Precision Cancer Therapy

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Experimental and Clinical Pharmacology
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Disclosure

I have no actual or potential conflict of interest in relation to this program/presentation.
Objectives

- Understand the types of treatments used to treat cancer
- Contrast precision medicine treatments and with traditional chemotherapy treatment
- Discuss the changes occurring in cancer treatments
- Understand the differences in side effects between precision medicine treatments and traditional chemotherapy
- Discuss how precision medicine applies to 2 cancer cases
Precision Medicine

• Precision medicine is underpinned by the fact that all humans are all different.
• What may be best for one individual may not be best for another.
• Precision medicine is tailored for an individual taking into account environment, lifestyle and genetics.
• Precision medicine addresses:
  – Why does a drug work for one patient but not another?
  – Why do some develop side-effects?
  – Why do some need twice the standard dose to be effective?
• Precision medicine challenges the current standard where cancer drug trials have traditionally defined treatment for a population not the individual.
Medications do not improve the health of all people.

Nature, 520, 609-611 (30 April 2015)
1999 The Wall Street Journal declared a “New Era of Personalized Medicine” based on genetic mapping of one-letter DNA differences between humans. Drug makers call it the start of a “grand experiment”.

Masonic Cancer Center
University of Minnesota
Comprehensive Cancer Center designated by the National Cancer Institute
Gleevec (imatinib) Transformed Leukemia Treatment

Survival of patients with early chronic phase chronic myeloid leukemia treated in different eras compared with those treated with imatinib, a targeted therapy. 2006 PMID: 16835977
There are two genomes with variation. Using genetic information in cancer therapy is complex.

Somatic mutations
- Occur in non-germline tissues
- Cannot be inherited

Germline mutations
- Present in egg or sperm
- Can be inherited

Mutation in tumor only (for example, breast)
Mutation in egg or sperm
All cells affected in offspring

Adapted from the National Cancer Institute and the American Society of Clinical Oncology
Cancer Treatments

**Surgery:**
physical removal of the tumor and affected tissue

**Chemotherapy/Radiation:**
most commonly used treatment, kills cancer cells rapidly but also kills or damages normal cells

**Precision Medicine:**
customized treatment using biomarkers (usually genetic markers) that apply to the patient

**Immunotherapy:**
treatment activates the immune system to recognize and kill the cancer cells
Traditional Anti-Cancer Chemotherapy Treatments are Imprecise
Growing and Improving Arsenal of Anticancer Treatments

- Surgery
- Radiation
- Chemotherapy
- Hormone therapy
- Tyrophostins/TKIs
- Immunotherapy

**FDA ~1938**

- 1865: First chemotherapy (arsenic trioxide for CML)
- 1884: First radical mastectomy
- 1903: First use of radiation to treat cancer
- 1941: Androgen deprivation for prostate cancer
- 1949: First chemotherapy drug approved (nitrogen mustard)
- 1983: Tamoxifen approved
- 1986: Interferon α approved
- 1988: Tyrphostins – proof of principle
- 1998: First TKI (Gleevec) approved. First antibody-drug conjugate approved.
- 2000: First monoclonal antibody (Rituximab) approved
- 2011: First checkpoint inhibitor (anti-CTLA4) approved
- 2018: CD19 CAR-T cells approved
# Precision Medicine Cancer Treatments

## Targeted Therapies

### Antibodies

- **Rituximab** (Rituxan)
- **Bevacizumab** (Avastin)
- **Cetuximab** (Erbitux)
- **Trastuzumab** (Herceptin)
- **Alemtuzumab** (Campath)
- Many, many others

### Small Molecules

- **Imatinib** (Gleevec)
- **Gefitinib** (Iressa)
- **Erlotinib** (Tarceva)
- **Dasatinib** (Sprycel)
- **Lapatinib** (Tykerb)
- **Nilotinib** (Tasigna)
- Many others

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**BIG MOLECULE MADE FROM LIVING CELLS**

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**SMALL MOLECULES**

---
Monoclonal antibodies target only certain cancer cells making treatment more precise.

<table>
<thead>
<tr>
<th>Approved Anti-Cancer Agent</th>
<th>Target on the Cancer</th>
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<tbody>
<tr>
<td>Rituximab</td>
<td>CD20</td>
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<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
</tr>
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<td>Cetuximab</td>
<td>EGFR</td>
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<tr>
<td>Trastuzumab</td>
<td>HER2</td>
</tr>
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<td>Alemtuzumab</td>
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<td>HER2</td>
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<td>Olaratumab</td>
<td>PDGFR-α</td>
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<tr>
<td>Denosumab</td>
<td>RANKL</td>
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</table>

There are >100 monoclonal antibodies. Available mAbs are directed against a large number of antigens and also used for the treatment of immunologic diseases (e.g. IBD, MS), reversal of drug effects (e.g. anticoagulants), and cancer therapy (hematologic malignancies and solid tumors).
Small molecules target mutations in cancer cells making treatment more precise

<table>
<thead>
<tr>
<th>Approved Anti-Cancer Agent (e.g.)</th>
<th>Target on the Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>BCR-ABL, KIT, PDGFRβ</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>EGFR</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>EGFR</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>BCR-ABL</td>
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<td>Lapatinib</td>
<td>HER2, EGFR</td>
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<td>Nilotinib</td>
<td>BCR-ABL, KIT and PDGFR-α</td>
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<tr>
<td>Crizotinib</td>
<td>ALK</td>
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<tr>
<td>Dabrafenib</td>
<td>BRAF</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAF</td>
</tr>
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</table>
How these drugs work

Mab's attack cells from the outside

Nib's attack cells from the inside
Identifying the “Driver” Mutation is Important in Controlling Cancer Growth

‘Passenger’ mutations

‘Driver’ mutations

Courtesy Dr. Pennell
Genetic Mutations in Lung Cancer Cells

somatic driver oncogenes in adenocarcinomas of the lung from former/current smokers

somatic driver oncogenes in adenocarcinomas of the lung from never-smokers
Somatic Mutations in Melanoma

Key Mutations by Subtype

**Cutaneous**
- **BRAF** 52%
- **NRAS** 28%
- **TP53** 15%
- **NF1** 14%
- **ARID2A** 14%
- **CDKN2A** 13%

**Uveal**
- **GNAQ** 50%
- **BAP1** 47%
- **GNA11** 32%

**Acral**
- **BRAF** 15%–20%
- **NRAS** 15%
- **KIT** 10%

**Mucosal melanoma**
- **KIT** 15%–20%
- **NRAS** 15%
- **BRAF** 5%
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Sensitivity</th>
<th>Target mutations</th>
<th>Cancer types</th>
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<tbody>
<tr>
<td>Gefitinib</td>
<td>+</td>
<td>EGFR-L858R</td>
<td>Lung cancer</td>
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<tr>
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<tr>
<td>Osimertinib</td>
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<td>EGFR-L718Q</td>
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<tr>
<td>Trastuzumab</td>
<td>–</td>
<td>HER2-A859T, -G776L</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Afatinib</td>
<td>+</td>
<td>HER2-p.Tyr772_Ala775dup</td>
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<td>–</td>
<td>HER2-T798I, -L869R</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>–</td>
<td>HER2-T798M</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>–</td>
<td>HER2-T798M</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Neratinib</td>
<td>+</td>
<td>HER2-S310, -L755, -V777,</td>
<td>Breast, cervical and biliary</td>
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<td>ALK-C1156Y, -L1196M</td>
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<tr>
<td>Lorlatinib</td>
<td>–</td>
<td>ALK-L1198F</td>
<td>Lung cancer</td>
</tr>
</tbody>
</table>
Immunotherapy

Chimeric Antigen Receptor (CAR-T)

- Tisagenlecleucel (Kymriah)
- Axicabtagene ciloleucel (Yescarta)

Immune Checkpoint Inhibitors (i.e.)

- Ipilimumab (Yervoy, CTLA4-blocking antibody)
- Nivolumab (Opdivo, antiPD1)
- Pembrolizumab (Keytruda, antiPDL1)
- Atezolizumab (Tecentriq, antiPDL1)
- Avelumab (Bavencio, antiPDL1)
- Durvalumab (Imfinzi, antiPDL1 and PD1)
Fig. 15.1. The promise of immunotherapy: Adapted from Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell* 161(2):205–214, 2015.
Case of Malignant Melanoma and Targeted Therapy Against a BRAF Genetic Mutation
Malignant melanoma

- Malignant cutaneous melanoma originates in melanocytes, specialized pigment cells, found in the skin.
- Melanoma accounts for 4-5% of all skin cancers but is responsible for 80% of deaths.
- Treatments for malignant melanoma in the past have been poor.

*Advanced melanoma*

*Image credit: National Cancer Institute*
The BRAF Gene

• The BRAF gene encodes for a signalling protein.

• Mutations in the BRAF gene are present in many types of cancer, including malignant melanoma.

• Vemurafenib is a oral inhibitor of BRAF(V600E) kinase mutation.
BRAF V600E MUTATION

Normal cell
Normal signal source

BRAF
Nucleus
Normal cell growth

BRAF mutation-positive melanoma cell
Normal signal source

Out-of-control
BRAF
Nucleus
Increased cancer cell growth
38-year-old man with *BRAF*-mutant melanoma and miliary, subcutaneous metastatic deposits. Photographs were taken (A) before initiation of PLX4032, (B) after 15 weeks of therapy with PLX4032, and (C) after relapse, after 23 weeks of therapy. MEK mutation was identified. Wagle N et al. J Clin Oncol 2011;29:3085-3096.
New drugs, new side effects

- **Traditional chemotherapy** attacks rapidly dividing cells within the body, which includes both cancerous and non-cancerous cells, such as hair follicles and the lining of the gut.

- **Precision medicine therapies**, particularly immunotherapy, the side effects are usually a result of an overstimulated or misdirected immune response. Called immune related adverse reactions (irARs).
Side Effects of Traditional Chemotherapy

- **brain fog, or "chemo brain"**
  Foggy thinking and memory problems are often referred to as having "chemo brain." This side effect can cause further anxiety and stress during your recovery.

- **anxiety and depression**
  Chemotherapy and its side effects add to the stresses of everyday life and can become overwhelming, leading to anxiety or depression.

- **hot flashes and menopause**
  Chemotherapy can affect the menstrual cycle, cause hot flashes, and trigger early menopause.

- **weak heart**
  Chemotherapy can weaken the heart muscle, especially if you have a preexisting heart condition.

- **nausea and vomiting**
  Nausea is one of the most common symptoms of chemotherapy.

- **discolored and cracked nails**
  During chemo treatments, you might develop brown, cracked fingernails and toenails.

- **loss of appetite**
  Chemotherapy can disrupt the entire digestive system, causing a wide variety of unpleasant symptoms that disturb appetite.

- **sexual dysfunction**
  A low libido is common after going through chemo. If symptoms are severe, it might be hard to "get in the mood," but it's usually a temporary issue.

- **skin sensitivity**
  Chemotherapy can cause dry, irritable skin. Your skin may also develop sensitivity to sunlight.

- **hair loss**
  Chemotherapy can damage hair follicles and cause them to temporarily stop producing new hairs. Hair loss can be disheartening, but remember that this side effect is only temporary.

- **mouth sores**
  The gums, insides of the cheeks, tongue, and throat are prone to sores. Early treatment can help prevent infections.

- **lower blood cell count**
  Chemotherapy can interfere with the body's ability to produce healthy blood platelets as well as red and white blood cells. Low blood counts can lead to a variety of serious side effects.

- **digestive distress**
  Chemotherapy can cause constipation, diarrhea, and other forms of digestive distress. As a result of this, you may also experience weight loss and weakness.

- **decreased urination**
  Decreased urination may be a sign that chemotherapy is harming the kidneys.

- **red urine**
  Your urine may be red due to certain chemotherapy drugs working their way out of your system.

- **bone loss**
  Osteoporosis, or loss of bone density, can be a long-term side effect. Women are especially susceptible to bone loss. Chemotherapy could worsen these effects as you age.

- **poor coordination and tired muscles**
  Tired, achy muscles can interfere with balance, coordination, and motor skills.

- **swollen hands and feet**
  Swollen hands and feet may also occur due to fluid retention from changes in your blood pressure.
Side Effects of Immuno-therapy

PD-1/PD-L1 targeted checkpoint inhibitors can affect many parts of the body. Circle size represents side effect incidence; blue color is any side effect, red is severe toxicity. Credit: Ann Intensive Care. Feb. 2019. National Cancer Institute
Onset of Toxicity of Immunotherapy

- Rash, pruritus
- Liver toxicity
- Diarrhea, colitis
- Hypophysitis

Toxicity grade vs. Time (weeks)
Estimation of the Percentage of Patients With Cancer Who Benefit From Genome-Driven Oncology

A  Best overall response rate, %

- CML Ph+
- CLL 17p
- NSCLC ALK
- Melanoma BRAF
- GIST c-kit
- NSCLC ROS1
- NSCLC EGFR
- NSCLC BRAF
- Ovarian BRCA
- Breast BRCA
- AML IDH2
- Breast ERBB2/HER2
- MSI-high Solid Tumor
- ALL Ph+
- Colorectal KRAS WT
- Gastric ERBB2/HER2
- AML FLT3

B  Total duration of response, mo

- Gastric ERBB2/HER2
- MSI-high Solid Tumor
- AML FLT3
- CLL 17p
- CML Ph+
- ALL Ph+
- NSCLC ALK
- NSCLC EGFR
- GIST c-kit
- Melanoma BRAF
- Breast ERBB2/HER2
- NSCLC ROS1
- Ovarian BRCA
- NSCLC BRAF
- Colorectal KRAS WT
- AML IDH2
- Breast BRCA

Estimated Responses of US Patients to Genomically Informed Drug Treatment, 2006-2018 ALK indicates anaplastic lymphoma kinase gene; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BRAF, B-raf gene; BRCA, breast cancer gene; CML, chronic myeloid leukemia; CML, chronic lymphocytic leukemia; EGFR, epidermal growth factor receptor gene; FLT3, Fms-like tyrosine kinase receptor 3 gene; GI, genome informed; GIST, gastrointestinal stromal tumor; GT, genome targeted; ERBB2/HER2, human epidermal growth factor receptor 2 gene; IDH2, isocitrate dehydrogenase 2 gene; KRAS WT, K-Ras wild-type gene; MSI-high, high microsatellite instability; NSCLC, non–small cell lung cancer; Ph+, Philadelphia chromosome positive; ROS1, c-ros oncogene 1. When median duration of response was not reported or not reached, we assumed 80 months.
Cost of Precision Medicine Cancer Therapies

- $5,000-$50,000 per month for targeted and immunotherapies
  – $2000 or more/month copays

- CAR-T Therapy - $250,000-$375,000 for ONE treatment
# Revenue of Top 10 Drugs Used in Cancer

<table>
<thead>
<tr>
<th>Cancer Drug</th>
<th>Estimated Revenue</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revlimid</td>
<td>$9.8 bn</td>
<td>Celgene</td>
</tr>
<tr>
<td>Herceptin</td>
<td>$7.9 bn</td>
<td>Roche</td>
</tr>
<tr>
<td>Avastin</td>
<td>$7.7 bn</td>
<td>Roche</td>
</tr>
<tr>
<td>Rituxan</td>
<td>$7.6 bn</td>
<td>Roche</td>
</tr>
<tr>
<td>Keytruda</td>
<td>$7.2 bn</td>
<td>Merck &amp; Co</td>
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<tr>
<td>Zytiga</td>
<td>$3.5 bn</td>
<td>Johnson &amp; Johnson</td>
</tr>
<tr>
<td>Imbruvica</td>
<td>$2.6 bn</td>
<td>Johnson &amp; Johnson/Pharmacyclics</td>
</tr>
<tr>
<td>Opdivo</td>
<td>$1.8 bn</td>
<td>Bristol Myers Squibb</td>
</tr>
<tr>
<td>Ibrance</td>
<td>$1.3 bn</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Neulasta</td>
<td>$1.1 bn</td>
<td>Amgen</td>
</tr>
</tbody>
</table>

Two University of Minnesota College of Pharmacy students worked to pass the Prescription Drug Repository Program through the MN legislature in order to reduce medication waste and provide medications to the un- and underinsured

**The program:**

- Donors may donate a drug or medical supply for use by an individual who meets the eligibility criteria
- Eligible medications include any prescription drug approved for use in the United States, including cancer and antirejection drugs
  - Must be in original, sealed, unopened, tamper-evident packaging
- Controlled substances are not eligible
- Individuals are eligible to participate if they are Minnesota residents and if they are uninsured or underinsured
- Goal is to have program running by summer 2020.

Using genetic information in cancer therapy is complex. There are two different genomes with variation.

**Somatic mutations**
- Occur in *nongermline* tissues
- Cannot be inherited

**Nonheritable**
- Mutation in tumor only (for example, breast)

**Germline mutations**
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

**Parent**

**Heritable**
- Mutation in egg or sperm
- All cells affected in offspring

**Child**

Adapted from the National Cancer Institute and the American Society of Clinical Oncology
Outcomes from Medications

Drug toxic but beneficial

Drug toxic but NOT beneficial

Patient group
Same diagnosis, same prescription

Drug NOT toxic but NOT beneficial

Drug NOT toxic but beneficial
Pharmacogenomics matches an individual's inherited genes to the most effective and least toxic medication.


Dr. Pennell
TPMT/NUDT15 – thiopurines
Updated 2018
CYP2C19 – clopidogrel
Updated Sept 2013
CYP2C9, VKORC1, CYP4F2 – warfarin
Updated Feb 2017

2012
CYP2D6 – codeine
Updated Apr 2014
HLA-B – abacavir
Updated Feb 2014
SLCO1B1 – simvastatin
Updated Oct 2014

2013
HLA-B – allopurinol
Updated Oct 2015
CYP2D6, CYP2C19 – TCAs
Updated Dec 2016
HLA-B – carbamazepine & oxcarbazepine
Updated Feb 2017
DPYD – 5FU / capecitabine
Updated 2017

2014
IFLN3 – PEG interferon α in HCV
Updated Feb 2106
CFTR – ivacaftor
Updated May 2016
G6PD – rasburicase
CYP2C9, HLA-B – phenytoin
Update 2019

2015
CYP3A5 – tacrolimus
Updated March 2017
CYP2D6, CYP2C19 – SSRIs
Updated March 2017
UGT1A1 – atazanavir
Updated March 2017

2016
CYP2C19 – voriconazole
CYP2D6 – 5HT3 antagonists

2017
CYP2D6 – tamoxifen

2018
RYR1 & CACNA1S – inhaled anesthetics and succinylcholine

2019
CYP2B6 - efavirenz
CYP2D6 – atomoxetine

In Progress 2020
CYP2C19 – proton pump inhibitors
CYP2C9 – celecoxib, flurbiprofen, diclofenac
CYP2D6 – opioids
mRNR1 - aminoglycosides

Guidelines under consideration
CYP2D6 – antipsychotics
CYP2C19/2D6 – SNRIs
UGT1A1 – irinotecan, nilotinib, belinostat
CYP2B6 - methadone

https://cpicpgx.org/guidelines/
Pharmacogenomic Markers are Mostly Related to Metabolism (how drugs are broken down in body)

- **Ultrarapid metabolizers\(^1\)**
  - Too rapid drug metabolism
  - No drug response at ordinary dosage (nonresponders)

- **Extensive metabolizers\(^2\) (normal)**
  - Expected response to standard dose

- **Intermediate metabolizers\(^2\)**
  - May experience some or a lesser degree of the consequences of the poor metabolizers

- **Poor metabolizers\(^1\)**
  - Too slow or no drug metabolism
  - Too high drug levels at ordinary dosage
  - High risk for ADRs
Advances in Cancer Therapy

- Unprecedented development of more powerful cancer therapies that target a specific gene or gene defect that maximizes efficacy.
- Identify the treatment that patient will most likely benefit.
- Harnessing of the immune system is key to control cancer.
- CAR-T therapies are the ultimate of personalized therapies.
Application of Precision Medicine

Case 1 - Katherine – stage 4, nonsmoking lung cancer

Case 2 – Pamala – stage 1 breast cancer
Lung Cancer is the No. 1 killer of all cancers

Anyone with Lungs can get Lung Cancer

Research Matters

https://youtu.be/SAibkfGTijU
Cancer statistics, 2019

**Estimated New Cases**

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td>Prostate</td>
<td>174,650</td>
<td>268,600</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,440</td>
<td>111,710</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>78,500</td>
<td>67,100</td>
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<tr>
<td>Urinary bladder</td>
<td>61,700</td>
<td>61,880</td>
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<td>Melanoma of the skin</td>
<td>57,220</td>
<td>39,260</td>
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<td>Kidney &amp; renal pelvis</td>
<td>44,120</td>
<td>37,810</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>41,090</td>
<td>33,110</td>
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<tr>
<td>Oral cavity &amp; pharynx</td>
<td>38,140</td>
<td>29,700</td>
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<tr>
<td>Leukemia</td>
<td>35,920</td>
<td>26,830</td>
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<tr>
<td>Pancreas</td>
<td>29,940</td>
<td>25,860</td>
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<td><strong>All Sites</strong></td>
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<td><strong>891,480</strong></td>
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**Estimated Deaths**

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<td>76,650</td>
<td>66,020</td>
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<tr>
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<td>31,620</td>
<td>41,760</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>27,640</td>
<td>23,380</td>
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<tr>
<td>Pancreas</td>
<td>23,800</td>
<td>21,950</td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
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<tr>
<td>Leukemia</td>
<td>13,150</td>
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<tr>
<td>Esophagus</td>
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<td>9,690</td>
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<tr>
<td>Brain &amp; other nervous system</td>
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<td><strong>All Sites</strong></td>
<td><strong>321,670</strong></td>
<td><strong>285,210</strong></td>
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Cancer statistics, 2019

### Estimated New Cases

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<tr>
<td>Colon &amp; rectum</td>
<td>78,500</td>
<td>61,880</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>61,700</td>
<td>39,260</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>57,220</td>
<td>37,810</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>44,120</td>
<td>33,110</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>41,090</td>
<td>29,700</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>38,140</td>
<td>26,830</td>
</tr>
<tr>
<td>Leukemia</td>
<td>35,920</td>
<td>25,860</td>
</tr>
<tr>
<td>Pancreas</td>
<td>29,940</td>
<td>3,560</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>870,970</strong></td>
<td><strong>891,480</strong></td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>76,650</td>
<td>66,020</td>
</tr>
<tr>
<td>Prostate</td>
<td>31,620</td>
<td>41,760</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>27,640</td>
<td>23,380</td>
</tr>
<tr>
<td>Pancreas</td>
<td>23,800</td>
<td>21,950</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>21,600</td>
<td>13,980</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,150</td>
<td>11,160</td>
</tr>
<tr>
<td>Esophagus</td>
<td>13,020</td>
<td>10,180</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,870</td>
<td>9,690</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,510</td>
<td>8,460</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>9,910</td>
<td>7,850</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>321,670</strong></td>
<td><strong>285,210</strong></td>
</tr>
</tbody>
</table>

143,670

Since the 1990s:
Progress by Many Measures

**Treatment**
- New therapies
- Imaging, radiation oncology and surgery advances
- Precision medicine
- Immunotherapy

**Prevention**
- Lung cancer screening
- Decrease smoking in the US
- Drug and surgical risk reduction strategies

**Quality of Life**
- Better toxicity management
- Less intensive therapies
- Palliative care integration

**Survivorship**
- Growing research area
- Late effects identified
- Surveillance strategies established
### Targeted Therapy
- Tarceva (Erlotinib) 100mg
- Afatanib (Gilotrif) 40mg
- Tagrisso (Osimertinib) 80mg
- Afatanib & Tagrisso
- Gefitinib (Iressa)

### Immunotherapy & Chemo IV
- Keytruda (Pembrolizumab) 200mg
- Alimta (Pemetrexed) 600mg
- Carboplatin (Paraplatin)

### Clinical Trial: JNJ-61186372

### Targeted Therapy
- Crizotinib (Xalkori) & Tagrisso

### ImPower150
- Taxol (Paclitaxel)
- Carboplatin (Paraplatin)
- Avastin (Bevacizumab)
- Tecentriq (Atezolizumab)

### Drugs for side effects
- Minocycline 100mg
- Psyllium
- Trazodone (Desyrel) 50mg
- Oxycodone (roxicodone) 5mg
- Lorazepam (Ativan) 0.5mg
- Ondansetron (Zofran) 8mg
- Prochlorperazine (Compazine) 10mg
- Dronabinol (Marinol) 5mg
- Dexamethasone 10mg IV
- Palonosetron (Aloxi) 0.25 IV
- Olanzapine (Zyprexa) 5mg
- Folic Acid 800mcg
- Laxative
- Sertraline (Zoloft) 50mg
- Tylenol
- Ibuprofen

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**Stage IV Non Small Cell Lung Cancer Adenocarcinoma EGFR Exon 19, Erbb2, T790M & MET**
DRIVER MUTATIONS IN LUNG ADENOCARCINOMA

<table>
<thead>
<tr>
<th>Driver mutations in lung adenocarcinoma</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR-sensitising</td>
<td>15%</td>
</tr>
<tr>
<td>EGFR other</td>
<td>2%</td>
</tr>
<tr>
<td>KRAS</td>
<td>25%</td>
</tr>
<tr>
<td>ALK</td>
<td>7%</td>
</tr>
<tr>
<td>HER2</td>
<td>2%</td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>2%</td>
</tr>
<tr>
<td>BRAF other</td>
<td>1%</td>
</tr>
<tr>
<td>ROS1</td>
<td>2%</td>
</tr>
<tr>
<td>RET</td>
<td>2%</td>
</tr>
<tr>
<td>NTRK1</td>
<td>0-5%</td>
</tr>
<tr>
<td>MET</td>
<td>3%</td>
</tr>
<tr>
<td>MAP2K1</td>
<td>0-5%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>1%</td>
</tr>
<tr>
<td>NRAS</td>
<td>0-5%</td>
</tr>
<tr>
<td>&gt;1 mutation</td>
<td>3%</td>
</tr>
<tr>
<td>Unknown</td>
<td>31%</td>
</tr>
</tbody>
</table>
Most Important Point

Wait, wait, wait.....
for genotyping to come back on newly diagnosed NSCLC before starting chemo/IO.

If treatment is an urgency, give chemo alone and hold off on IO
Application of Precision Medicine

**Case 1** - Katherine – stage 4, nonsmoking lung cancer

**Case 2** – Pamala – stage 1 breast cancer
Positive benefits of tamoxifen and chemotherapy after surgery and radiation are well-known.
Likelihood of distant recurrence is 15% at 10 years with tamoxifen alone (no chemotherapy) after surgery.
This means that 85% are treated with chemotherapy that do not need it.
This multigene genetic assay guides what women are at highest risk and should receive chemotherapy with tamoxifen.

A high score on the Oncotype Dx test of the breast cancer tissue indicates risk of recurrence is high and chemotherapy is advisable.

**Figure 2. Likelihood of Distant Recurrence, According to Recurrence-Score Categories.**

A low risk was defined as a recurrence score of less than 18, an intermediate risk as a score of 18 or higher but less than 31, and a high risk as a score of 31 or higher. There were 28 recurrences in the low-risk group, 25 in the intermediate-risk group, and 56 in the high-risk group. The difference among the groups is significant (P<0.001).
Finding Information on Cancer Treatments

- Drugs approved for each cancer type: [https://www.cancer.gov/about-cancer/treatment/drugs/cancer-type](https://www.cancer.gov/about-cancer/treatment/drugs/cancer-type)

- Information on the clinical impact of molecular biomarkers (mutations) in cancer-related genes: [https://www.mycancergenome.org/](https://www.mycancergenome.org/)

- Descriptions of open cancer trials supported by the National Cancer Institutes: [http://www.cancer.gov/about-cancer/treatment/clinical-trials/search](http://www.cancer.gov/about-cancer/treatment/clinical-trials/search)