Mastering Comprehensive GI Cancer Care: APP & Nursing Workshop

Precision Oncology Primer - Cancer Treatments Tailored for Personalized Care

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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:

- *Ensure all language barriers are addressed when seeing informed consent for genomic/genetic testing*
- *Underrepresentation of certain ethnic or racial groups in genetic research and databases can lead to less accurate and applicable results for individuals from underrepresented background. This could lead to disparities in effectiveness of testing and treatment*

- Patient Stories
- What is Precision Oncology Medicine
  - Why it's important?
  - Testing
  - Treatment
- Nursing Considerations & Implications

Patient Story – Colorectal Cancer

- Diagnosed with stage IV colon cancer at 28 years old over ten years ago (negative for Lynch Syndrome)
- Treated at various academic and community hospital centers where a 50 gene genomic panel was performed three years after diagnosis with no actionable mutations found. Received standard of care and treatments through clinical trial
- Came to City of Hope in three years after diagnosis seeking 2nd opinion after a rechallenge with oral drug (regorafenib) was only treatment offered
- 324 genomic panel completed and found ERBB mutation (confirmed later with IHC as HER expressing tumor)
- Went on to receive several off label targeted therapies for 3 ½ years – HER2 directed drugs that were approved for breast cancer (trastuzumab, ado trastuzumab emtansine, lapatinib, & fam-trastuzumab deruxtecan-nxki)

Repeat Genomic Testing May Be Justified For Patients Initially Sequenced With Limited Genomic Test Panels

Kopetz S, Mills Shaw KR, Lee JJ, et al. Use of a Targeted Exome Next-Generation Sequencing Panel Offers Therapeutic Opportunity and Clinical Benefit in a Subset of Patients With Advanced Cancers. *JCO Precis Oncol*. 2019;3:PO.18.00213. Published 2019 Mar 8. doi:10.1200/PO.18.00213

Patient Story – Gastric Cancer

- 66-year-old female
- Diagnosed with HER2 negative stage IV gastric cancer in 2016
- Presented to City of Hope soon after for 2nd opinion
- Molecular testing completed in 2016 found BRCA1 mutation
- Genetic testing and counseling – BRCA germline mutation confirmed
- Treated with standard of care chemotherapy until progression in late 2017 when she began immunotherapy through clinical trial based on BRCA1 mutation and continued for 2 years until progression
- Offered chemotherapy but refused due to side effects
- Began treatment with PARP inhibitor (Olaparib) in early 2019
- Continues treatment to this day

Power of Precision Medicine

What is Precision Oncology Medicine?

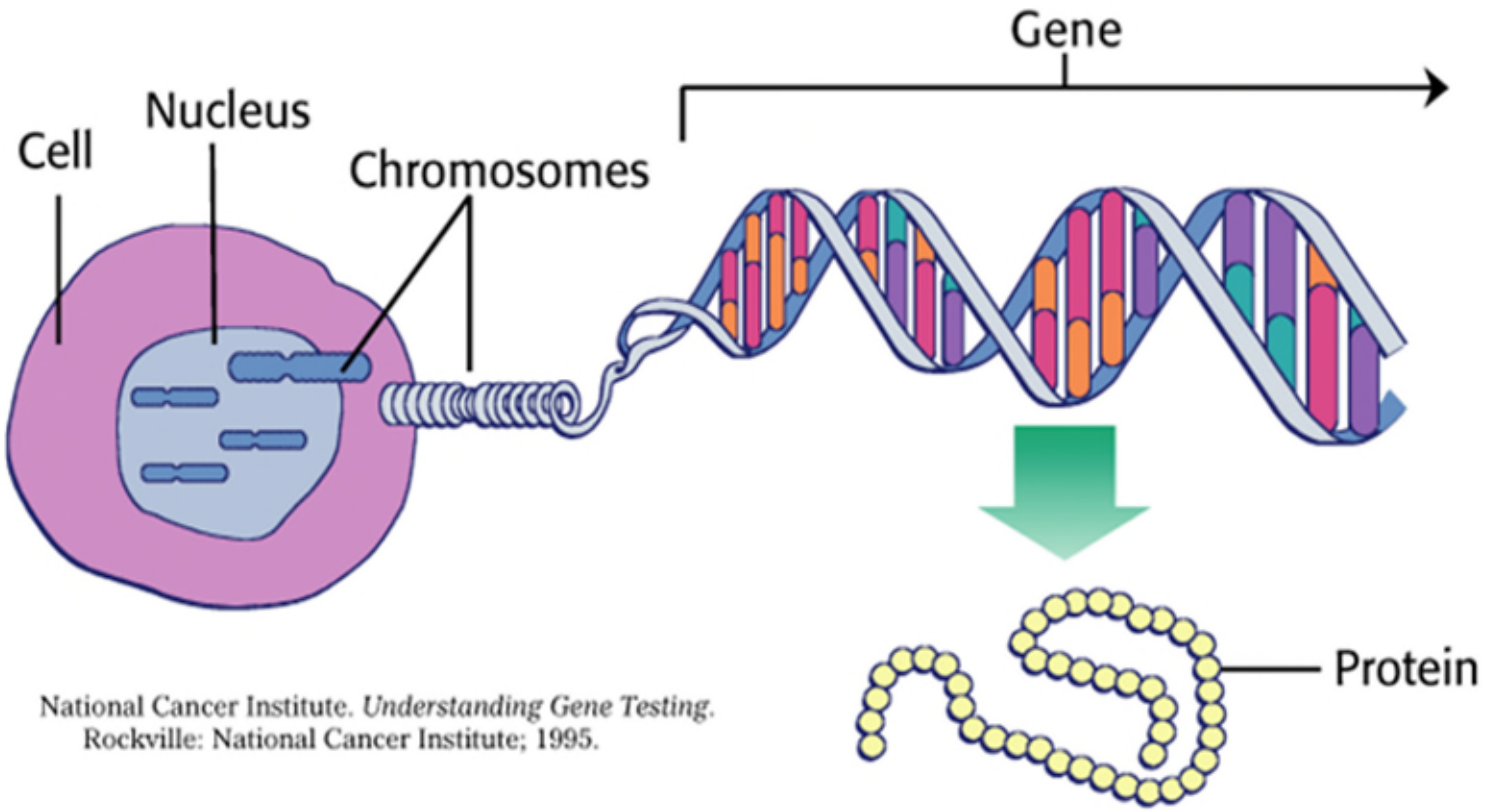
Precision Oncology Medicine 101

Precision Oncology 101

- Cancer is a Genetic Disease
- Why Precision Oncology is so Important
- Testing
- Treatment

Cancer is a Genetic Disease

Cancer is a Genetic Disease



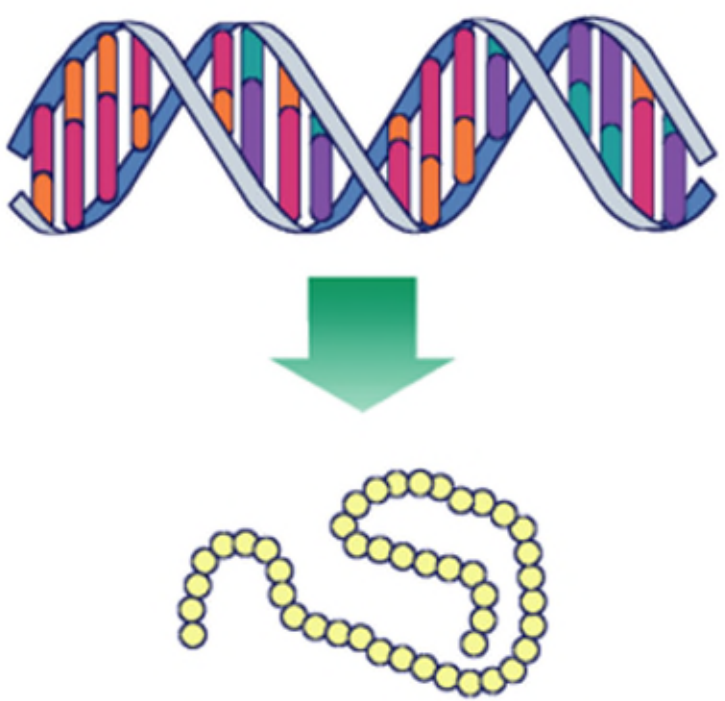
National Cancer Institute. *Understanding Gene Testing*. Rockville: National Cancer Institute; 1995.

A mutation is a change in the normal base pair sequence

The term “mutation” is commonly used to define DNA sequence changes that alter protein function

GENE MUTATIONS ARE CAUSED BY:

random events, viruses, UV rays, chemicals, or inherited from our parent



Functional Protein – normal cell growth and replication

Non-Functional or Missing Protein – abnormal cell growth and replication

Cancer is a Genetic Disease

Genes Responsible for Cell Growth

- Oncogenes – mutation causes accelerator to be applied excessively leading to uncontrolled cell replication

- Tumor Suppressor Genes – mutation causes the brakes to not work leading to uncontrolled cell replication

- DNA Repair Genes – mutation causes normal repairs to not happen leading to uncontrolled cell replication

Why Precision Oncology Medicine is so Important

What is Precision Oncology?

- Innovative approach
- Molecular testing
- Identify mutations (inherited and acquired)
- Targeted therapy treatment and management based on these tests results

Precision Oncology Medicine

Right Drug for the Right Patient at the Right Time

Precision Medicine Treatments

Pre-Precision Oncology

Systemic Cytotoxic (Chemotherapy) Agents

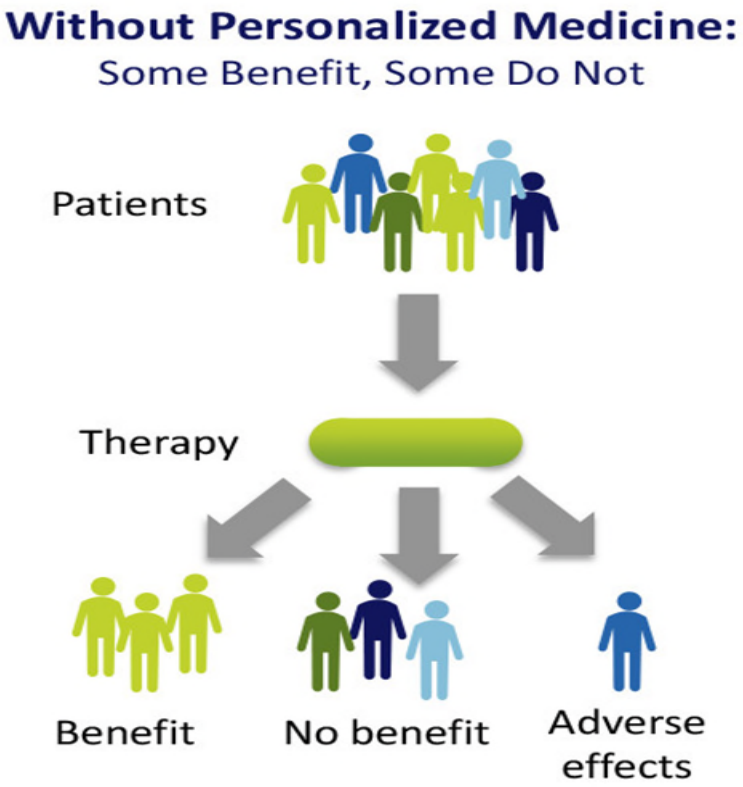
- affects rapidly dividing cells
- treatment based on cancer type (location) and stage
- harm to healthy cells leading to severe side effects
- substantial toxicity leading to early termination of treatment or missing doses

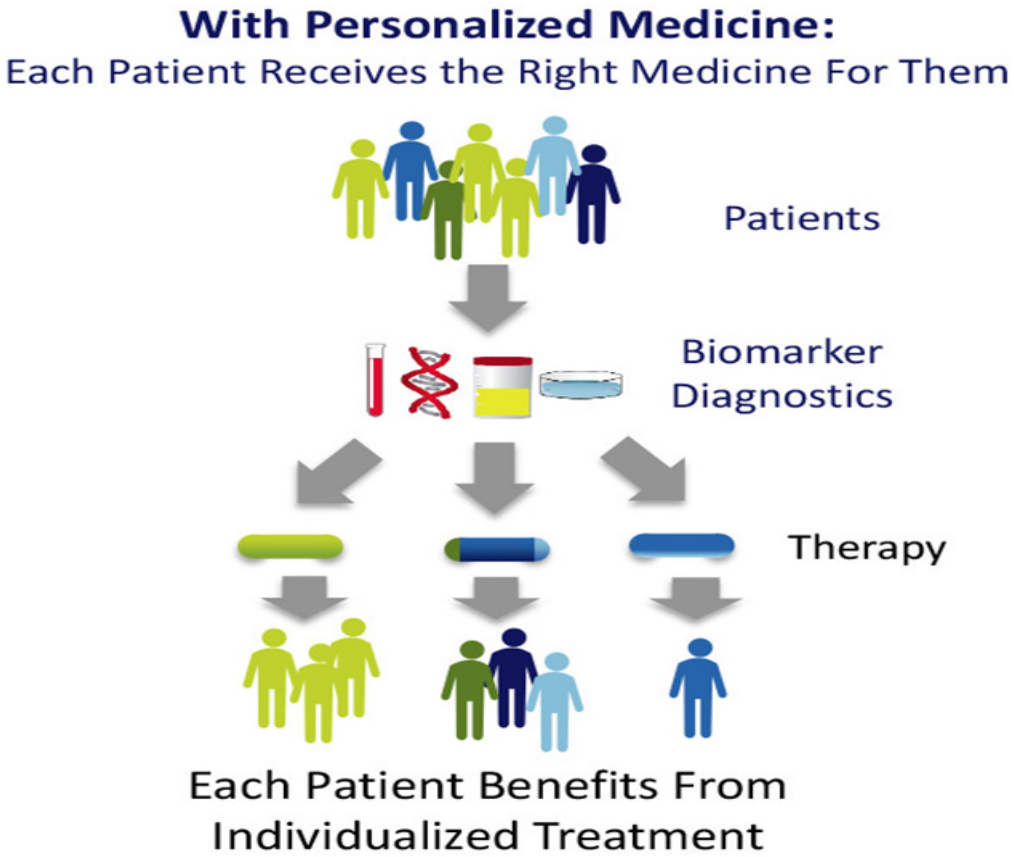
Post-Precision Oncology

Targeted Therapies & Immunotherapy

- selective killing of cells
- treatment based on mutation driving cancer growth
- less harm to normal cells which can mean fewer side effects

Precision Oncology Medicine Benefits





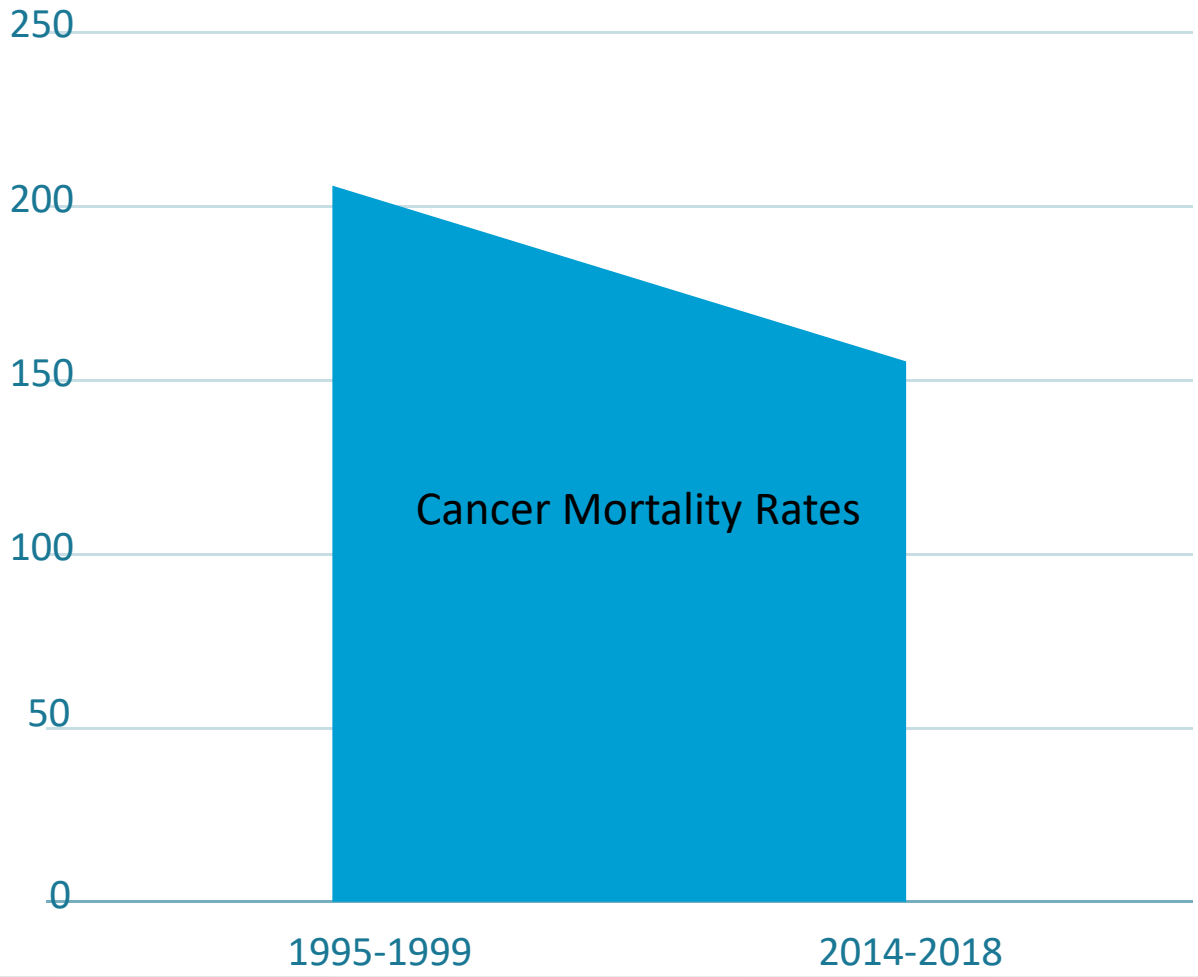
Why Precision Medicine for Patients with Cancer?

- Improve Clinical Outcomes
  - 2020 study found that patients with advanced cancer who received precision medicine treatments based on recommendations from molecular tumor boards were more likely to survive or have longer periods without their disease progressing than those who received standard therapies
- Improve Treatment Efficiency
  - Rule out interventions that are not effective for a given patient
- Patient Access and Options
  - Additional treatment strategies through clinical trials that might not otherwise been considered

Kato S, Kim KH, Lim HJ, et al. Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy. *Nature Communications*. 2020;11(1):4965.

Cancer Mortality Rates Have Dropped

- Cancer mortality rates dropped from 206 to 155.5 per 100,000
- 2016 to 2017 - largest single year drop in mortality 2.2%
- Rapid declines in lung cancer mortality attributed to immunotherapy and other targeted therapies

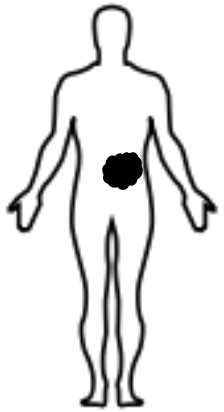


National Cancer Institute. Common Cancer Sites - Cancer Stat Facts. SEER. Published 2018.

Precision Oncology Testing

Somatic vs Germline Mutations

Somatic (tumor) Mutations
Acquired

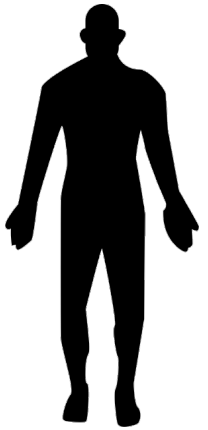


Present in the tumor but not the rest of the body

NOT inherited from parents and NOT passed on to children

Does not increase risk of other cancers but may impact cancer treatment

Germline (genetic) Mutations
Inherited



Present in all the cells that make up the body

Usually inherited from parents and can be passed on to children

Increase risk for cancer and impact cancer screening or treatment

Precision Oncology Testing

- Testing Methodology
  - RNA and/or DNA Sequencing (Next Generation Sequencing/NGS)
    - Hot Spot
    - Comprehensive Genomic Profiling
    - Whole Exome
    - Whole Genome
    - Cell Free DNA (cfDNA) – "Liquid Biopsy"
  - Immunohistochemistry (IHC)
  - Fluorescence in situ hybridization (FISH)

Precision Oncology Testing

- Testing (somatic or germline)
  - Biomarker Testing
    - Susceptibly - Germline BRCA
    - Diagnostic - HER2 expression
    - Monitoring - ctDNA
    - Prognostic - Recurrence probability
    - Predictive - Somatic or Germline BRCA
    - Pharmacodynamic – UGT1A1 genotyping

Genomic Alterations in GI Cancers

- Colorectal Cancer:
  - RAS (KRAS, NRAS) mutations are associated with poor clinical outcomes in CRC[1]
  - Approximately 5% of metastatic CRC cases have MSI or dMMR[2]
- Gallbladder and Biliary Tract Cancer
  - Recent approvals for targeted therapies for fusions and IDH alterations
    - FGFR fusions occur in 10-15% of intrahepatic cholangiocarcinoma cases[3,4]
    - IDH1 mutations observed in 9-13% of cholangiocarcinoma cases[5]
- Pancreatic Cancer
  - 12-25% of pancreatic cancer cases harbor actionable mutations[6]

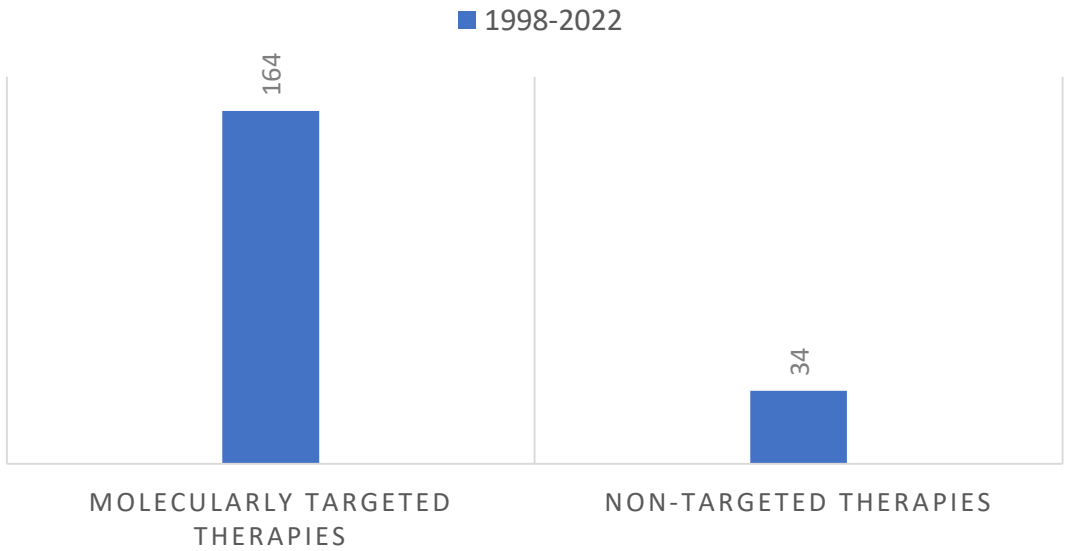
1. Xie, Y. et al. *Signal Transduct Target Ther*. 2020;5(1):22. 2. Quintanilha J, et al. JAMA Netw Open. 2023:6(1);e225244. 3. Saborowski A, et al. *Ther Adv Med Oncol* 2020; 12:1758835920953293. 4. Goyal L, et al. *Cancer Treat Rev*. 2021;95:102170. 5. Boscoe AN, et al. *J Gastroninest Oncol*. 2019,10(4); 751-765. 6. 6. Pishvaian MJ, et al. *Lancet Oncol*. 2020;21(4); 508-518.

Precision Oncology Treatments

Precision Oncology Treatments

The growing number of actionable biomarkers in solid tumors will continue to drive precision oncology

Approved Oncology Drugs



Suehnholz SP, Nissan MH, Zhang H, et al. Quantifying the Expanding Landscape of Clinical Actionability for Patients with Cancer. *Cancer Discovery*. Published online October 18, 2023.

Today there are >100+ approved targeted therapies encompassing more than 30 tumor types

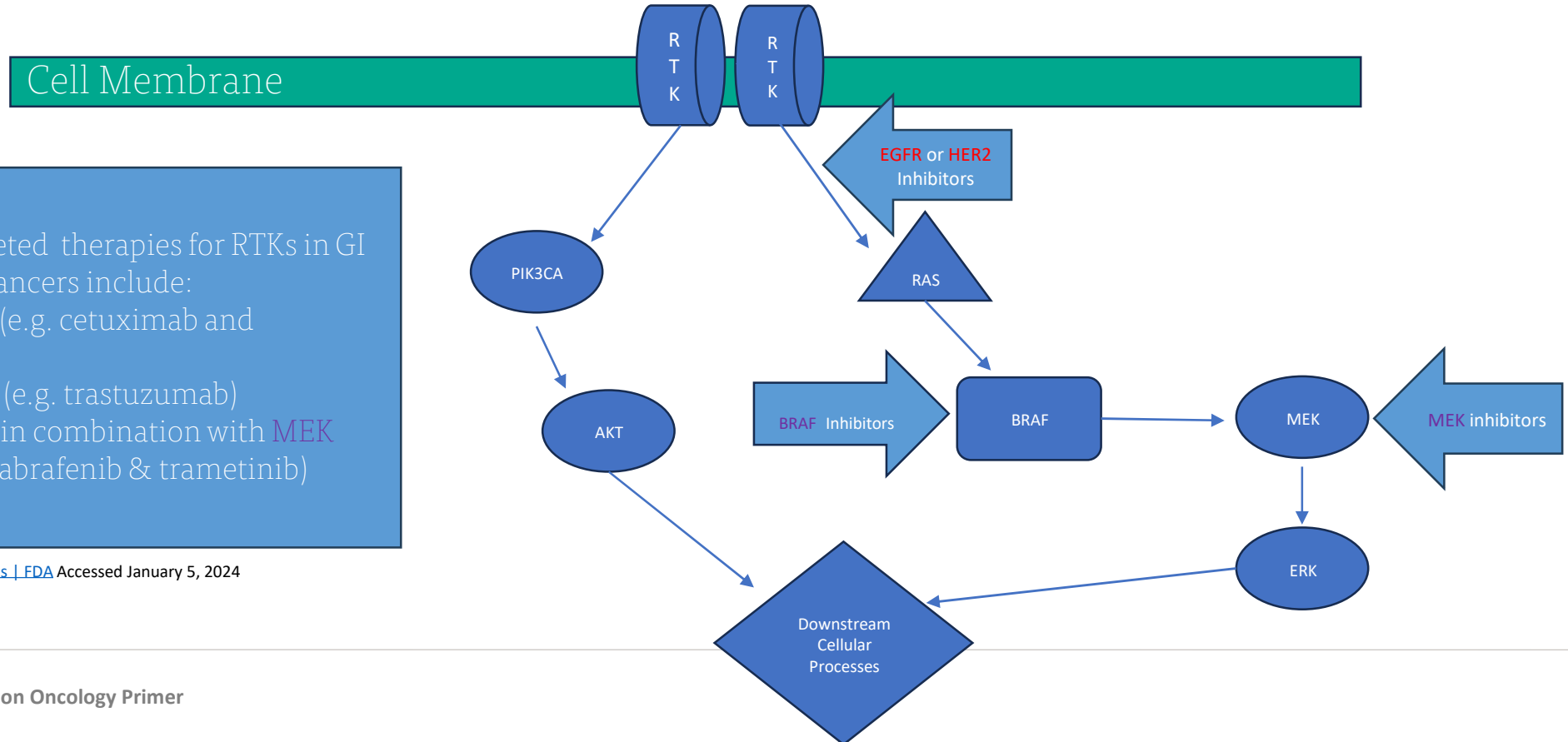
Targeted Therapy Drug List by Cancer Type - NCI. www.cancer.gov. Published October 3, 2022.

Pathways and Targeted Therapies

Cell Survival Pathways involved in GI Cancer Progression
BRAF, ERBB2 and RAS alterations are commonly observed in GI Cancers

EGFR is a Receptor Tyrosine Kinase (RTK) that is Overexpressed in 70% to 80% of CRC

HER2 (protein expression of ERBB2 gene) is a commonly overexpressed RTK in GI cancers

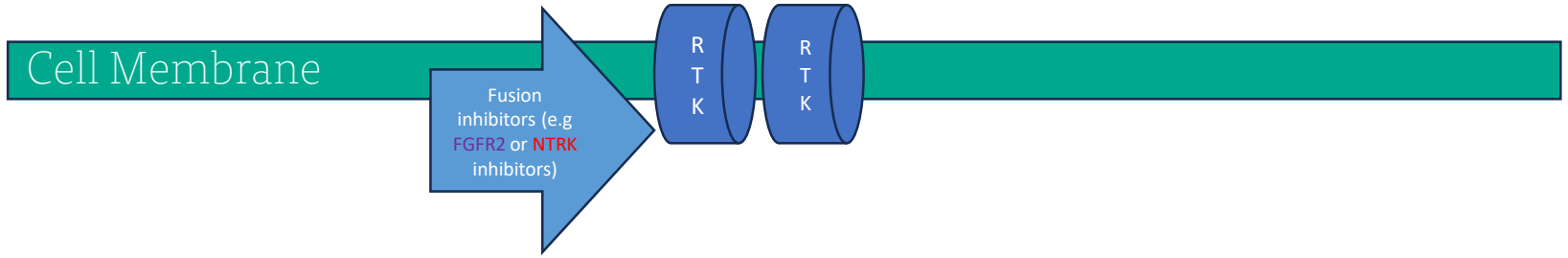


Approved targeted therapies for RTKs in GI cancers include:
EGFR inhibitors (e.g. cetuximab and panitumumab)
HER2 inhibitors (e.g. trastuzumab)
BRAF inhibitors in combination with MEK inhibitors (e.g. dabrafenib & trametinib)

Drug Approvals and Databases | FDA Accessed January 5, 2024

Gene Fusions & Targeted Therapies

NTRK, FGFR and other rare fusions are observed in GI cancers



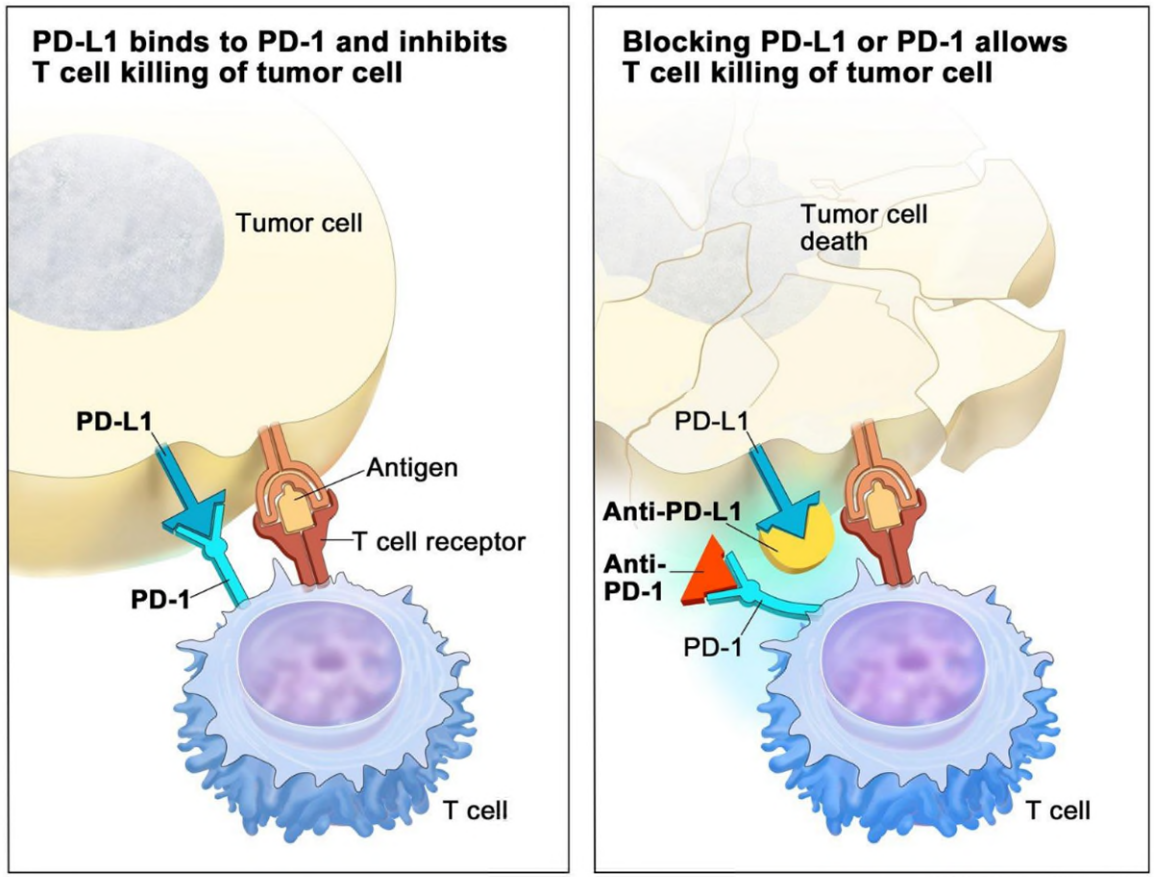
- Alterations/Fusions in Receptor Tyrosine Kinases such as FGFR, NTRK and ALK are found in various GI malignancies, including CRC and intrahepatic cholangiocarcinoma.
- Fusion gene alterations impact the kinase domain of fusion partners, resulting in changes in cell signaling

FDA approved Tyrosine Kinase Inhibitors[1]

- Larotrectinib (NTRK) – pan tumor approval
- Entrectinib (NTRK) – pan tumor approval
- Futibatinib (FGFR2) - cholangiocarcinoma
- Pemigatinib (FGFR2) - cholangiocarcinoma
- Infigratinib (FGFR2) - choangiocarcinoma

Drug Approvals and Databases | FDA Accessed January 5, 2024

Immune Signaling Pathways, Biomarkers and Immunotherapies



Source: National Cancer Institute. Immune Checkpoint Inhibitors. National Cancer Institute. Published April 7, 2022. https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors

Immunotherapy Biomarkers

- MSI-H - Microsatellites are repetitive DNA sequences prone to DNA replication error
- MMRd - Deficiency in mismatch repair pathway increases mutation rate and length of microsatellite regions in tumor DNA
- Tumor Mutational Burden - Number of somatic mutations per DNA megabase (Mb)
- PDL1 – Protein that plays a role in the body's immune system

FDA approved immune checkpoint inhibitors for GI Cancers[1]

- Pembrolizumab
- Nivolumab (as a single agent or in combination with ipilimumab)
- Dostarlimab

Drug Approvals and Databases | FDA Accessed January 5, 2024

Nursing Implications & Considerations

Nursing Implications

- Somatic Biomarker Testing Outcomes
  - Education on biomarker directed therapy plan
  - Reinforce ordering clinician's interpretation of the test results
  - Provide emotional support and reinforce that tumor is constantly changing and new biomarkers and treatments are possible
  - Identify findings on somatic biomarker test and clinical history that warrant a need for germline analysis and referral to genetics professional
    - >50% variant allele frequency, MSI-H tumors, concerns related to person or family history, or biomarkers not usually associated with the identified cancer type*
  - Educate the patient and family about clinical trial options

*If you do not understand findings on a somatic biomarker test report, consult with a genetics healthcare professional

Pittsburgh ONS 125 ED, Us P 15275 866-257-4. ONSContact. Nursing Implications Based on Somatic Biomarker Testing Outcomes | ONS Oncology Nursing Society | ONS | ons.org. Accessed January 6, 2024.

Nursing Considerations

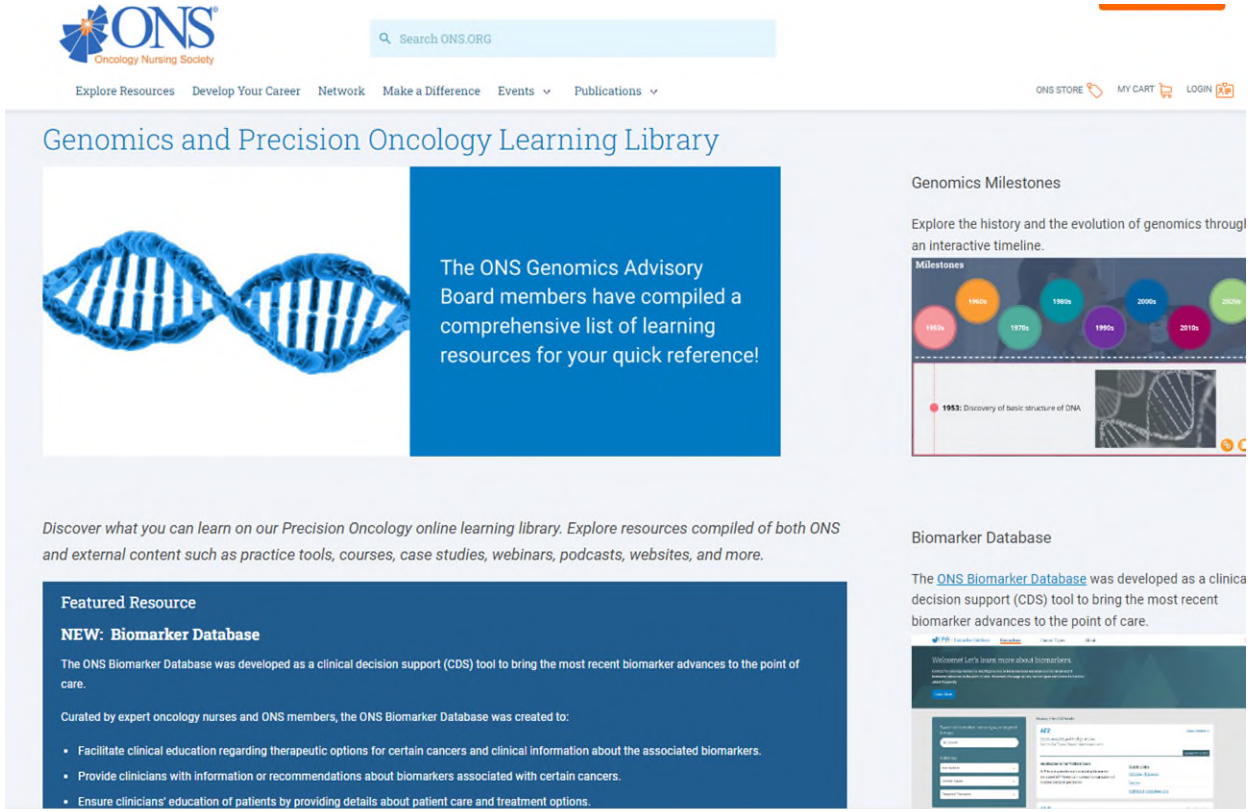
- Oncology nurses **can potentially influence** whether cutting-edge research discoveries are brought to the bedside through **education and advocacy**
- Clinical integration of genetic/genomic information has the potential to make a difference for patients' quality and length of lives through enhanced **health outcomes** brought about from precision oncology
- **This is the future of how oncology healthcare will be delivered**. The nursing profession's holistic philosophy and evidence-based practice approach positions nurses as leaders to implement precision health for patients now and in the future

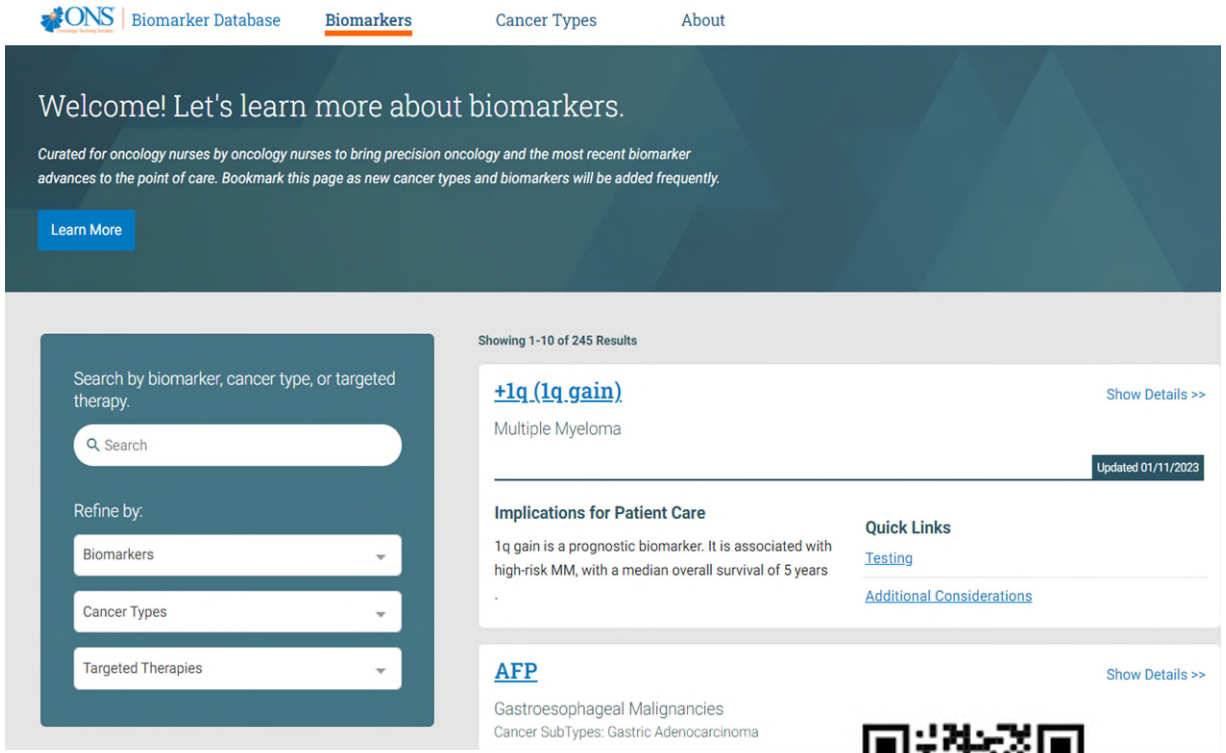
Summary, Resources & Questions

Summary

- Cancer is a genetic disease
- Precision oncology medicine testing and treatment have revolutionized how we treat cancer over the last 20 years
    - Innovative testing and treatments
    - Right Drug, Right Patient at the Right Time
- Nursing Implications – Somatic Testing
    - Educate, Identify, Support & Reinforce

ONS Educational Resources





Questions?


City of Hope®