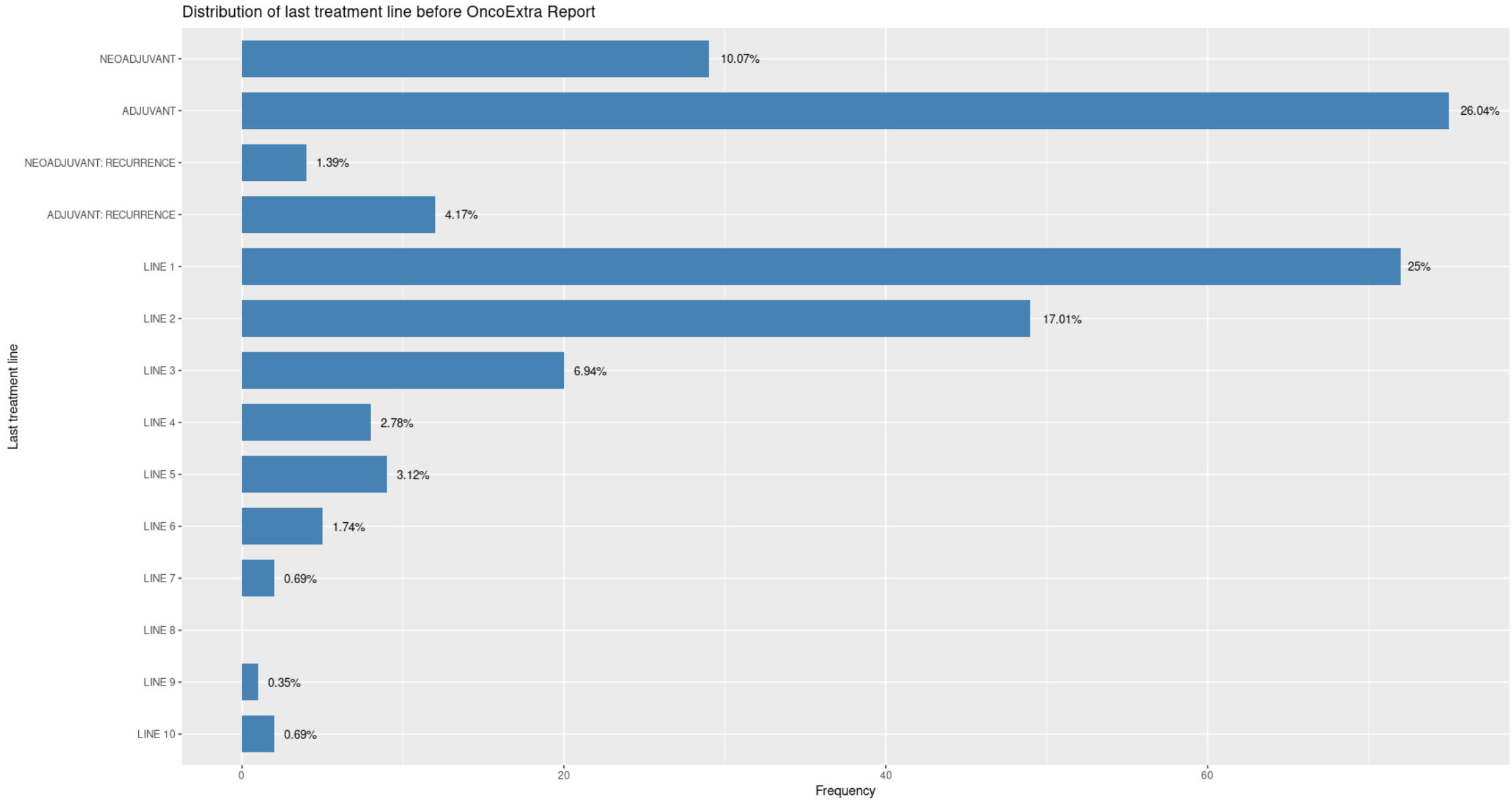
Treatment Trajectory for Stage IV CRC – closer look



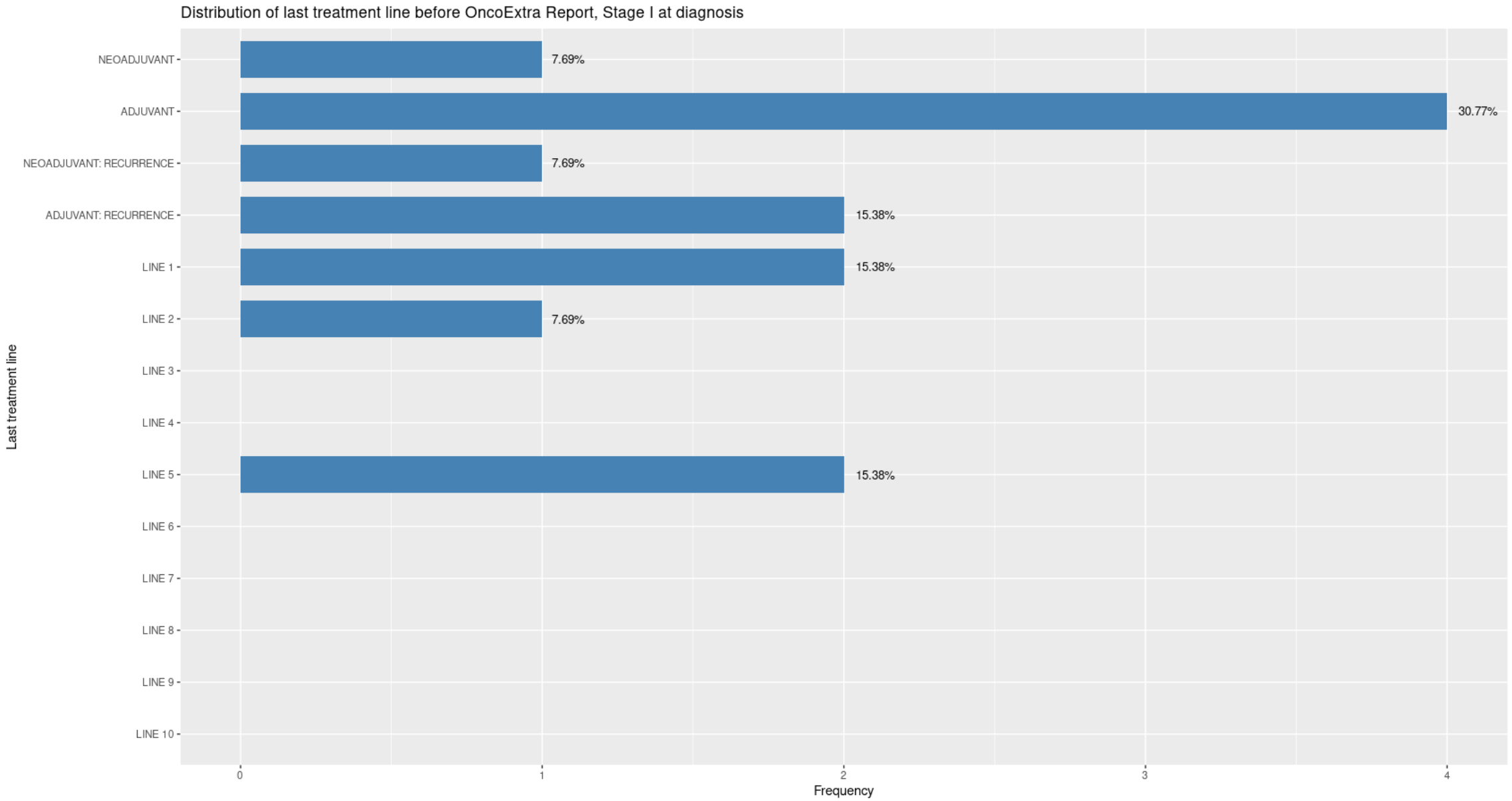
Treatment Trajectory for Stage III MSI-High CRC



Timing of Somatic Genomic Profiling



Timing of Somatic Genomic Profiling – Stage I at Dx



Impact on Clinical Care: Provider Perspectives

"The Precision medicine program has been life-changing for my practice. It provides the very timely genetic testing without insurance barriers or genetic testing criteria barriers. Patients love it and I love it."

Increased access to genomic profiling

- Germline (84%)
- Somatic (79%)

Positive impact on:

- Research at COH (73%)
- Patient & provider satisfaction (>70%)

"The quality, coverage and calls of the data is changing quality of care… COH is now truly practicing precision medicine and improving outcomes for our patients"

Summary

- Multidisciplinary precision medicine brings genetic & genomic analyses to patients for improved outcomes.
- Universal access improves detection of hereditary gastrointestinal cancer syndromes.
- Lynch Syndrome and other GI cancer syndromes are common, under-recognized and actionable.
- Enterprise-wide solutions improve access for diverse patient populations.
- Clinical trajectories of patients are complex, with genomic profiling guiding therapeutic choices.