Lessons From Our Molecular Tumor Board: A Team Approach!

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Precision Medicine Clinical Service Attending

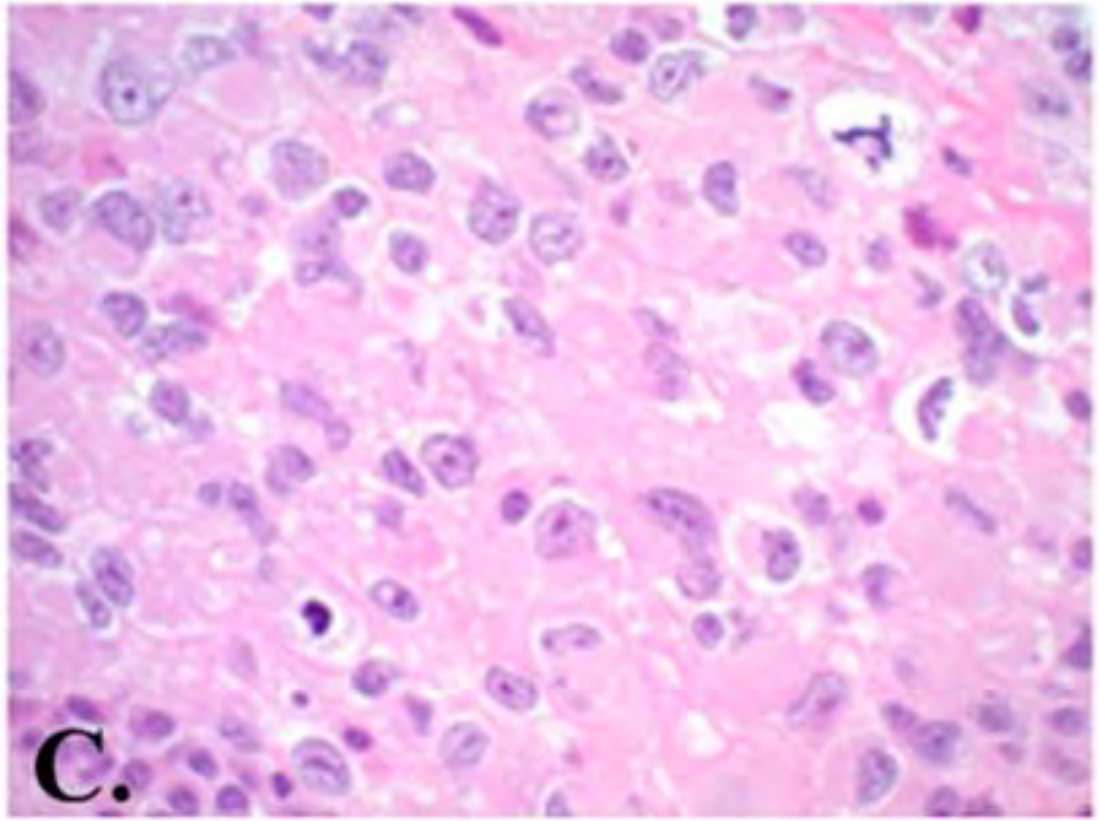
Moffitt Cancer Center, Tampa, FL

The Early Days of Precision Medicine…

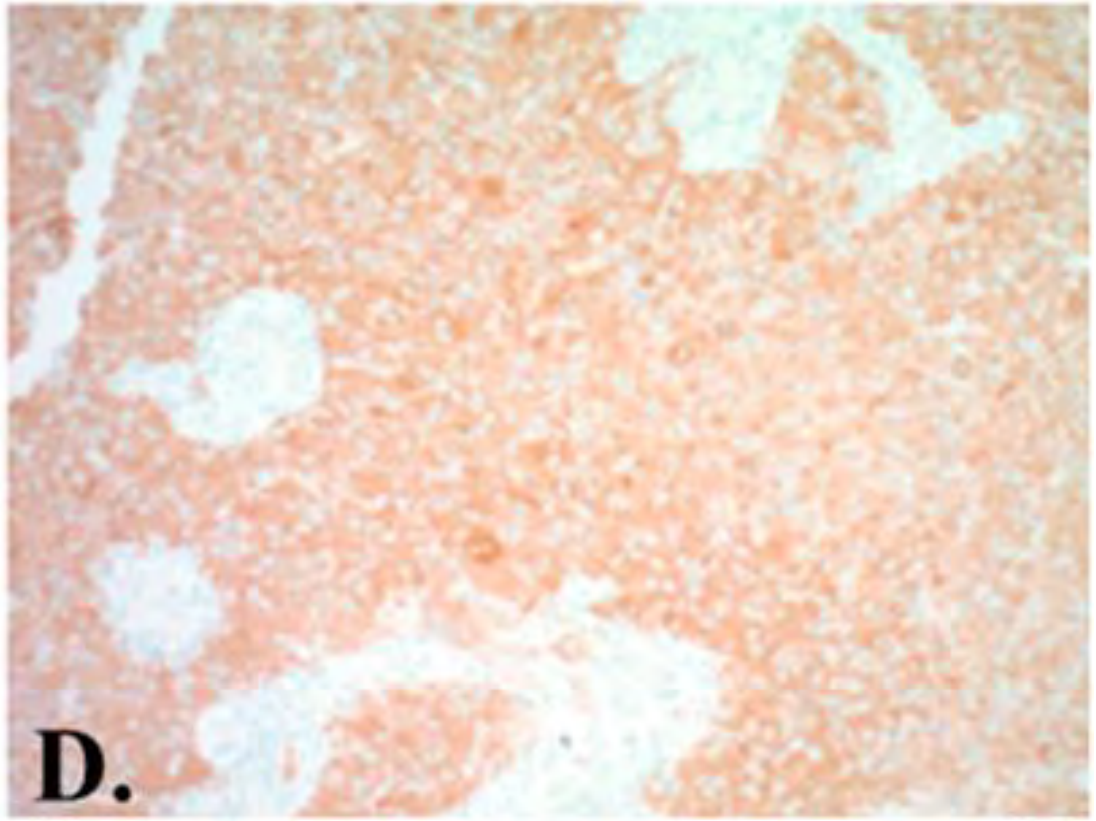
- Ms. K is a 33 yo female who initially presented in 2015 with worsening vision loss in her left eye.
- Brain MRI showed a cystic right parietal mass with peripheral enhancement measuring 5.5 x 4.4 x 5.5 cm.
- She underwent right parietal craniotomy and pathology confirmed:
  - **Epithelioid glioblastoma, IDH-wildtype, WHO grade 4**
  - ATRX retained by IHC
  - Negative for co-deletion of 1p/19q
  - MGMT promoter methylated
  - Positive **BRAF V600E IHC**
  - FoundationOne NGS testing confirmed a **BRAF V600E** mutation

BRAF V600E positive Glioblastoma

Pathology Credit: thank you Dr. Rob Macaulay!



Mitotically active atypical epithelioid cells (H&E x 400)

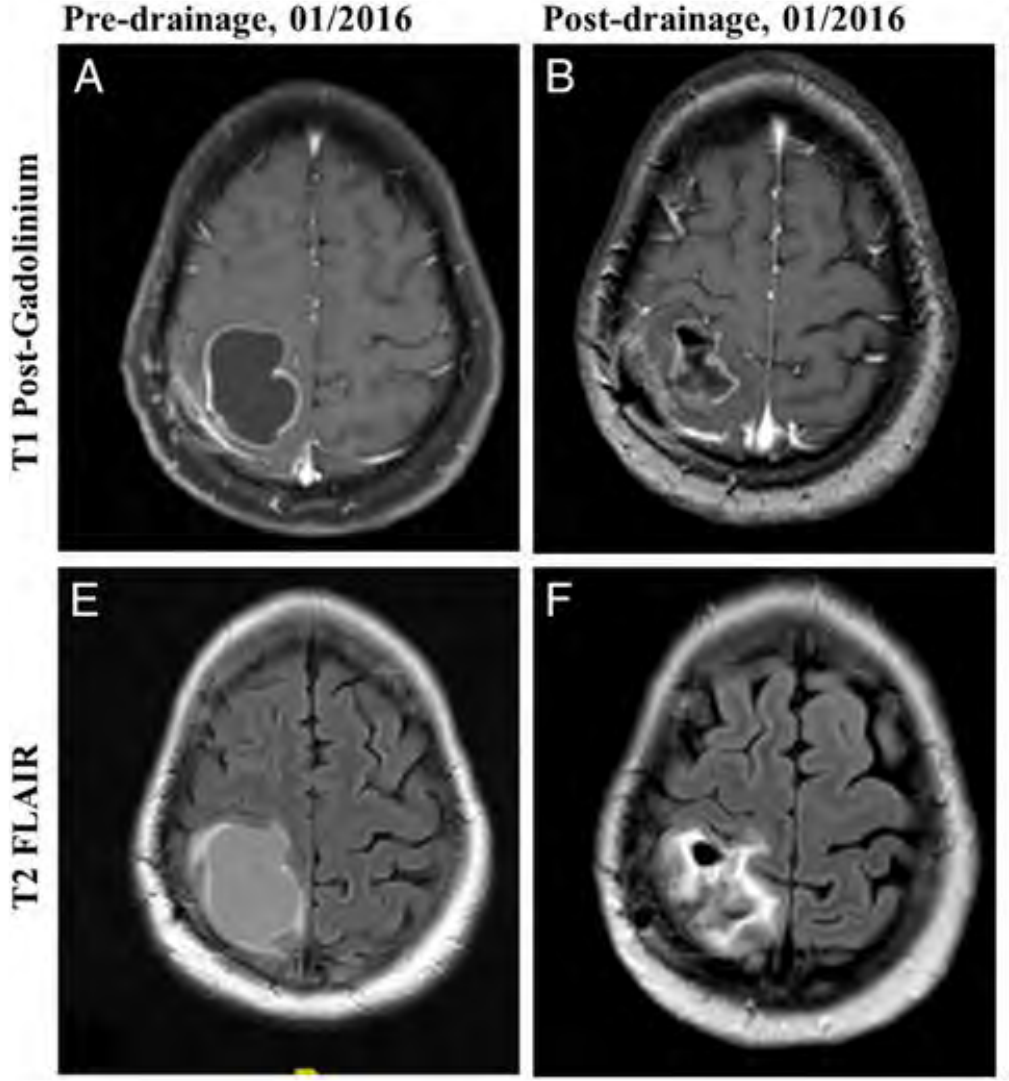


Strong BRAF V600E expression(x 200)

Fusco MJ, Pina Y, et al. Cancer Control. 2021;28:1-10

BRAF V600E positive Glioblastoma

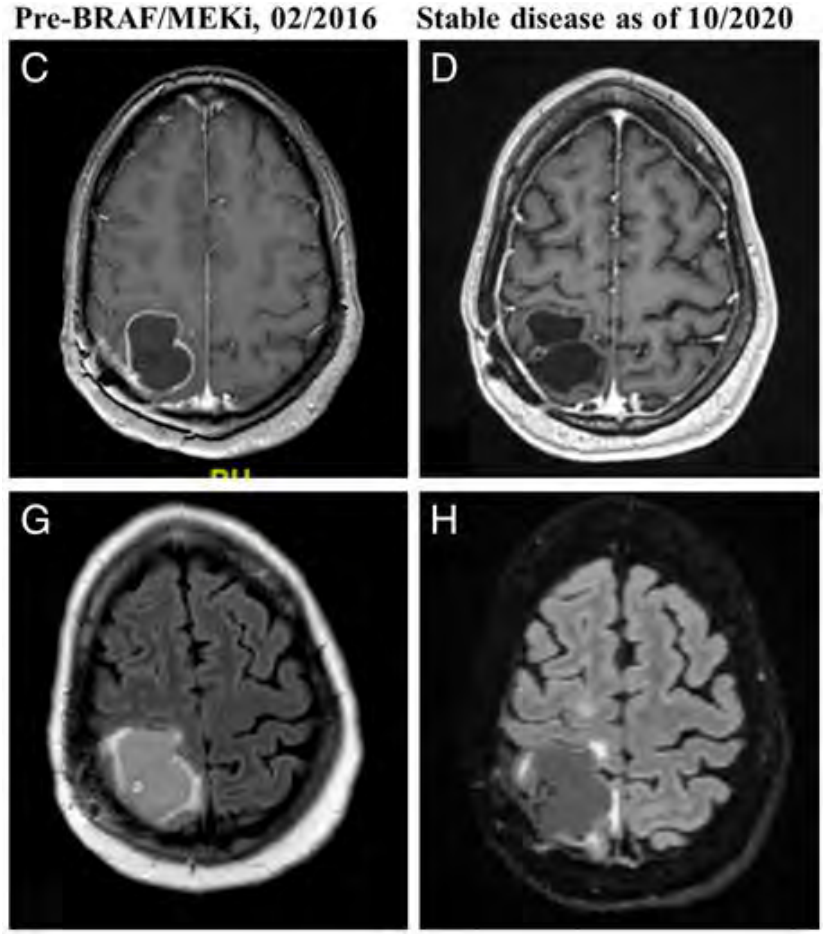
- She was treated with standard therapy that included concurrent radiation and temozolomide x 6 weeks.
- Shortly after, she developed a symptomatic increase in the size of the cystic region and underwent drainage x 2
- She then started standard temozolomide maintenance but progressed after 2 cycles



Fusco MJ, Pina Y, et al. Cancer Control. 2021;28:1-10

BRAF V600E positive Glioblastoma?

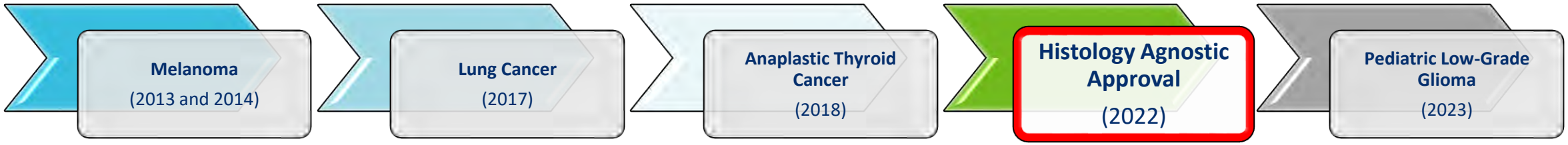
- She was started on dabrafenib and trametinib (BRAF + MEK combination) in 3/2016
- Dabrafenib and trametinib received FDA approval for most BRAF V600E mutated solid tumors 7/21/2022
- Recurrence 11/2022 with re-resection followed by PF-07284890 from 1/2023 to 6/2023
- Recurrence 6/2023 and treated with radiation followed by encorafenib and binimetinib started 4/2024 to present with good response
- **Subsequent methylation testing at the NIH suggested an integrated diagnosis of pleomorphic xanthoastrocytoma, WHO grade 3**



Fusco MJ, Pina Y, et al. Cancer Control. 2021;28:1-10

Establishing Clinical Evidence

- **Translation of Next Generation Sequencing results depends on the availability of clinical evidence!**
- Need to determine the clinical utility of diagnostic tests and evaluate the evidence supporting the clinical efficacy of the targeted agent
  - Historically, clinical trial data is used to change therapy and make treatment recommendations
- Evolution of Precision Medicine trials
  - Her2, BCR-ABL, and BRAF occurred in large subsets of the population
  - Enabled enrollment and completion of large scale, prospective studies
  - Demonstrated clinical utility of the diagnostic marker (i.e. BRAF V600E) and companion diagnostic tests as well as clinical efficacy of targeted drugs
  - Dabrafenib and Trametinib FDA approval example:



Moscow JA, et al. Nat Rev Clin Oncol. 2018;15:183-192

Current Tissue Agnostic Approval

- DNA Mismatch Repair Deficiency (dMMR) and Microsatellite Instability (MSI)
  - Pembrolizumab
  - Dostarlimab-gxly
- Tumor Mutation Burden (TMB) ≥ 10 mutations/megabase (Mb)
  - Pembrolizumab
- BRAF V600E activating mutations (except for colorectal cancer)
  - Dabrafenib and trametinib
- Her2 IHC 3+ positive solid tumors
  - Trastuzumab deruxtecan
- NTRK1-3 activating fusions
  - Larotrectinib
  - Entrectinib
  - Repotrectinib
- RET fusion positive solid tumors
  - Selpercatinib

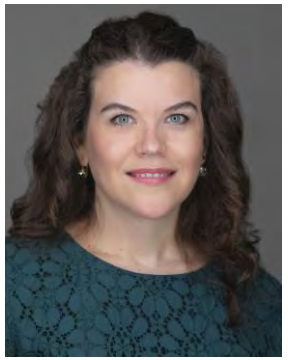
Precision Medicine Trials

- In general, precision medicine trials have shown benefits
- Analysis of 570 trials (32,149 patients) enrolled on phase II novel therapy trials
  - Response rates, PFS and OS compared in targeted therapy arms using a precision medicine strategy vs. those that did not
  - Multivariate analysis showed treatment allocated by personalized approach consistently and independently correlated with:
    - Higher response rate: 31% vs. 10.5% ($p<0.0001$)
    - Longer median PFS: 5.9 vs. 2.7 months ($p< 0.0001$)
    - Longer median OS: 13.7 vs. 8.9 months ($p=0.0001$)

Schwaederle M, et al. J Clin Oncol. 2015;33:3817-25

Precision Medicine Clinical Service

Precision Med Associates



Dr. Juliana Balliu

Paige Parkinson, MPH

Faculty

Dr. Kevin Hicks
- Thoracic
- Pancreatic
- Germline PGx
- Implementation

Dr. Teresa Ho
- Pancreatic
- GI
- Breast
- Germline PGx

Dr. Todd Knepper
- Hematology
- Cutaneous

Dr. Christine Walko
- Genitourinary
- Gynecologic
- Head & Neck
- Neuro-oncology
- Sarcoma
- GI

Our mission is to seamlessly translate biomarker testing throughout the patient journey to inform treatment options including targeted therapies, clinical trials eligibility, and patient safety risk mitigation

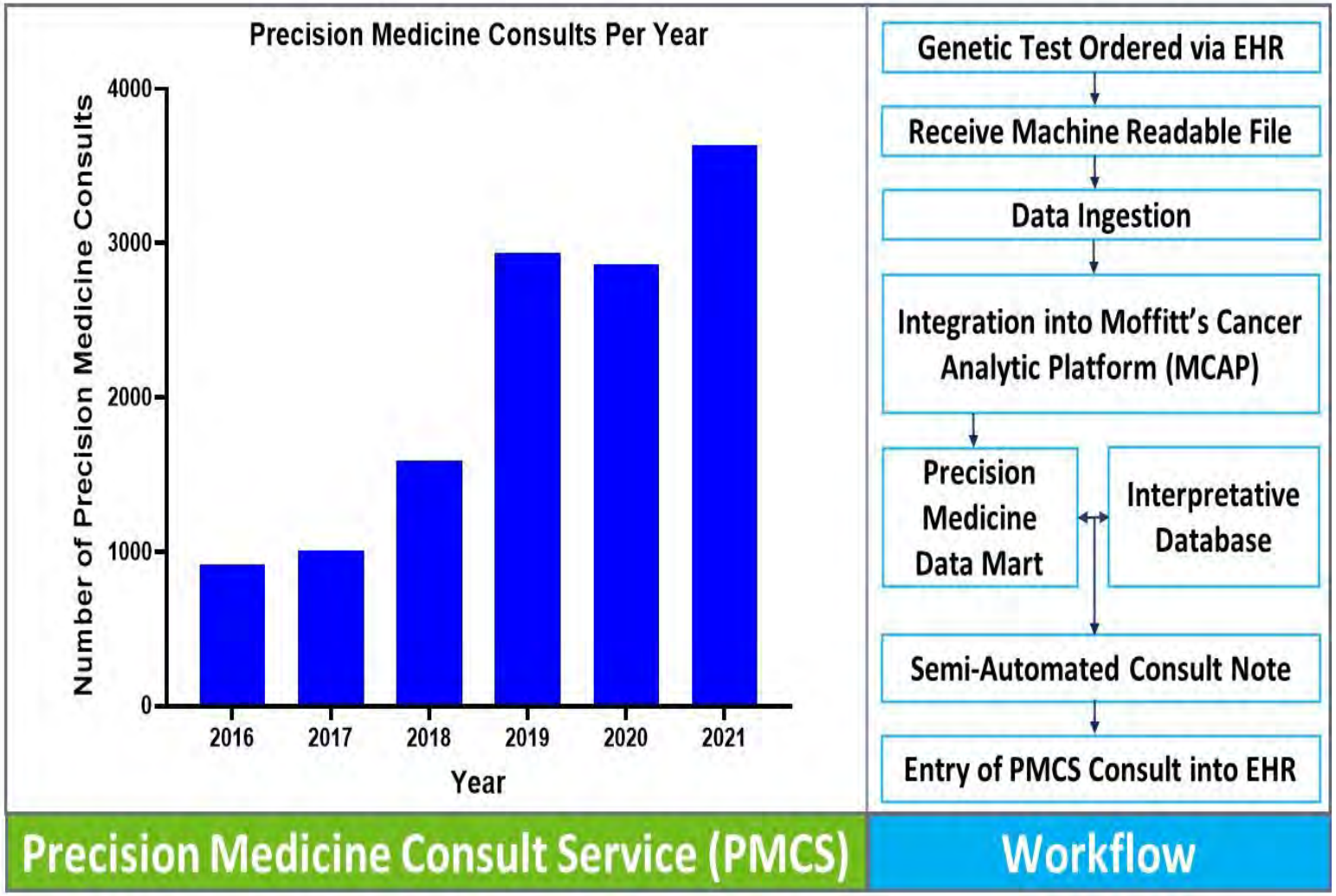
Precision Medicine Clinical Service at Moffitt

- Application of molecular biomarkers to oncology patient care for **therapeutic decision making** and **clinical trial matching** is becoming increasingly complex
  - Somatic Next generation sequencing of hundreds or thousands of genes
  - Somatic RNA for fusion events and gene expression
  - Immunohistochemistry including PD-L1, HER2, MMR
  - Other biomarkers including TMB, LOH, MSI
  - Pharmacogenetics/germline testing

- There are gaps and barriers to integrating molecular biomarkers into patient care. Precision Medicine can help identify barriers and bridge gaps
  - Perform interpretative consults for targeted therapy and trials
  - Participate on/Chair Moffitt Molecular Tumor Boards
  - Lead the implementation of Precision Medicine into the EHR

Precision Medicine Clinical Workflow

Collaboration with Health Informatics with efforts led by Phil Reisman and Jordan Creed and Precision Medicine led by Dr. J Kevin Hicks

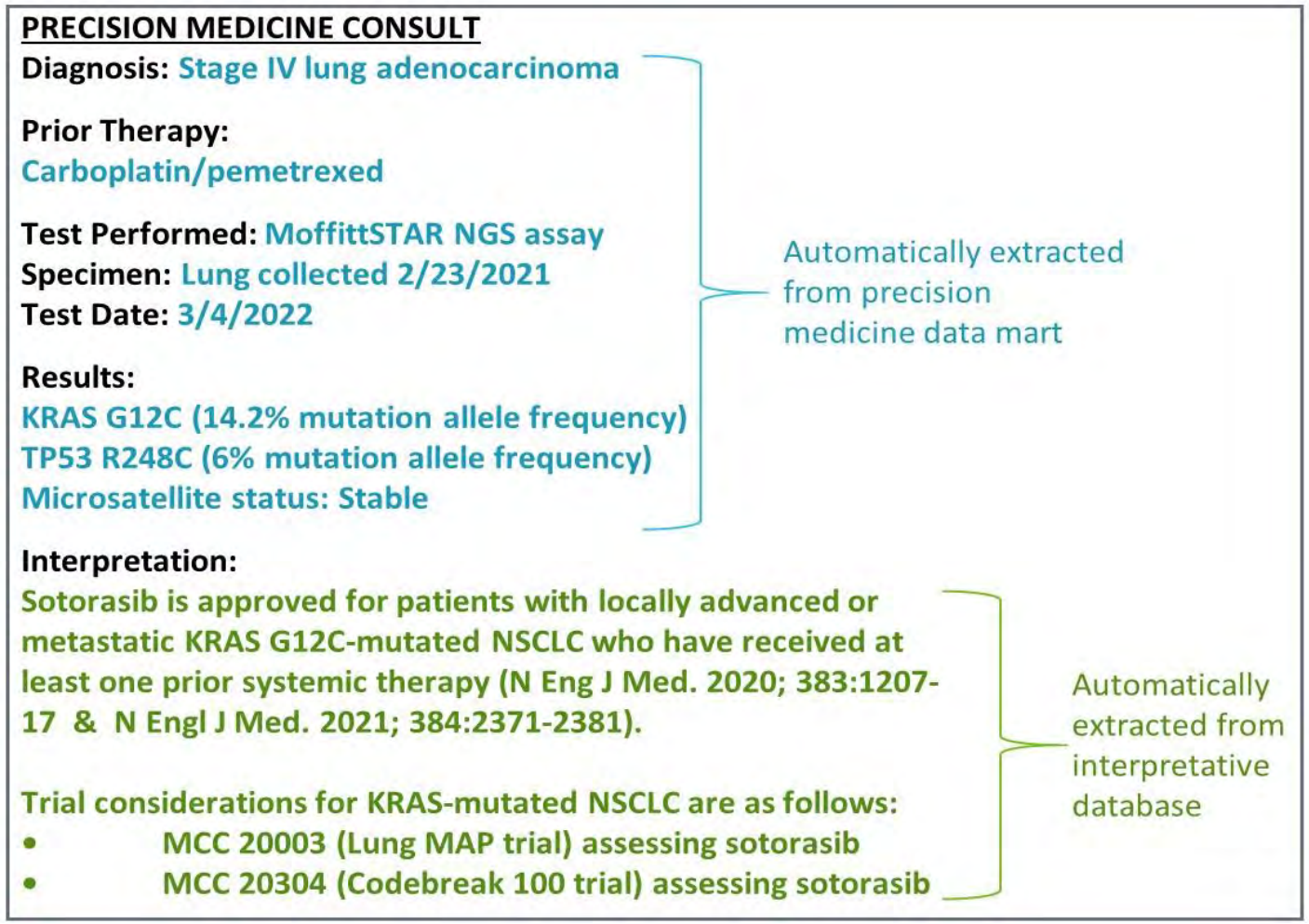


Precision Medicine Data Mart

- Currently includes >23,000 test results from more than 18,700 unique patients
- Drives our clinical workflow
- Provides the ability to extract data for:
  - Retrospective, IRB-approved clinical trials
  - Quality improvement projects
  - Identification of patients for biomarker-driven clinical trials
  - Identification of patients for new FDA-approved biomarker-targeted therapies

Precision Medicine Clinical Consult

Semi-automated PM consult notes can efficiently bridge gaps in knowledge about availability for targeted therapies and clinical trials



Precision Medicine Essential Partners

Partner	Who?	How we work together
Genetics	• Genetic counsellors • Medical geneticists	• Informal questions • Direct referrals
Tumor boards	• Clinical team	• Discussion of patients/information gathering • Discussion of genomic testing results
Pathology	• Pathologists	• Sample collection • Genomic sequencing
Patient care team	• Physician • Nurses • NPs/PAs • Pharmacists	• Understanding the goals of care • Prescription and procurement of therapy
Information Technology	• IT specialists	• Electronic health record
Bioinformatics and Medical Informatics	• Bioinformaticians	• Creation and development of clinical database
Clinical Trials	• Clinical trial coordinators • Primary investigators	• Identify patients for targeted therapy clinical trials • Identify clinical trial needs based on patient trends

Looking Forward…

- Institution needs, technology and patient care standards change over time
  - There is constant need to re-evaluate and innovate based on changing environment
- One Molecular Tumor Board model may not be the best fit everywhere
  - Tumor histology agnostic MTB
  - Cancer Specific (ie. Lung cancer MTB)
  - Education focused MTB
- Education and communication helps us to continue to evolve!

The standard of care in oncology is PROGRESS!

Questions and Discussion

Extra slides if time/needed

MOFFITT CANCER CENTER

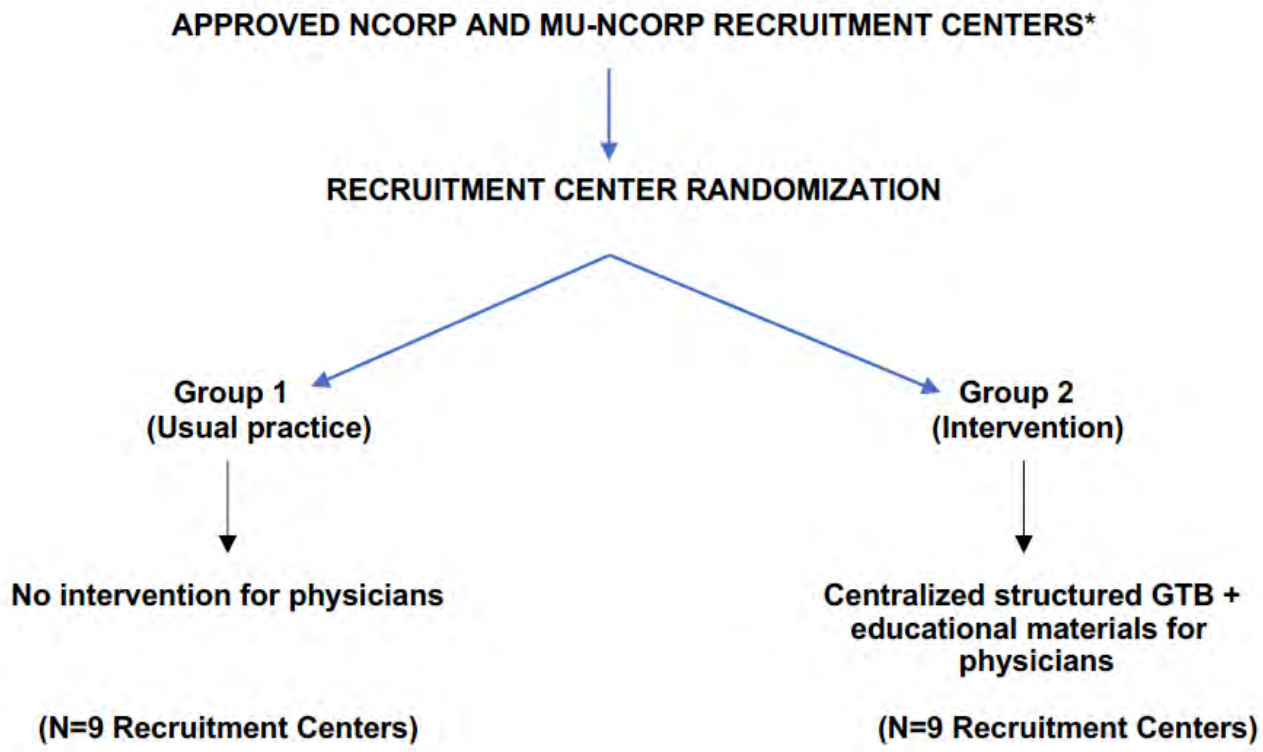
SWOG S2108CD (NCT #05455606)

A Cluster Randomized Trial Comparing an Educationally Enhanced Genomic Tumor Board (EGTB) Intervention to Usual Practice to Increase Evidence-Based Genome-Informed Therapy

- Study Chairs:
  - Jens Rueter, MD (The Jackson Laboratory)
  - Meghna S. Trivedi, MD, MS (Columbia University)
  - Banu E. Symington, MD (Rural Medical Oncology, Sweetwater Regional Cancer Center)
  - Douglas Reding, MD (NCORP Representative)
  - Dawn L. Herschman, MS, MS (Columbia University)
- **Precision Medicine Variant Experts:**
  - **Todd Knepper, PharmD**
  - **Christine Walko, PharmD, BCOP**

We hypothesize that a GTB that offers a combination of **expert opinion**, a **guideline-enabled summary of the available evidence**, and **supporting educational material** (the educational GTB intervention) will eliminate both under- and over-interpretation of genomic information and yield an increase in evidence-based genome-informed therapy.

SWOG S2108CD: Study Design



Sites in MN, IL, AZ, KY, HI, MO and NC

Sites in IA, MN, ND, WI, GA, MO, KS, MI, ID, PA and Puerto Rico

- NCORP: NCI Community Oncology Research Program
- A Recruitment Center is defined as an outpatient clinic, or group of clinics, belonging to the same NCORP or MU-NCORP that will be contributing physician and patient participants to the study
- **Currently just opened to accrual**: anticipate first EGTB in late November/early December 2022

SWOG S2108CD: Objectives

- Primary Objective
  - To determine whether an EGTB intervention compared to usual practice increases the proportion of patients who receive evidence-based genome-informed therapy within 6 months after registration to the study
- Secondary Objectives
  - To compare physician genomic confidence and physician experience with genomic tumor testing (GTT) between arms at baseline and end of study.
  - To compare clinical outcomes between arms by assessing patient survival and time to treatment discontinuation
  - To compare physician assessment of evidence-based genome-informed therapy to the central study team determination of evidence-based genome-informed therapy, both overall and separately by arm
- Implementation Objectives