CDC & Florida DOH Attribution

“We acknowledge the Centers for Disease Control and Prevention, for its support of the Florida Cancer Data System, and the printing and distribution of the materials for the 2015-2016 FCDS Webcast Series under cooperative agreement DP003872-03 awarded to the Florida Department of Health. The findings and conclusions in this series are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention”.

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Outline

- Revised Common Rule and Cancer Surveillance
- 2017 Incidence & Mortality Estimates
- AACR Cancer Progress Report 2016
- National Toxicology Program - 14th Report on Carcinogens
- ASCO 2017 Clinical Cancer Advances
- NCCN Annual Report 2016 – At Our Core
- Explosion of Data / Fragmented Data Sources
- CAP Solid Tumor Selected Tests by Tumor Type
- New Diagnostic Tools & Techniques
- Next Generation Genomic Sequencing
- Next Generation Immuno & Precision Therapies
- Questions
Revised Common Rule and Cancer Surveillance

Intent to modernize and strengthen the regulations embodied in the Common Rule
Goal is to make significant improvements in facilitating productive, scientific research outcomes which continue to support the ethics of public health activities in disease surveillance

1) The recognition and exclusion from IRB oversight of public health surveillance activities, including the collection and testing of bio specimens;
2) The requirement that a research study in which more than one institution located in the United States is engaged be reviewed by a single IRB with the others entering a relationship of reliance; and
3) The expansion of exemption categories to include many research studies involving the collection of identifiable human subjects’ data through survey and interview procedures.

The definition of public health surveillance activities is, nevertheless, broadly consistent with the data collection and analyses performed by state cancer registries and the activities of registries that participate in federal cancer surveillance programs, such as database linkages.

Source: American Association for Cancer Research (AACR), June 5, 2017 - doi: 10.1158/0008-5472.CAN-17-0758

2017 Incidence & Mortality Estimates

Source: American Cancer Society – 2017 Cancer Facts and Figures
2017 Survival Rate Estimates

Source: American Cancer Society – 2017 Cancer Facts and Figures

2017 Trends in Rare Cancers

Source: American Cancer Society – 2017 Cancer Facts and Figures

- The American Cancer Society (ACS), the Centers for Disease Control and Prevention (CDC), the National Cancer Institute (NCI), and the North American Association of Central Cancer Registries (NAACCR) collaborate to provide annual updates on cancer occurrence and trends in the United States. This Annual Report highlights survival rates.

- Overall cancer death rates from 2010 to 2014 decreased by 1.8% (95% confidence interval [CI] ¼ –1.8% to –1.8%) per year in men, by 1.4% (95% CI ¼ –1.4% to –1.3%) per year in women, and by 1.6% (95% CI ¼ –2.0% to –1.3%) per year in children.

- Death rates decreased for 11 of the 16 most common cancer types in men and for 13 of the 18 most common cancer types in women, including lung, colorectal, female breast, and prostate, whereas death rates increased for liver (men and women), pancreas (men), brain (men), and uterine cancers.

- In contrast, overall incidence rates from 2009 to 2013 decreased by 2.3% (95% CI ¼ –3.1% to –1.4%) per year in men but stabilized in women.

- For several but not all cancer types, survival statistically significantly improved over time for both early and late-stage diseases. Survival varied by race/ethnicity and state.

- Conclusions: Cancer death rates continue to decrease in the United States. However, progress in reducing death rates and improving survival is limited for several cancer types, underscoring the need for intensified efforts to discover new strategies for prevention, early detection, and treatment and to apply proven preventive measures broadly and equitably.


AACR Cancer Progress Report 2016
Given that approximately 12 percent of human cancers worldwide may be attributed to viruses, and there are no vaccines currently available for these five viruses, prevention strategies to reduce the infections that can lead to cancer are even more critical,” said Linda Birnbaum, Ph.D., director National Institute of Environmental Health Sciences (NIEHS) and National Toxicology Program (NTP).
ASCO 2017 State of Cancer Care in America

The Path Forward

ASCO 2017 Clinical Cancer Advances

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ADVANCE OF THE YEAR: IMMUNOTHERAPY 2.0

This year, ASCO has named Immunotherapy 2.0 as the advance of the year. The paradigm recognizes the growing awareness of cancer immunotherapy, which has expanded and improved the treatment of patients across a spectrum of cancers, including melanoma, lung, and prostate cancer. Immunotherapeutic approaches are now being used in combination with other treatments to improve outcomes.

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ASCO 2017 State of Cancer Care in America

ASCO 2017 Clinical Cancer Advances

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ADVANCE OF THE YEAR: IMMUNOTHERAPY 2.0

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ASCO “Hot Topics” from ASCO Meeting

- Combination Clinical Trials – 765 drug combination studies available
  - One or More Immunotherapy Agent(s)
  - One or More Targeted Agent(s)
  - One or More Conventional Therapies – chemotherapy, radiation therapy, etc.

- Keytruda in Combination for Many Cancers – 268 Keytruda drug combination studies available

- The Looming New Epidemic – “Financial Toxicity” from New Expensive Drug Costs

- Larotrectinib – TRK Fusion Gene – 17 different types of cancer – not organ specific

- Zytiga (abiraterone) + standard hormone therapy for Advanced Prostate Cancer – reduced chance of death by 40% for men with newly diagnosed advanced disease.

- CAR T-cell Therapy for Multiple Myeloma - removing T cells from patients' blood, genetically altering them to boost their cancer-fighting potential and infusing them back into the patient.
Keytruda’s Fast Track for Approvals

- Pembrolizumab is approved to treat:
  - US Brand Name(s) – Keytruda
  - Type: Immune Checkpoint Inhibitor
  - FDA Approved - Yes
- FDA Approval for Pembrolizumab for Microsatellite Instability - High
- FDA Approval for Pembrolizumab for Urothelial Carcinoma
- FDA Approval for Pembrolizumab for Non-Small Cell Lung Cancer (2017)
- FDA Approval for Pembrolizumab for Hodgkin Lymphoma
- FDA Approval for Pembrolizumab for Non-Small Cell Lung Cancer (2016)
- FDA Approval for Pembrolizumab for Head and Neck Cancer
- FDA Approval for Pembrolizumab for Melanoma (2015)
- FDA Approval for Pembrolizumab for Non-Small Cell Lung Cancer (2015)
- FDA Approval for Pembrolizumab for Melanoma (2014)

The process of mismatch repair enables cells to correct mistakes in their DNA code that sometimes occur during DNA replication. It’s “like a spell-checker” for DNA, explained Dr. Gulley. Mismatch repair deficient (dMMR) cells, which lack this failsafe process, acquire multiple DNA mutations. Some dMMR cells acquire alterations in short, repetitive DNA sequences called microsatellites and are referred to as microsatellite instability-high (MSI-H).

Colon Tumor Location and Treatment

- Analysis of data from a large clinical trial showed patients with advanced colorectal cancer live longer if the cancer begins on the left side of the colon rather than on the right side.
- Patients received a combination of FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (fluorouracil, leucovorin, and irinotecan) chemotherapy with either of the two standard targeted therapies for advanced colorectal cancer: cetuximab or bevacizumab.
- Median survival for patients with left-sided tumors was 33 months.
- Median survival for patients with right-sided tumors was only 19 months.
- Overall, patients with left-sided tumors had a 20% lower risk of death.
- Conclusion: the location of primary tumor should be considered when establishing prognosis and designing future clinical trials in both early and advanced colorectal cancers.
- Patients with a right-sided colorectal cancer, cetuximab may not provide a benefit. However, for those patients whose tumors originate in the left colon, either a bevacizumab- or cetuximab-based regimen is effective, with cetuximab seeming to produce the best outcomes when combined with chemotherapy.
Colon Tumor Location and Treatment

Median Overall Survival by Tumor Location and Therapy

<table>
<thead>
<tr>
<th></th>
<th>Left-Sided Tumors</th>
<th>Right-Sided Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>33.3 months</td>
<td>19.4 months</td>
</tr>
<tr>
<td>Patients Treated with Cetuximab</td>
<td>36 months</td>
<td>16.7 months</td>
</tr>
<tr>
<td>Patients Treated with Bevacizumab</td>
<td>31.4 months</td>
<td>24.2 months</td>
</tr>
</tbody>
</table>

Although patients whose tumors originated in the left colon lived substantially longer after treatment than patients whose tumors originated in the right colon, the survival improvement for patients treated with cetuximab was more pronounced. And patients with right-sided tumors had better outcomes when treated with bevacizumab.

NCCN Annual Report 2016 – At Our Core
Explosion of Data / Fragmented Data Sources

The Pathologist in the Era of Genomic Medicine

Multiplex Testing May Become Standard

Combination Therapy Means Managing Multiple Treatment Data Sources

CAP Solid Tumor Selected Tests by Tumor Type

Clinical Solid Tumor Molecular Oncology: Selected Tests by Tumor Type

This table is for quick reference only. Clinical decision making, including diagnosis and therapy, should not be based solely on this information. The information should be considered in conjunction with clinical examination, imaging, and laboratory studies. Additional reading and investigation should be undertaken regarding the tabular entries before information is used in the clinical setting.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Gene/Loci</th>
<th>Somatic Alteration</th>
<th>Clinical Use</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal Adenocarcinoma</td>
<td>ARA5A, K-RAS, NRAS</td>
<td>Mutation, Loss of expression</td>
<td>Treatment response to EGFR inhibitors</td>
<td>5, 22, 25, 26, 30, 31, 32</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Lung Adenocarcinoma</td>
<td>EGFR, ALK</td>
<td>Mutation</td>
<td>Response to EGFR inhibitors</td>
<td>5, 22, 25, 26, 30, 31, 32, 53</td>
</tr>
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<td></td>
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</tbody>
</table>

Source: College of American Pathologists (CAP) Allison M. Cushman-Vokoun, MD, PhD
# CAP Solid Tumor Selected Tests by Tumor Type

## Breast Carcinoma
- **HER2/ERBB2**: Amplification, Response to HER2 monoclonal antibodies, 18, 51

## Gastric Adenocarcinoma
- **HER2/ERBB2**: Amplification, Response to HER2 monoclonal antibodies, 45

## Thyroid Carcinoma
- **Papillary Thyroid Carcinoma / Follicular Thyroid Cancer**
  - **BRAF**
    - pV600E mutation
    - Proprognostic FNA diagnosis and prognosis, potential therapeutic target, 9, 36, 40
  - **NRAS, HRAS, KRAS**
    - Mutation
    - Proprognostic FNA diagnosis, 36

## Melanoma
- **Cutaneous & Mucosal**
  - **BRAF codon 600**
    - Mutation
    - Response to BRAF inhibitors, 19–20, 33

## Uveal
- **GNAQ or GNA11**
  - Mutation
  - Diagnostic, 60

## GIST
- **KIT**
  - Mutation
  - Response to TKI, 41

## CNS Neoplasms
- **Glioma**
  - **MGMT**
    - Promoter methylation
    - Favorable response to alkylating agents, 21
  - **IDH1 and IDH2**
    - Mutation
    - Distinguishing reactive gliosis from glioma, favorable prognosis, 27, 54

## Oligodendroglioma
- **Chromosome 1p and 19q**
  - Co-deletion
  - Favorable prognosis and response to therapy, 6, 22

## Pilocytic Astrocytoma
- **BRAF**
  - Duplication/ fusion and pV600E mutation (extracerebellar)
  - Diagnostic, 27, 47

## Pleomorphic Xanthoastrocytoma and Ganglioglioma
- **BRAF**
  - pV600E mutation
  - Diagnostic, 47

## Cholangiocarcinoma / Pancreatic Carcinoma
- **KRAS codons 12, 13, 61**
  - Mutation
  - Proprognostic bile duct brushing diagnosis, 26

## Oropharyngeal Squamous Cell Carcinoma
- **HR HPV-related**
  - Positive detection
  - Favorable response to chemoradiation therapy, 48

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Source: College of American Pathologists (CAP) Allison M. Cushman-Vokoun, MD, PhD
New Diagnostic Tools & Techniques

Major trends shaping healthcare and life science markets in genomics:

1) Integration of Genomic Data into Clinical Workflows
2) On the Rise: Pharmacogenomic
3) Emergence of Advanced Genomic Editing Techniques
4) Noninvasive Cancer Screening – Liquid Biopsy
5) More Direct-to-Consumer Genetics
6) Growth of Newborn Genetic Screening Programs
7) Integration of New Data Streams

Source: Genetic Engineering & Biotechnology News, "A Look Ahead: Seven Trends Shaping Genomics in 2017 and Beyond"
Next Generation Genomic Sequencing

- Advances in Genome Sequencing, Pharmacogenomics, Gene Editing, and Biometric Wearables Will Provide New Pathways to Improve Cancer Therapy Options – fast, reliable, standardized, portable, and beyond proof of concept
- Next-generation sequencing (NGS) is arguably one of the most significant technological advances in the biological sciences of the last 30 years. NGS has evolved to point where now in routine use when establishing cancer diagnosis.
- NGS in turn is translating to rapid development and approvals for new diagnostic, prognostic & therapeutic targets
- Multi-Gene Assays cropping up everywhere – these are not standardized and are often proprietary and under study
- Example: Prostate - New three-in-one blood test could transform treatment of advanced prostate cancer through use of precision drugs such as PARP Inhibitor, olaparib, designed to target mutations in BRCA2 and PALB2 genes
  - Olaparib is good at killing cancer cells that have errors in genes that have a role in repairing damaged DNA.
  - Some patients respond to the drug for years
  - Other patients, the treatment either fails early, or the cancer evolves resistance.
  - Study also identified specific genetic mutations used to resist treatment with olaparib
  - The test is designed for use both before and after treatment
- Using the absolute amounts of cancer DNA in the bloodstream and also a readout of the specific mutations within that genetic material – researchers believe the test can usher in a new era of precision medicine for prostate cancer.

Source: ICR, The Royal Marsden, UCL and Imperial College London

Next Generation Immuno & Precision Therapies

- Checkpoint Inhibitors – Keytruda – “humanized” monoclonal antibodies
- PARP Inhibitors - PARP enzymes help repair damaged DNA. PARP inhibitors block this repair mechanism, causing some cancer cells to die.
- CAR-T Cells – immunotherapy using patient’s own immune cells
- CRISPR/Cas9 – intentional gene sequence alteration – gene editing technique
- Cellular Immunotherapy – targeted immunotherapy
  - G12D is a Target for KRAS, NRAS, HRAS Mutant Cancers – mutations in KRAS gene
    - 95% of all pancreatic cancers
    - 50% of all colorectal cancers
  - Infusion of the patient’s own Tumor Infiltrating Lymphocytes (TILs), called adoptive T cell transfer immunotherapy, to mediate effective antitumor immune responses against cancers that express the KRAS G12D mutation “presenting” the neoplasm as foreign to immune system
- Limitations: Managing Cytokine Release Syndrome (CRS) – CRS can be fatal
Next Generation Precision Therapies

Checkpoint Inhibitors

- Immune checkpoint inhibitors are drugs—often made of antibodies—that unleash an immune system attack on cancer cells.
- When immune system T-cells encounter another cell, they probe certain proteins on its surface, which serve as insignia of the cell’s identity.
- If the proteins indicate the cell is normal and healthy, the T cell leaves it alone.
- If the proteins suggest the cell is infected or cancerous, the T cell will lead an attack against it.
- Once T cells initiate an attack, the immune system increases a series of additional molecules to prevent the attack from damaging normal tissues in the body.
- These molecules are known as immune checkpoints.
- Cancer cells use immune checkpoint molecules to trick the immune system such that the immune system identifies the cancer cells as normal cells with normal proteins on its surface, and leaves the cancer cell alone to reproduce and proliferate unfettered.
- Example: genomic alterations in 196 tumors related to development of Hepatocellular Carcinoma include mutations in the TERT gene promotor, mutations in the TP53 and CTNNB1 (β-catenin) genes, and elevated expression of several immune checkpoint genes. These are now therapies for therapeutic intervention using Checkpoint Inhibitors targeting TERT, TP53 and CTNNB1.

Next Generation Precision Therapies

CAR-T and CRISPR/CAS9

- **CAR-T** = Chimeric Antigen Receptor T Cells
  - Aim is to “reprogram” the immune system to target specific proteins on cancer cells
  - New Therapy Based on Anti-CD19 CAR-T cells
  - BCMA-targeted CAR T-Cells for Plasma Cell Myeloma
  - KTE-C19 for Diffuse Large B-Cell Lymphoma
  - CTL019 for Acute Lymphoblastic Leukemia
  - JCAR015 for Leukemia

- **CRISPR/CAS9 – Gene Editing Approach**
  - Specific Manipulation of the Defective Gene Sequence Targets Errant DNA in Cancer Cells
  - Intentional Break in Gene Sequence Used to Trigger Self-Repair Mechanism in Cellular DNA
  - Inject Genome-Edited Immune Cells into Patient – NSCLC
  - Gene Editing Approach more promising for solid tumors
Next Generation Precision Therapies
PARP Inhibitors

• PARP enzymes help repair damaged DNA. Below example is olaparib (Lynparza) for glioma.
• PARP inhibitors block this repair mechanism, causing some cancer cells to die.
• How It Works - some cancer therapies, like chemotherapy and radiation, damage DNA. If the damage is not extensive, cells can often repair it and carry on. But if cells have defects in their ability to repair DNA, they may not be able to recover and die. Ex: BRCA1 & BRCA2 genes have reduced DNA-repair abilities.
• Cancer cells with DNA repair mechanism mutations, which in low grade glioma affect a gene called IDH, similar to BRCA1 or BRCA2 gene mutation, have an impaired ability to repair DNA damage. Treating these cells with PARP inhibitors, drugs that further disrupt DNA repair, effectively killed the cancer cells.
• IDH-mutant gliomas are more vulnerable to chemotherapy
• Amplifying this vulnerability enhanced toxic effects resulting in kill of more glioma cells.
• PARP inhibitors killed glioma cells with IDH mutations but not cells with normal IDH.
• PARP inhibitor enhanced the toxic effects of chemotherapy treatment on IDH-mutant cells
• Combining olaparib with temozolomide (alkylating chemo agent) enhanced DNA-damage and killing effects

Update on NCI MATCH Trial & SubProtocols
Update on NCI MATCH Trial & Protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>MATCH</th>
<th>Resistance</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAYH1 - T</td>
<td>Tumors with SHH-driven (SMO or Patched1 (PTCH1) mutation)</td>
<td>Basal Cell carcinoma</td>
<td>GDC-094 (Ganiteh) 150 mg QD PO</td>
</tr>
<tr>
<td>BAYH1 - U</td>
<td>Tumors with NF2 Loss</td>
<td>Increasing number of</td>
<td>VS-6064 (Fluminetin) 450 mg BID PO</td>
</tr>
<tr>
<td>BAYH1 - W</td>
<td>Tumors with KIT mutations (Bases 517, 13 or 14, 620 or 716 harbored)</td>
<td>GIST</td>
<td>Imatinib 300 mg QD PO for 28 days per cycle</td>
</tr>
<tr>
<td>BAYH1 - X</td>
<td>Tumors with alterations in EGFR pathway</td>
<td>EGFR 1L amplifications</td>
<td>AZD9291 80 mg BID PO</td>
</tr>
<tr>
<td>BAYH1 - Y</td>
<td>Tumors with RRAS2 mutations</td>
<td>NRAS mutations (22q13.3)</td>
<td>Dabrafenib 150 mg QD PO</td>
</tr>
<tr>
<td>BAYH1 - ZA</td>
<td>Tumors with NRAS mutations (Codons 12, 13, 61)</td>
<td>NRAS or BRAF variants</td>
<td>AZD6244 600 mg BID PO (4 days on, 3 days off, for each week of the 28-day cycle)</td>
</tr>
<tr>
<td>BAYH1 - ZB</td>
<td>Tumors with CDKN2A 1 or 2 amplifications</td>
<td>CDKN2A or CDKN2B gene deletions</td>
<td>Palbociclib 260 mg QD PO for 21 days on, 7 days off, for each 28-day cycle</td>
</tr>
<tr>
<td>BAYH1 - ZC</td>
<td>Tumors with Microsatellite repair deficiencies</td>
<td>Colorectal cancer excluded</td>
<td>pembrolizumab 240 mg IV or 300 mg nebulized in 1 and 1.7 mg/kg of nivolumab</td>
</tr>
<tr>
<td>BAYH1 - ZD</td>
<td>Tumors with NTRK Fusions (NTRK1, 2 or 3 gene fusion)</td>
<td>NTRK Fusions excluded</td>
<td>LUX-015 150 mg PO</td>
</tr>
<tr>
<td>BAYH1 - ZE</td>
<td>BRCA 1 or 2 gene mutations</td>
<td>BRCA 1 or 2 gene mutations</td>
<td>ATRX/IDH 30 mg QD PO for 5 days on, 2 days off for 2 cycles</td>
</tr>
</tbody>
</table>

Information Sources and Resources

- American Association for Cancer Research (AACR), June 5, 2017 - doi: 10.1158/0008-5472.CAN-17-0758
- American Cancer Society – 2017 Cancer Facts and Figures
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- The Pathologist in the Era of Genomic Medicine – PathGroup - College of American Pathology (CAP)
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- Institute of Cancer Research, The Royal Marsden, UCL and Imperial College London
- NCI MATCH Trial – National Cancer Institute
Questions

STAY FOCUSED