What is Precision Medicine?

Cancer Precision Medicine Research Symposium
June 5th, 2017, 12:45-1:45pm
Henry Ford Hospital
E&R Building, Room 2096 A,B,C

Dhananjay Chitale, MD
Vice Chair, Anatomic Pathology
Division Head, Molecular Pathology and Genomic Medicine
Director, Tissue Biorepository and research IHC core
Clinical Assistant Professor, Wayne State School of Medicine
Henry Ford Hospital, Detroit, Michigan
Notice of Faculty Disclosure

In accordance with ACCME guidelines, any individual in a position to influence and/or control the content of this CME activity has disclosed all relevant financial relationships within the past 12 months with commercial interests that provide products and/or services related to the content of this CME activity.

The individual below has responded that he/she has no relevant financial relationship(s) with commercial interest(s) to disclose.

Dhananjay Chitale, MD
Agenda

• What is Precision Medicine (PM)
• What is Precision Medicine Initiative (PMI)?
• Role of pathology and laboratory medicine in healthcare and PM
• Historic and current perspective on PM and molecular genetics in healthcare
• Detection of molecular alterations to support Precision medicine
  – What is Next Generation Sequencing (NGS)?
  – NGS powering PM
• Molecular tumor boards & precision medicine program
• Limitations of Precision Diagnostics and Precision Medicine
Traditional Medicine

• Most medical treatments have been designed for the “average patient.”

• This is a “one-size-fits-all-approach” to treatment
  – Successful for some patients but not for others
    • Especially not effective in the clinical management of cancer
  – Potentially very expensive therapeutic guesses
    • TKI may be generally given as first line in advanced metastatic lung adenocarcinomas or in conjunction with conventional chemotherapy for more complex cases.

https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative
What is Precision Medicine?

• Precision medicine uses an innovative approach to disease prevention and treatment that takes into account individual differences in people’s genes, environments, and lifestyles.
• Precision Medicine acknowledges that major part of uniqueness in disease is at the genomic (DNA) level.
  – Example of lung adenocarcinoma
    • TKI may be generally given as first line in advanced metastatic lung adenocarcinomas or in conjunction with conventional chemotherapy for more complex cases.
    • Molecular tests decide whether TKI will be effective or not, and avoids treatment in negative tests.
    • Molecular tests do offer complete savings on cost of

Is “Precision Medicine” a new concept?

• Medicine has always been personalized or “precision.”
  – prevention and treatment strategies that take individual variability into account

• So far the main tools doctors had to personalize care were information about
  – Personal history, family history, comorbid conditions, patient preferences, and aspects of the patient’s history that might impact which treatment would be most appropriate.

• The tools to personalize care weren’t that “precise,” making precision far less than we as physicians might have liked.

https://sciencebasedmedicine.org/precision-medicine-hope-hype-or-both/
What is different about Precision Medicine?

• Precision medicine is a new and emerging field with a large scope
  – Includes but not limited to:
    • Basic science in ‘Omics, pharmacology, translational science
    • Large scale data analytics- “Big Data”
    • Clinical decision making
    • And much more…

• Genomics
• Epigenomics
• Transcriptomics
• Proteomics
• Metabolomics
• Lipidomics
• Exposomics
• Microbiomics
What is Precision Medicine?

• Precision medicine gives doctors tools to better understand the complex mechanisms underlying a patient’s health, disease, or condition, and to better predict and tailor which treatments will be most effective for individual patient.

• Precision medicine is more cost-effective, treating only patients who are genetically qualified and likely to benefit from expensive new therapies.

• This approach provides hope when conventional therapies are not effective by potentially qualifying patients for clinical trials.
"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"

- President Obama, January 30, 2015
Pres. Obama’s Precision Medicine Initiative

“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 Barak Obama

The promise: $215 million investment split among the NIH, NCI, FDA, & ONC

- More and better treatments for cancer
- Creation of a voluntary national research cohort
- Commitment to protecting privacy
- Regulatory modernization
- Public-private partnerships

$130 million allocated to NIH to build a national, large-scale research participant group (cohort)
$70 million allocated to National Cancer Institute to lead efforts in cancer genomics
$10 million to FDA to acquire additional expertise and advance the development of high quality, curated databases
$5 million to Office of the National Coordinator for Health Information Technology (ONC) to support the development of interoperability standards and requirements that address privacy and enable secure exchange of data across systems

https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative
PMI Objectives

• Develop ways to measure risk for a range of diseases based on environmental exposures, genetic factors, and interactions between the two
• Identify the causes of individual differences in response to commonly used drugs (pharmacogenomics)
• Discover biological markers that signal increased or decreased risk of developing common diseases
• Use mobile health technologies to correlate activity, physiological measures and environmental exposures with health outcomes
• Develop new disease classifications and relationships;
• Empower study participants with data and information to improve their own health
• Create a platform to enable trials of targeted therapies

PMI Objectives-near term and long term

• “Two main components: a near-term focus on cancers and a longer-term aim to generate knowledge applicable to the whole range of health and disease.”

• Oncology is the clear choice for enhancing the near-term impact of precision medicine
  – Because of advances in molecular biology, genomics and bioinformatics

Francis Collins, NEJM 2015:
The Rise of Targeted Therapy
Agenda

• What is Precision Medicine (PM)
• What is Precision Medicine Initiative (PMI)?
• Role of pathology and laboratory medicine in healthcare and PM
• Historic and current perspective on PM and molecular genetics in healthcare
• Detection of molecular alterations to support Precision medicine
  – What is Next Generation Sequencing (NGS)?
  – NGS powering PM
• Molecular tumor boards & precision medicine program
• Limitations of Precision Diagnostics and Precision Medicine
ROLE OF LABORATORY IN POWERING PRECISION MEDICINE

PRECISION DIAGNOSTICS
Role of laboratory in healthcare

- 2% CMS expenditure
- 70-80% EMR data comes from laboratory
- 60% to 70% of all clinical decisions are based on laboratory test results
  - Diagnosis, treatment, hospital admission, discharge
- PALM heavily regulated by federal agencies
  - CLIA, CAP, AABB, FDA etc.

PALM service line serves: 5 hospitals, 30 clinic delivery sites, growing outreach program
12 Million laboratory tests, 80,000 surgical pathology accessions, 120,000 specimens, 70,000 cytopathology, 7000 molecular tests, 5200 cytogenetics cases

Adapted from American Clinical Laboratory Association
http://www.acla.com/importance-of-clinical-lab-testing-highlighted-during-medical-lab-professionals-week/
Role of pathologist in PMI
“Personalized predictive pathology”

• The quest for “personalized” medicine started many years back in pathology

• If one looks at the evolution of the WHO classification e.g.
  – lung adenocarcinoma, we are striving to achieve a goal to identify tumors which will behave differently

• Started with grading of the tumor.....
<table>
<thead>
<tr>
<th>Year</th>
<th>Subtype</th>
<th>Description</th>
<th>Year</th>
<th>Subtype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967</td>
<td>Bronchogenic</td>
<td>Acinar adenocarcinoma</td>
<td>1981</td>
<td>Acinar</td>
<td>Acinar</td>
</tr>
<tr>
<td></td>
<td>Acinar</td>
<td>Papillary adenocarcinoma</td>
<td></td>
<td>Papillary</td>
<td>Papillary adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Papillary</td>
<td>Bronchiolo-alveolar carcinoma</td>
<td></td>
<td>Bronchiolo-alveolar carcinoma</td>
<td>Bronchiolo-alveolar carcinoma</td>
</tr>
<tr>
<td></td>
<td>Bronchiolo-alveolar</td>
<td>Solid carcinoma with mucus formation</td>
<td></td>
<td>Nonmucinous</td>
<td>Nonmucinous</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mucinous</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mixed mucinous and nonmucinous</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Solid adenocarcinoma with mucin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adenocarcinoma with mixed subtypes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Variants</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Well-differentiated fetal adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mucinous (colloid) adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mucinous cystadenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Signet-ring adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clear-cell adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1999</td>
<td>Adenocarcinoma, mixed subtype</td>
<td>Adenocarcinoma, mixed subtype</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acinar adenocarcinoma</td>
<td>Acinar adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Papillary adenocarcinoma</td>
<td>Papillary adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bronchiolo-alveolar carcinoma</td>
<td>Bronchiolo-alveolar carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonmucinous</td>
<td>Nonmucinous</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mucinous</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mixed mucinous and nonmucinous</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Solid adenocarcinoma with mucin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adenocarcinoma with mixed subtypes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Variants</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Well-differentiated fetal adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mucinous (colloid) adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mucinous cystadenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Signet-ring adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clear-cell adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td>Fetal adenocarcinoma</td>
<td>Fetal adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mucinous (colloid) adenocarcinoma</td>
<td>Mucinous (colloid) adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mucinous cystadenocarcinoma</td>
<td>Mucinous cystadenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Signet-ring adenocarcinoma</td>
<td>Signet-ring adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clear-cell adenocarcinoma</td>
<td>Clear-cell adenocarcinoma</td>
</tr>
</tbody>
</table>
Current WHO subclassification of NSCLC

- **Squamous cell carcinoma.**
  - Papillary.
  - Clear cell.
  - Small cell.
  - Basaloid.

- **Adenocarcinoma.**
  - Acinar.
  - Papillary.
  - Bronchioloalveolar carcinoma.
    - Nonmucinous.
    - Mucinous.
    - Mixed mucinous and nonmucinous or indeterminate cell type.
  - Solid adenocarcinoma with mucin.
  - Adenocarcinoma with mixed subtypes.
  - Variants.
    - Well-differentiated fetal adenocarcinoma.
    - Mucinous (colloid) adenocarcinoma.
    - Mucinous cystadenocarcinoma.
    - Signet ring adenocarcinoma.
    - Clear cell adenocarcinoma.

- **Large cell carcinoma.**
  - Variants.
    - Large-cell neuroendocrine carcinoma.
    - Combined large-cell neuroendocrine carcinoma.
    - Basaloid carcinoma.
    - Lymphoepithelioma-like carcinoma.
    - Clear cell carcinoma.
    - Large cell carcinoma with rhabdoid phenotype.

- **Adenosquamous carcinoma.**

- **Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements.**
  - Carcinomas with spindle and/or giant cells.
  - Spindle cell carcinoma.
  - Giant cell carcinoma.
  - Carcinosarcoma.
  - Pulmonary blastoma.

- **Carcinoid tumor.**
  - Typical carcinoid.
  - Atypical carcinoid.

- **Carcinomas of salivary-gland type.**
  - Mucoepidermoid carcinoma.
  - Adenoid cystic carcinoma.
  - Others.

- **Unclassified carcinoma**
Invasive with BAC
Mixed adenocarcinoma
Invasive acinar type
Invasive papillary

Solid nodule
Part-solid nodule-peripheral GGO
What information can molecular pathologists provide to our clinicians and patients?

• Diagnosis
• Prognosis
• Risk stratification
• Prediction of response to therapy (precision / personalized medicine)
• Monitoring therapeutic responses
  – Minimal residual disease
• Pharmacogenomics
  – Drug dosing / response algorithms
“Personalized predictive pathology”

• Beyond morphology, margins and staging
  – Select the tumor tissue
  – Microdissect and enrich tumor
  – Test for mutations at molecular level
    • Genotyping (now using NGS), RT-PCR, in-situ hybridization,
    • Proteomic- by immunohistochemistry
  – Combine morphologic, molecular and clinical data to give the oncologist a comprehensive report
Agenda

• What is Precision Medicine (PM)
• What is Precision Medicine Initiative (PMI)?
• Role of pathology and laboratory medicine in healthcare and PM
• Historic and current perspective on PM and molecular genetics in healthcare
• Detection of molecular alterations to support Precision medicine
  – What is Next Generation Sequencing (NGS)?
  – NGS powering PM
• Molecular tumor boards & precision medicine program
• Limitations of Precision Diagnostics and Precision Medicine
Historical Milestones

- Mendel publishes his work on invisible inherited factors/"genes" (1866)
- DNA first identified by Friedrich Miescher — "Nuclein" (1869)
- Marshall Nirenberg cracks genetic code for protein synthesis (1953)
- Watson & Crick identify molecular structure of DNA (1961)
- Frederick Sanger develops rapid DNA sequencing method (1977)
- PCR invented; Huntington’s disease is first genetic disease mapped (1983)
- Human Genome Project launched (1990)
- First draft of human genome (2001)
- Personalized health care initiative launched by NIH (2003)
- Human genome project completed (2007)
- Precision Medicine Initiative announced during SOTU (2015)
- Cancer Moonshot announced during SOTU (2016)

What have we learnt from genomic profiling?

• We are 99.9% identical at DNA level
• But... everyone of us is unique.
• If we print DNA sequence ... that is 3 billion bases in a haploid genome of your entire genetic code
  – would occupy some 262,000 pages, or 175 large books!
  – just about 500 pages would be unique to us.
Conserved genomic regions across species

Source: Javier Herrero, European Molecular Biology Laboratory—European Bioinformatics Institute

DNA similarities between species | % similarity
--- | ---
Human to human | 99.9%
Human to chimpanzee | 96%
Human to cat | 90%
Human to cow | 80%
Human to chicken | 65%

But.. what molecular alterations occur in different cancer cells / types that make individual patient unique?
DNA alterations – the bigger stuff

Deletion/Insertion

Example:
22q11.2 region – DiGeorge syndrome

Amplification

Example:
17q21.1 (ERBB2) – Breast cancer

Translocation

Example:
t(11;22)(q24;q12) – Ewing’s sarcoma
Translocations in lymphomas and leukemias

Translocations with fusion product: Hematologic Tumors

- Tumor type
  - B-ALL/BURK (post-Rx)
  - Large cell B lymphoma
  - Mantle cell Lymphoma
  - Follicular lymphoma
  - T-cell ALL
  - T-cell ALL (post-Rx)
  - AML
  - Ewing's Sarcoma
  - Alveolar Rhabdomyosarcoma
  - Anaplastic large cell (pediatric)
  - Synovial sarcoma
  - DSRCT
  - Myxoid/round cell liposarcoma
  - Clear cell sarcoma
  - Extraskeletal chondrosarcoma

Translocations with fusion product: Solid Tumors - Sarcomas

- Tumor
  - Aggressive fibromyxoid sarcoma
  - Askin's tumor
  - Ewing's Sarcoma
  - Liposarcoma
  - Malignant fibrous histiocytoma
  - Mesenchymal chondrosarcoma
  - Synovial sarcoma
  - Clear cell sarcoma
  - Extraskeletal chondrosarcoma

Translocations with fusion product: Solid Tumors - Carcinomas

- Non-sarcoma Solid Tumors
  - Aggressive fibromyxoid sarcoma: ERG-NUT, ERG-HUT
  - Askin's tumor: KIAA1242-ATF1, P53/ATF1
  - Ewing's Sarcoma: ETV6-NTRK3
  - Liposarcoma: ETV6-NTRK3
  - Malignant fibrous histiocytoma: ETV6-NTRK3
  - Mesenchymal chondrosarcoma: ETV6-NTRK3
  - Synovial sarcoma: ETV6-NTRK3
  - Clear cell sarcoma: ETV6-NTRK3
  - Extraskeletal chondrosarcoma: ETV6-NTRK3

- Fusion Oncogenes
DNA alterations – the small stuff

**Point mutation**

CCTGAGGAG → CCTGGAGG

*Example*: hemoglobin, beta – sickle cell disease
L858R EGFR mutation in lung adenocarcinoma

**Deletion/Insertion**

GAATTAAGAGAAAGCA → GAAGCA

*Example*: epidermal growth factor receptor – lung cancer

**Repeat alteration**

TTCCAG...(CAG)₅...CAGCAA
TTCCAG...(CAG)₆₀...CAGCAA

*Example*: Huntington disease, Fragile X
What are common mutations in cancer?

Cancer Genome Landscapes. Science 339, 1546 (2013); Bert Vogelstein et al. DOI: 10.1126/science.1235122
Molecular test volumes rose 5 times due to increasing volumes and merger of DNA and cytogenetics lab with Pathology in 2014 – and projections.

Precision medicine – single gene testing since 2004.
Clients outside HFHS that have used our molecular and cytogenetics service

- MSKCC, NY, NY
- Yale University School of Medicine, New Haven, CT
- City of Hope, Duarte, CA
- Hershey Penn State University, PA
- Univ. of Pittsburg, Pittsburg, PA
- CSI laboratories, Alpharetta, GA
- ARUP laboratories, Univ. Utah, Salt Lake City, UT – One of the largest national reference labs
- University of Virginia, Charlottesville, VA
- Good Samaritan Regional Medical Center, Corvallis, OR

<table>
<thead>
<tr>
<th>National</th>
<th>Local</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John –Providence Hospital, Grosse Pointe, MI</td>
<td></td>
</tr>
<tr>
<td>St. John Macomb Hospital, Warren, MI</td>
<td></td>
</tr>
<tr>
<td>University of Michigan, Ann Arbor, MI</td>
<td></td>
</tr>
<tr>
<td>Beaumont Health, Royal Oak, MI</td>
<td></td>
</tr>
</tbody>
</table>
Henry Ford Health System data from cancer registry 1996-2012

Test Volumes

<table>
<thead>
<tr>
<th>SEER Site Group</th>
<th>Count of SEER Site Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>11575</td>
</tr>
<tr>
<td>Breast</td>
<td>5980</td>
</tr>
<tr>
<td>Lung</td>
<td>5896</td>
</tr>
<tr>
<td>Other Non-</td>
<td></td>
</tr>
<tr>
<td>Other Male</td>
<td></td>
</tr>
<tr>
<td>Other Female</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Other Urinary Bladder</td>
<td></td>
</tr>
<tr>
<td>Rectosigmoid</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td></td>
</tr>
<tr>
<td>Small Intestine</td>
<td></td>
</tr>
<tr>
<td>Spleenic Flexure</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
</tr>
<tr>
<td>Thymus</td>
<td></td>
</tr>
<tr>
<td>Tongue</td>
<td></td>
</tr>
<tr>
<td>Transverse Colon</td>
<td></td>
</tr>
<tr>
<td>Ureter</td>
<td></td>
</tr>
<tr>
<td>Uterus NOS</td>
<td></td>
</tr>
<tr>
<td>Vagina</td>
<td></td>
</tr>
<tr>
<td>Vulva</td>
<td></td>
</tr>
</tbody>
</table>

Sandy Stenhouse, JFCI Systems Coordinator, HFHS

Work load projections vs expectation
In-sourcing - Hub-Spoke model
Agenda

• What is Precision Medicine (PM)
• What is Precision Medicine Initiative (PMI)?
• Role of pathology and laboratory medicine in healthcare and PM
• Historic and current perspective on PM and molecular genetics in healthcare
• Detection of molecular alterations to support Precision medicine
  – What is Next Generation Sequencing (NGS)?
  – NGS powering PM
• Molecular tumor boards & precision medicine program
• Limitations of Precision Diagnostics and Precision Medicine
How do we test all these mutations on small amount of tumor tissue available for testing?
Previous strategies to detect DNA alterations

**Cytogenetics:**
Large indels, amplification, translocations

**In situ hybridization:**
Large indels, amplification, translocations

t(6;15) in woman with repeated abortions

Not Sustainable and Feasible

http://www.indianmedguru.com

http://moon.ouhsc.edu
Older Assays: Lot of DNA required, one gene at a time

RFLP

Sanger sequencing

Different single gene testing platforms and methodologies, different sensitivities

Not Sustainable and Feasible
How do we test all these mutations on small amount of tumor tissue available for testing?

Next generation sequencing
(Massively parallel sequencing)
What is Next Generation Sequencing (NGS)?

• New technology to sequence selected parts or the entire human genome

• Better terminology: Massive parallel sequencing
  • High-throughput DNA sequencing where numerous small fragments of DNA are sequenced simultaneously
  • The short sequences are then aligned to a reference genome
  • Variants are identified based on changes in the nucleotide sequence
  • Clinical significance is determined by querying different public databases to complete clinically meaningful analysis
Components of NGS

Sample
- DNA / RNA extraction
- Quality / quantity
- Fragmentation

Library prep
- Hybrid capture
- Amplicon capture

Sequencing
- Platform selection

Bioinformatics
- 1°, 2°, 3°
- In-house
- Commercial platforms

Data storage & Reporting
- LIS
- General IT
As sequencing occurs on the flow cell hundreds of thousands to millions of reads are generated. Local sequences that are similar are grouped together into clusters. These groups are used to create contiguous sequences containing both forward (blue) and reverse (purple) reads. Contiguous sequences are then aligned against the reference genome and variant alleles (differ from the reference allele) are identified.

48 gene panel – 225 amplicon x 150 bp x 2 x 500X coverage = 3.4 million bases analyzed per sample
• Bioinformatics data analysis pipeline involves multiple sets of one or more computational algorithms performed in series to analyze biological data.

• Critical to collect and check quality metrics along the way.

• Many software packages vary in quality and are not limited to NGS data.

• Genome, variant, and annotation databases include:
  - 1000 Genomes
  - My Cancer Genome
  - Genetic Test Registry
  - PubMed
  - COSMIC
  - OMIM
  - dbSNP
  - ClinVar
  - My Cancer Genome
  - PubMed
  - COSMIC
  - OMIM
  - dbSNP
  - ClinVar

Raw sequence data → Demultiplexing
(Packaging into FASTQ files)

FASTQ file
• Align sequences to reference genome
• Generate SAM file; Compress to BAM File

BAM file
• Computation to detect variants from reference

VCF file

Annotations and Interpretation

QC Code

QC Code

QC Code

QC Code

QC Code
Cluster density

Quality Matrix – 1° and 2° analyses

Q-score and Percent Clusters Passing Filter

Amplicon Mean Coverage Depth

Uniformity of Coverage

Percent Reads on Target

Number of Required Variant Reads

Minimum Required Variant Reads (95% Confidence) for Detecting 5% Variants with 1% Inherent Error Rate

% Variant Reads Required = 0.0563 * Actual Reads + 5.563
Which Next Generation Sequencing (NGS) to do in clinical practise?

Current reimbursable approach

• Single gene testing
• Panel
• Exome
• Genome

Panel

• 48 gene-Solid tumor gene panel Feb 2016
• 54 gene-Myeloid gene panel May 2016
• 94 gene-Cancer Predisposition panel May 2017
• RNA fusion panel (506 gene) July 2017

Exome

Genome

~ 6 feet (~2 meters) of DNA in each nucleated cell of your body needs to fit into a nucleus ~4-6 microns (4-6 x 10^-6 meters): a 300,000 to 500,000 compaction

• 22,000 genes, ~1% of human genome

3 billion bases

• Currently not reimbursed
• Research use
• Therapies in clinical trial settings
• Many variants of unknown significance
Cost per Raw Megabase of DNA Sequence

http://core-genomics.blogspot.com/2015/01/the-not-so-rapid-decreasing-costs-of.html
Clinical applications and examples of NGS
NGS Application - solid tumors

Molecular alterations
- Germline: Cancer susceptibility genes
- Somatic: driver mutations
  - Gain / loss of function
- Methylation
  - Epigenetic changes
- Micro-RNAs
  - Alterations in gene expression
  - Post translational modifications

Clinical scenarios
- Cancer predisposition risk
- Risk assessment & Risk management
- Diagnostic
- Patient stratification
- Targeted therapy-
  - personalized treatment
- Therapeutic response & MRD
- Prognosis

Genotypic – phenotypic correlation
- Molecular Tumor classification
- Molecular profiling
Need for multiple tests for comprehensive analysis of molecular genetic changes - limitations

Different NGS platforms have different capabilities

RNA and DNA Sequencing

DNA copy number variations

Gene rearrangements

RNA expression

Methylation

miRNA

A single method usually provides part of the molecular genetic information – therefore need for comprehensive testing

Current limitations: cost, specimen type, and application, CPT codes, reimbursement
Broad categories of clinical NGS testing

• Germline testing (inherited)
  • Inherited Cancer predisposition (BRCA 1-2, ATM, Li-Fraumeni (TP53), Lynch syndrome)
  • Diagnostic (CF, Thrombophilia panel- F5, F2, MTHFR, Warfarin )
  • HLA - transplant
  • Pharmacogenomics (warfarin sensitivity, CYP2D6 polymorphism –tamoxifen Tx
  • Identity testing
  • Blood grouping -red cell and platelet antigen systems, coagulation profiles

• Somatic (acquired) testing (e.g., cancer)
  • Diagnostic
  • Predictive
  • Prognostic

• Molecular microbiology (virus, bacteria, fungus)
Current assay methods at HFHS

- Gel electrophoresis
- Capillary electrophoresis
  - Sanger sequencing
  - Fragment analysis
- TaqMan RT-PCR
- ARMS-PCR
- Signal probe recognition via electrochemical detection
- Methylation specific PCR
- In-situ hybridization

1p 19q LOH
bcr/abl t(9;22), p190 kD, M-bcr
bcr/abl t(9;22), p210 kD, M-bcr
B Cell Gene Rearrangement
BRAF
CBFB-MYH11, inv(16)
CALR
EGFR TKI
EGFRvIII Mutation Detection
FLT3 Mutation Analysis
IDH1
IDH2
JAK2 Mutation Analysis
KRAS
PML-RARA t(15;17)
MGMT-MSP
Molecular Identity/ Gestational Profile
MSI/ MLH1
NPM1 Mutations
NRAS
T Cell Receptor Gamma Gene Rearr.
Cystic Fibrosis
Poyl T
Fragile X
FMF
Hereditary Hemochromatosis
Factor V, MTHFR, Prothrombin, COAG panel
Sarcoma translocations-SYT, EWSR1, WT1, PAX3/7
FISH-Her2, ALK, ROS1, SYT, EWSR1, IgH, Myc, Bcl6
CISH- EBV, Kappa, Lambda

BEFORE NGS ASSAY
Simplifying methods at HFHS

- Gel electrophoresis
- Capillary electrophoresis
  - Sanger sequencing
  - Fragment analysis
- TaqMan RT-PCR
- ARMS-PCR
- Signal probe recognition via electrochemical detection
- Methylation specific PCR
- In-situ hybridization
- Next-Gen Sequencing

1p 19q LOH
bcr/abl t(9;22), p190 kD, m-bcr
bcr/abl t(9;22), p210 kD, M-bcr
B Cell Gene Rearrangement
BRAF
CBFB-MYH11, inv(16)
CALR
EGFR TKI
EGFRvIII Mutation Detection
FLT3 Mutation Analysis
IDH1
IDH2
JAK2 Mutation Analysis
KRAS
PML-RARA t(15;17)
MGMT-MSP
Molecular Identity/ Gestational Profile
MSI/ MLH1
NPM1 Mutations
NRAS
T Cell Receptor Gamma Gene Rearr.
Cystic Fibrosis
Poyl T
Fragile X
FMF
Hereditary Hemochromatosis
Factor V, MTHFR, Prothrombin, COAG panel
Sarcoma translocations-SYT, EWSR1, WT1, PAX3/7
ALK, ROS1, SYT, EWSR1, IgH, Myc, Bcl6
CISH- EBV, Kappa, Lambda, FISH-Her2

AFTER NGS ASSAY
Utility of common molecular assays in solid tumors

MOLECULAR ASSAY EXAMPLE- DIAGNOSTIC ASSAY
Sarcoma fusion assays

- Immunohistochemistry (IHC)
- Fluorescence in situ hybridization (FISH)
- Reverse transcription polymerase chain reaction (RT-PCR)
- Next generation sequencing (NGS)

<table>
<thead>
<tr>
<th>Molecular assay examples - Diagnostic assay</th>
<th>FLI-1</th>
<th>CD99</th>
</tr>
</thead>
<tbody>
<tr>
<td>EWS-Fli1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EWS-ERG</td>
<td>t(21;22)(q22;q12)</td>
<td>5%</td>
</tr>
<tr>
<td>EWS-ETV1</td>
<td>t(7;22)(p22;q12)</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>EWS-E1AF</td>
<td>t(17;22)(q12;q12)</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>EWS-FEV</td>
<td>t(2;22)(q33;q12)</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>EWSR1 Break-apart FISH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT-PCR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
LUNG CANCER AS AN EXAMPLE FOR TARGETED GENOMIC TESTING

Lung cancer facts:
• 65-70% stage III/IV
• 10-15% 5 year survival
• Cancer care cost in the U.S. an overall $12.1 of $124.6 billion due to lung cancer in 2010 (NIH).
• Lung cancer has many ‘drugable’ targets discovered over last decade.
Clinical case

• 66 y.o. male presented dermatology consult for two atypical nevi
• Never smoker, in excellent state of health until severe lower back pain while bending down
• Prompted MRI: multiple discrete lesions in S2-3
• Suspicious for melanoma [h/o of atypical nevi]
• X-ray chest - left lower lobe lung nodule
• CT scan: tumor in left lower lobe of lung, wide spread lytic lesions in the spine, lesions in the liver
• Liver biopsy was reviewed
Treatment

• Treated with cisplatin and dacetaxel in conjunction with erlotinib based on EGFR mutation profile
Based on review of large published literature
Tumor Responses to Crizotinib in ROS1-Rearranged Non–Small-Cell Lung Cancer.

Current Algorithmic testing approach in lung adenocarcinoma

- **EGFR**
  - If Pos - STOP
  - If Neg

- **ALK**
  - If Pos - STOP
  - If Neg

- **ROS1**
  - ??
  - ??

Rest all the tests are currently not reimbursed and considered at this time investigational only and are being tested in the clinical trial setting

- MET, Her2
- BRAF, PIK3CA
- ….many more
<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Frequency</th>
<th>Histology</th>
<th>Smoking history frequent patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Mutation</td>
<td>10–35%</td>
<td>Adenocarcinoma, few adenosquamous carcinoma</td>
<td>Frequent in never smokers</td>
</tr>
<tr>
<td>KRAS</td>
<td>Mutation</td>
<td>15–25%</td>
<td>Mostly in adenocarcinomas, frequently mucinous morphology</td>
<td>Former/current smokers, rarely never smokers</td>
</tr>
<tr>
<td>FGFR1</td>
<td>Amplification</td>
<td>20%</td>
<td>More frequent in squamous cell carcinoma than adenocarcinoma</td>
<td>Former/current smokers</td>
</tr>
<tr>
<td>MET</td>
<td>Amplification</td>
<td>5-20%</td>
<td>Acquired resistance to EGFR TKIs-adenocarcinoma</td>
<td>Frequent in never smokers</td>
</tr>
<tr>
<td>MET</td>
<td>Amplification</td>
<td>2–4%</td>
<td>Previously untreated- patients-adenocarcinoma</td>
<td>Frequent in never smokers</td>
</tr>
<tr>
<td>PTEN</td>
<td>Mutation</td>
<td>4–8%</td>
<td>Squamous cell carcinoma</td>
<td>Ever smokers</td>
</tr>
<tr>
<td>DDR2</td>
<td>Mutation</td>
<td>~4%</td>
<td>Adenocarcinoma and squamous cell carcinoma</td>
<td>No significant association yet described</td>
</tr>
<tr>
<td>ALK</td>
<td>Rearrangement</td>
<td>3–7%</td>
<td>Adenocarcinoma, acinar histology or signet-ring cells</td>
<td>Light smokers (&lt;10 pack years) and/or never-smokers</td>
</tr>
<tr>
<td>BRAF</td>
<td>Mutation</td>
<td>1–3%</td>
<td>Mostly in adenocarcinomas.</td>
<td>Former/current smokers</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Mutation</td>
<td>1–3%</td>
<td>More frequent in squamous cell carcinoma than adenocarcinoma</td>
<td>Ever smokers and never smokers</td>
</tr>
<tr>
<td>NTRK1</td>
<td>Rearrangement</td>
<td>3%</td>
<td>Adenocarcinoma</td>
<td>Never smokers</td>
</tr>
<tr>
<td>HER2</td>
<td>Mutation</td>
<td>2–4%</td>
<td>Adenocarcinoma</td>
<td>Never smokers</td>
</tr>
<tr>
<td>ROS1</td>
<td>Rearrangement</td>
<td>2%</td>
<td>Adenocarcinoma</td>
<td>Light smokers (&lt;10 pack years) and/or never-smokers</td>
</tr>
<tr>
<td>AKT1</td>
<td>Mutation</td>
<td>1%</td>
<td>Adenocarcinoma and squamous cell carcinoma</td>
<td>No significant association yet described</td>
</tr>
<tr>
<td>MEK1</td>
<td>Mutation</td>
<td>1%</td>
<td>Mostly in adenocarcinomas than squamous cell carcinoma.</td>
<td>No significant association yet described</td>
</tr>
<tr>
<td>NRAS</td>
<td>Mutation</td>
<td>1%</td>
<td>Adenocarcinoma</td>
<td>Former/current smokers</td>
</tr>
<tr>
<td>RET</td>
<td>Rearrangement</td>
<td>1%</td>
<td>Adenocarcinoma</td>
<td>Frequent in never smokers</td>
</tr>
</tbody>
</table>
# Actionable rearrangements in lung cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Pathway</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTRK 1,2,3</td>
<td>MAPK</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>FGFR 1,2,3</td>
<td>MAPK</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>BRAF</td>
<td>MAPK</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>ALK</td>
<td>MAPK</td>
<td>3-5%</td>
</tr>
<tr>
<td>ROS1</td>
<td>MAPK</td>
<td>1.5%</td>
</tr>
<tr>
<td>RET</td>
<td>MAPK</td>
<td>1.5%</td>
</tr>
<tr>
<td>MET</td>
<td>MAPK</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>ERBB4</td>
<td>MAPK</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>NRG</td>
<td>MAPK</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>PRKCA</td>
<td>cAMP</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>PRKCB</td>
<td>cAMP</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>PRKACA</td>
<td>cAMP</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

John Iafrate, MGH
Timeline of Selected Major Discoveries in Lung Cancer Treatment

1997
- Discovery of EGFR mutations in lung adenocarcinomas sensitive to gefitinib and erlotinib
- Erlotinib approved for second-line treatment of locally advanced or metastatic NSCLC
- EGFR inhibitors enter clinical development

2004
- Bevacizumab approved for first-line treatment of NSCLC combined with chemotherapy

2005
- BATTLE study launched (biopsies become more mainstream for NSCLC)

2006
- ALK rearrangements in lung cancer first described

2007
- First ALK crizotinib-resistant point mutation identified (additional ones identified in subsequent years)

2008
- FGFRI amplification described in squamous cell lung cancer

2009
- TCGA genomic characterization of squamous cell lung cancer completed

2010
- Accelerated approval granted to crizotinib for ALK-positive lung cancer

2011
- Accelerated approval granted to ceritinib for ALK-positive lung cancer in patients intolerant to crizotinib or after progression on crizotinib

2012
- Erlotinib and afatinib approved for first-line treatment of patients with metastatic NSCLC whose tumors have an EGFR exon 19 del or L858R mut

2013
- Ramucirumab approved for second-line treatment of NSCLC

2014
- Nivolumab approved for second-line treatment of squamous cell carcinoma of the lung

2015
- Mutation burden found to be associated with response to anti-PD-1 therapy

Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer
## 2016

### Non-small cell lung cancer

<table>
<thead>
<tr>
<th>Molecular alteration</th>
<th>Drugs</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR mutation</td>
<td>erlotinib, gefitinib, afatinib</td>
<td>FDA approved</td>
</tr>
<tr>
<td>ALK rearrangements</td>
<td>crizotinib, ceritinib</td>
<td>FDA approved</td>
</tr>
<tr>
<td>EGFR T790M mutation</td>
<td>osimertrinib</td>
<td>FDA approved</td>
</tr>
<tr>
<td>PD-L1 expression</td>
<td>pembrolizumab</td>
<td>FDA approved</td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>Trametinib, dabrafenib</td>
<td>FDA approved</td>
</tr>
<tr>
<td>ROS1 rearrangements</td>
<td>crizotinib</td>
<td>FDA approved</td>
</tr>
<tr>
<td>MET amplifications</td>
<td>crizotinib</td>
<td>NCCN</td>
</tr>
<tr>
<td>HER2 mutations</td>
<td>trastuzumab, afatinib</td>
<td>NCCN</td>
</tr>
<tr>
<td>KRAS mutations</td>
<td>Resistance to TKI’s</td>
<td>NCCN</td>
</tr>
</tbody>
</table>
A Transformative 20 Years
Cancer Care 20 Years Ago

- Cancer treated primarily based on **histology, location** and **size**; few biomarkers
- Roughly **200 fewer treatment options than today**
- Three **basic treatment modalities**
  - Surgery
  - Chemotherapy
  - Radiation
- **Limited supportive care options**

[https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/12/oncology](https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/12/oncology)
Since the 1990s:
Mortality Down, Survivorship Up

In the United States...

Since the 1990s:
**Progress by Many Measures**

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

**Prevention**
- Interventions for infection-related cancers
- Cancer susceptibility genes
- 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
But Precision Medicine has brought new complexity – & challenges

A. Before initiation of vemurafenib

B. After 15 weeks of therapy with vemurafenib

C. At relapse, after 23 weeks of therapy.

Acquired resistance to therapy, recurrences, need for additional genomic profiling, deepen understanding of tumor heterogeneity

Source: Wagle, N et al. Dissecting Therapeutic Resistance to RAF Inhibition in Melanoma by Tumor Genomic Profiling. JCO August 1, 2011 vol. 29 no. 22 3085-3096
Artificial Intelligence – Deep Learning - Molecular tumor boards
Multidisciplinary Molecular tumor boards
Why molecular tumor boards?

• Genetic profiling of tumors is a potentially powerful tool to predict drug sensitivity and resistance,
  – routine use has been limited because often unfamiliarity with interpretation and incorporation of the information into practice.
  – MTB to interpret individual patients’ tumor genetic profiles
    • provide treatment recommendations
    • Follow-up and monitoring
    • Recurrence / resistance
Cancer Care Continuum - Breast cancer

Risk Assessment, Reduction & Screening
- Risk Biomarker
  - ATM, BRCA1/2, BARD1, BRIP1, CDH1, CHEK2, MRE11A, MUTY, HNBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, TP53

Diagnosis
- Diagnostic Biomarker
  - Estrogen Receptor, Her2/neu, GATA3, GCDFP-15, Mammaglobin

Treatment Selection
- Prognostic Biomarkers
  - OncotypeDx
- Predictive Biomarkers
  - Estrogen Receptor, CYP2D6

Treatment Plan Management
- Predictive Biomarkers

Host & Disease Response Assessment
- Response Biomarker
  - Tumor Burden, Tumor Resistance, Host Toxicity

Supportive Care Pharmacogenomics
Precision Medicine: Molecular tumor boards

Tissue Acquisition and Analysis
- Tumor Sample Genomic Panel Results & Analytics including EPIC non genomic data

Data & VDW Management by Precision Medicine Biomedical Informatics Team
- Biomedical Informaticist (PhD) 0.2 FTE
- Bioinformatician 0.5 FTE
- Data Programmers 1.5 FTEs
- Biostatistician 1.0 FTE

Pre-Tumor Board Molecular Tumor Board Review Team
- Molecular Tumor Board (MTB) Preliminary Evaluation
  - Pathologist
  - Med Onc
  - Rad Onc
  - Surg Onc
  - PHS Liaison
  - Medical Geneticist
  - Genetic Counselor
  - Nurse Navigator
  - Biomed Informatics Team IT Support

MTB Recommendation
- Provided by Bioinformatician and/or Medical Geneticist
- w/ Syapse Platform Supplements

Tumor Boards
- Brain
- Breast
- Cancer Pain
- Gastrointestinal
- GenitourINARY
- Gynecologic
- Head & Neck
- Liver
- Lung
- Lymphoma & Leukemia
- Melanoma
- Musculoskel. & Bone
- Pancreas
- Spine
- Thyroid

Non-Cancer Genomic Services

Treatment Plan Recommendation Delivered
Focused on following in-house developed treatment protocols and enrollment in targeted clinical trials
Unselected Population
Selected Population

Predictive Biomarker

Predict Treatment Efficacy

Informs Drug Selection

Mia Levy, MD, PhD, Vanderbilt
Treat Selected

Targeted Therapy

Primary Sensitivity

Primary Resistance

Disease Progress

Acquired Resistance

Mia Levy, MD, PhD, Vanderbilt
Core elements

- Risk assessment
- Screening
- Diagnosis
- Staging, Margins
- Prognosis
- Therapy selection
- Monitoring – MRD, PET, Liquid bx
- Surveillance – MRD, PET, Liquid bx

Palm

- Biorepository
Molecular tumor boards

The Role of Pathologists in the Era of Personalized Medicine, Eric E. Walk, Arch Pathol Lab Med—Vol 133, April 2009
Limitations of Precision Diagnostics and Precision Medicine
Limitations of NGS testing in solid tumors

• False positive rate
  – Mutation confirmation usually by Sanger sequencing (SS)
    • SS has low sensitivity and low allelic frequency may not be confirmed with other technology

• Specimen variability
  – Variable % tumor cells
  – Variable % intratumor heterogeneity in tumor cells with secondary mutation
  – What is clinical acceptable ‘clinically actionable’ threshold for VAF?
    • Currently not defined in prospective trials
% Variant Reads Required=0.06465*Actual Reads+5.965

- Generally >10% VAF clinically significant
- What about VAF between 5-9%?
  - depends....
  - 5% VAF of 10% cellular tumor sample would be clinically significant
100 cells in a specimen

10 cells are actual tumor cells

2 tumor cells contain mutation

2% of 10% tumor cells = 20% mutation burden = clinically “actionable”

Surgical pathologists review + molecular pathologist interpretations + oncologists input = correct interpretation of results and accurate targeted therapy selection
Variants of unknown significance (VUS)

• Which variants are clinically actionable?
• Development of evidence-based scientific standards to evaluate utility in different patient populations for
  – accurate risk estimation
  – Targeted therapies
• Risk of over interpretation leading to
  – unnecessary medical action
  – unwarranted psychological stress
• Careful selection of patients for genome sequencing and genetic counseling-crucial

Multidisciplinary molecular tumor boards
Informed Consent & Ethical Considerations

• Do we need informed consent for somatic testing?
  • Create patient awareness of benefits and harms
  • No specific guidance exists
    • Even institutional policies vary
  • Potential for anxiety and uncertainty, especially for VUS should be explained
    • Genetic counsellor? Ordering Oncologist? Pathologist?
• How to handle discovery of incidental findings unrelated to the disease in question?
Reimbursement

• What assays are considered under ‘clinical necessity’?
  – Challenging reimbursement issues
  – CPT codes for individual mutations & NGS assays

• Development of an affordable system of common access to genes
“Hydra hope”
Historically PALM is an integral part of ‘Precision Medicine’ initiative

Comprehensive data on molecular genetic alterations and other clinical data in cancers is transforming the way we diagnose, treat and monitor patients

To tackle the ‘tsunami’ of “omic” data to support Precision medicine Program needs coordination of multiple disciplines
Maximum stage condensation

~ 6 feet (~2 meters) of DNA in each nucleated cell of your body needs to fit into a nucleus ~4-6 microns (4-6 x 10^-6 meters): a 300,000 to 500,000 compaction

(There are about 100 trillion cells in human body)