Optimizing genomic-driven precision medicine at Duke

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Key points

1) We are reaching the end of initial genomic discovery of alterations driving cancers.

2) Next generative sequencing has arrived as a clinical diagnostic.

3) There are huge obstacles to connecting data generation to treatment decisions and improved outcomes.
Massively parallel sequencing and the growth of cancer genomic information

See: The Economist June 17th 2010
Reduced! $1,000
Opportunity for genomic discovery: T cell lymphomas

• T cell lymphomas comprise only 15% of lymphoma cases

• Dozens of subtypes of T cell lymphomas exist so each subtype is a rare disease

• We know very little about the biology of these diseases
HSTL overview

• First described by Farcet and Gaulard in 1990 based on report of similar cases
• Usually $\gamma\delta$ –TCR phenotype with sinusoidal infiltration of liver/spleen/bone marrow
• Isochromosome 7q frequently present
• Occurs more frequently in young males and associated with anti-TNF agents for IBD
• No standard treatment approach exists
HSTL is a rare disease with dire outcomes

![Graph showing overall survival rates for different types of T-cell lymphoma](image)

- Primary cutaneous ALCL
- Subcutaneous panniculitis-like T-cell lymphoma
- Enteropathy-type T-cell lymphoma
- Hepatosplenic T-cell lymphoma

Approach to understand HSTL biology

HSTL cases (n = 67, paired normal tissue n=20)

Somatic and rare tumor variants (exome seq)
Clinical correlative data

Molecular/clinical integrative genomics

+ HSTL cell line phenotype mutation modeling
The genomic landscape of HSTL
Enhancement of clonogenic potential and \textit{in vitro} proliferation with SETD2 loss

Evolution of understanding cancer types

[Diagram showing the evolution of understanding cancer types across years 1996, 2006, and 2016 for different cancer types such as NSCLC, Breast Cancer, Colorectal Cancer, Melanoma, and Prostate.]

Source: FDA.gov and Drugs@FDA, Mar 2017; QuintilesIMS, ARK R&D Intelligence, Feb 2017; QuintilesIMS Institute, Mar 2017
Proliferation of anti-cancer therapies

Source: Drugs@FDA, Feb 2017; QuintilesIMS, ARK R&D Intelligence, Feb 2017; QuintilesIMS Institute, Mar 2017
Clinical “next gen” sequencing

- A plethora of commercial CLIAA-certified genomic assays now exist
- Generally focus on sequencing of tumor biopsy tissue for somatic mutations
- Similarly, numerous start-ups offer analysis/treatment pathway pipelines
- Molecular testing offers potential genomic “basket” approach versus drug approved by anatomic site of cancer
- 1st FDA approval based on molecular test occurred May 2017 (pembrolizumab for MSI-high solid tumors)
Molecular analysis drives development of precision medicine strategies

**Traditional model of drug development**

Patients

A

B

Clinical trial

No treatment selection based on molecular profile of tumor

**Personalized medicine model**

Patients

Molecular analysis of tumor

Choice of treatment dependent upon molecular profile of tumor
Tumor genetics ≠ Normal genetics

Tumors have somatic changes in genetic/genomics plus germline variation

Tumors acquire:

  Chromosomal rearrangements

  Gene deletion/amplification

  Mutations

  Gene expression changes and epigenetic dysregulation
### Current Gene List

Entire coding sequence (base substitutions, indels, copy number alterations).

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### Select Rearrangements

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**FoundationOne** (solid tumor) panel genes

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Duke University
### Therapeutic Implications

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<th>Genomic Findings Detected</th>
<th>FDA-Approved Therapies (in patient’s tumor type)</th>
<th>FDA-Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
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<td>ATM E2052fs*1</td>
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<td>MCL1 amplification</td>
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For more comprehensive information please log on to the Interactive Cancer Explorer. To set up your Interactive Cancer Explorer account, contact your sales representative or call 1-888-988-3639.
## Duke Clinical NGS panels

<table>
<thead>
<tr>
<th>Panel</th>
<th>Genes assayed</th>
<th>Disease type(s)</th>
<th>Sample collection</th>
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<tr>
<td>FoundationOne</td>
<td>~500 (mutations/fusions/amplifications)</td>
<td>Solid tumors</td>
<td>Tissue block</td>
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<tr>
<td>FoundationOne Heme</td>
<td>~500 (mutations/fusions/amplifications)</td>
<td>Myeloid/lymphoid/sarcomas</td>
<td>Tissue block</td>
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<td>Guardant360</td>
<td>72 genes</td>
<td>Solid tumors</td>
<td>Blood/(cell free DNA)</td>
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<td>Duke Lung Hotspot</td>
<td>~50 genes</td>
<td>Non small cell lung cancer</td>
<td>Tissue block</td>
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<tr>
<td>Duke Colon Hotspot</td>
<td>~50 genes</td>
<td>Colorectal cancer</td>
<td>Tissue block</td>
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<td>Duke Melanoma Hotspot</td>
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<td>Myelodysplasia/leukemia</td>
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Lung cancer: Targeting driver mutations improves survival

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<th>Patients (N)</th>
<th>Median survival</th>
<th>95% C.I. (years)</th>
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<td>Oncogenic driver treated with targeted therapy</td>
<td>280</td>
<td>3.5 years</td>
<td>3.0-4.3 (P &lt;0.001)</td>
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<td>Oncogenic driver not treated with targeted therapy</td>
<td>318</td>
<td>2.4 years</td>
<td>1.8-2.9</td>
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<tr>
<td>No driver mutations identified</td>
<td>360</td>
<td>2.1 years</td>
<td>1.8-2.5</td>
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Biomarker testing in lung cancer

NCCN Guidelines Version 6.2018
Non-Small Cell Lung Cancer

CLINICAL PRESENTATION

- Establish histologic subtype with adequate tissue for molecular testing (consider rebiopsy if appropriate)
- Smoking cessation counseling
- Integrate palliative care (See NCCN Guidelines for Palliative Care)

HISTOLOGIC SUBTYPE

- Adenocarcinoma
- Large cell
- NSCLC not otherwise specified (NOS)

TESTING

- Molecular testing
  - EGFR mutation testing (category 1)
  - ALK testing (category 1)
  - ROS1 testing
  - BRAF testing
  - Testing should be conducted as part of broad molecular profiling
  - PD-L1 testing

- Molecular testing
  - Consider EGFR mutation and ALK testing in never smokers or small biopsy specimens, or mixed histology
  - Consider ROS1 testing
  - Consider BRAF testing
  - Testing should be conducted as part of broad molecular profiling
  - PD-L1 testing

TESTING RESULTS

- Sensitizing EGFR mutation positive (see NSCL-18)
- ALK positive (see NSCL-21)
- ROS1 positive (see NSCL-24)
- BRAF V600E positive (see NSCL-25)
- PD-L1 positive and EGFR, ALK, ROS1, BRAF negative or unknown (see NSCL-29)
- EGFR, ALK, ROS1, BRAF negative or unknown, PD-L1<50% or unknown (see NSCL-27)
- Sensitizing EGFR mutation positive (see NSCL-18)
- ALK positive (see NSCL-21)
- ROS1 positive (see NSCL-24)
- BRAF V600E positive (see NSCL-25)
- PD-L1 positive and EGFR, ALK, ROS1, BRAF negative or unknown (see NSCL-29)
- EGFR, ALK, ROS1, BRAF negative or unknown, PD-L1 <50% or unknown (see NSCL-28)
Example of precision medicine: *NTRK* gene fusions

Larotrectinib is a selective TRK inhibitor.

NTRK gene fusions are rare but recurrent oncogenic drivers.

- Larotrectinib is a highly potent small-molecule inhibitor of TRKA, TRKB, and TRKC (5–11 nM IC$_{50}$ in cellular assays).
- Demonstrated activity in CNS disease.$^1$
- Liquid formulation allows dosing of children as young as at birth and delivers equivalent pharmacokinetics to capsules.

Presented By Ulrick Lassen at 2018 ESMO Meeting
Frequency of NTRK Fusions Across Histologies
Larotrectinib for \textit{NTRK}+ tumors: Tumor response

- **Presented By Ulrick Lassen at 2018 ESMO Meeting**

### Tumor Response

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Maximum change in tumor size (%)</th>
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<td>Infantile fibrosarcoma</td>
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<td>Soft tissue sarcoma</td>
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<td>Melanoma</td>
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<td>Gastrointestinal stromal tumor</td>
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<td>Congenital mesoblastic nephroma</td>
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<td>Unknown primary</td>
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<tr>
<td>Bone sarcoma</td>
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### Table: Integrated Response

- **Integrated\(^{\dagger}\) (n=109)**
- **ORR (95\% CI)\(^{\dagger}\)**: \(81\% \text{ (72–88\%)}\)
- **Best response\(^{\dagger}\):**
  - PR: 63\%
  - CR: 17\%

\(^{\dagger}\)Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment.

*Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy; \#Surgical CR; \#RECIST 1.1
Larotrectinib for \textit{NTRK}+ tumors: Substantial benefit

Presented By Ulrick Lassen at 2018 ESMO Meeting
The future is here…

• Precision cancer medicine improves patient outcomes

• A basic (?expert) understanding of tumor biomarkers is critical to management of cancer patients (and part of the guidelines)

• Resources are needed to assist clinicians understand key biomarkers and provide decision-making support

• Infrastructure is needed to consume and handle results of multiplexed clinical genomic assays
Duke Molecular Tumor Board (V2.0)

- First meeting: 1/29/2018
- Multi-disciplinary group of oncologists, surgeons, pathologists, geneticists
- ~1208 cases reviewed in 2018
- 20-30 cases per week
- ~20% - recommend targeted therapy
- ~10% - recommend genetic counseling
- ~50% cases have discussion re: diagnostic/prognostic implications
- QC issues identified
- Multiple research concepts generated
Duke MTB Mission

• Foster precision medicine within the DCI
  – Support patient enrollment/treatment on molecular/biomarker directed therapies/trials
  – Deliver high impact genomic information to scientists/clinicians/pathologists/clinical trial staff and our patients
Most cases reviewed are based on Foundation Medicine and Myeloid NGS testing
Detection of germline alterations – referral to genetic counseling discussed

alterations with germline HRD implications

none

FANCA
CHEK2
BRCA2
BRCA1
ATM
PMS2
PALB2
Case example

- 61 yo M with metastatic pancreatic cancer, progression on frontline chemotherapy.
- FoundationOne assay revealed BRCA2 mutation, confirmed to be germline by separate testing.
- Important implications for patient re: genetic counseling and PARP inhibition as option.

TUMOR TYPE: PANCREAS DUCTAL ADENOCARCINOMA

Genomic Alterations Identified†
- BRCA2 E260fs*15
- KRAS G12V
- CDKN2A/B loss
- CHD4 splice site 4515+1G>C
- MLL2 R2235fs*1
- SMAD4 D537fs*40

Additional Findings†
- Microsatellite status: MS-Stable
- Tumor Mutation Burden: TMB-Low; 5 Muts/Mb

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix.
Why MTB database is needed: MyPathway trial

- **EGFR activating mutation**
  - erlotinib

- **BRAF V600E**
  - vemurafenib/cobimetinib

- **SMO activating mutation, PTCH1 loss of function**
  - vismodegib

- **ALK mutation, fusion, CNV**
  - alectinib

- **PD-L1 gain, MSI-high, TMB > 10 muts/mb, dMMR**
  - atezolizumab

- **ERBB2 amplification**
  - trastuzumab/pertuzumab
10-15% of patients have an actionable alteration for My Pathway
Why MTB database is needed: MyPathway trial

• 6/2016: Duke Phase I clinical trial team opened a multi-cohort “basket” clinical trial to pair molecular alterations with targeted therapies
• 6 molecular targets/ all solid tumors eligible
• 49 sites nationally
• Over 1,000 Duke patients received NGS profiling
• Total enrollment over 2 years: 6 patients
  – Initial plan: “Word of mouth” to match patients with trials
  – No mechanism to alert MD that pt has an actionable alteration
  – No mechanism to alert the clinical trial team that there are patients potentially eligible for trial
Where is the disconnect?
Clinical trial schematic

Timeline (months)

1st line treatment
2nd line Treatment
3rd line treatment
4th line treatment
5th line treatment
Supportive care

Foundation Medicine
Genes: A, B, D

G360
Genes: B, D, E

Trials Available for Gene
A
B
C
D
E

Window for trial
PRECISE: A Clinical Grade Automated Molecular Eligibility and Just-In-Time Physician Decision Support Solution for Molecularly-Selected Oncology Trials

Building a PRECISE Cohort

INSTITUTIONAL DATABASE

Patient Scheduling System → Surgical Pathology

MSK-IMPACT Results → Electronic Medical Record

Molecular inclusion/exclusion criteria
- Gene
- Alteration class
- Variant

Vital Status → Tumor Type

PRECISE Cohort
Conclusions

- PRECISE prospectively identified 327 (44%) of patients who subsequently enrolled in a clinical trial
- Facilitated accrual of a wide range of molecular alterations and tumor types
- Reveals that matches do not occur immediately after sequencing:
  - Median time from sequencing to consent: 163 days
  - Identification by PRECISE to consent: 87 days
- More refined criteria required to increase precision of patient-trial matches
Future Avenues for PRECISE

- Inclusion of additional patient characteristics in matching
- Automated, Just-In-Time primary oncologist alerts
- Artificial intelligence and machine learning for more specific patient-trial matches

**darwin**

Notification of potential eligibility
IRB Protocol 13-140

Dr. Baselga,

The below are patient under your care with a scan today and a previously detected \textit{ERBB2} mutation potentially qualifying them for participation in our basket study of neratinib (MSK IRB# 13-140), an oral pan-HER inhibitor. If, based on these results, you feel this patient might be appropriate I would be happy to discuss with you more or see this patient anytime.

Thank you,
David Hyman

Key Eligibility:
- no max prior therapies
- must have measurable disease OR PET avid lesions (bone only ok).
- no prior lapatinib

Study Design
- Monthly visits
- No required biopsies or PKs
- Scans every 2 months

**Upcoming Scans**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Qualifying Aberrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Patient name]</td>
<td>\texttt{ERBB2 - L755S}</td>
</tr>
<tr>
<td></td>
<td>\texttt{del(7/14)}</td>
</tr>
</tbody>
</table>

Click here to permanently exclude this patient for consideration on this study
Molecular registry

https://mrt.dhe.duke.edu

Total Specimens: 2426

adrenal gland ampulla of vater anus appendix bile duct bladder blood bone bone marrow brain breast cervix colon colon/rectum craniopharyngioma duodenum esophagus fallopian tube gallbladder gastro-esophageal junction gist (gastrointestinal stromal tumor) head and neck head or neck kidney leiomyosarcoma liver liver/bileduct lung lymph node mediastinum nasopharynx and paranasal sinuses not provided ovary pancreas parathyroid penis peritoneum pleura prostate rectum salivary gland skin small intestine soft tissue spine stomach testis thymus thyroid unknown unspecified primary ureter urethra urothelial carcinoma uterus vulva
I pity the fool who doesn’t know how many \textit{SETD2} mutations his institution has seen in the last 6 months!
Mr. T continuously updates Foundation Medicine & Guardant360 data in a curated form using standards-compliant nomenclature in a DHTS-secured environment. PHI is protected by program-specific roles. Robust APIs allow for data consumption from any source. Clinical trial/treatment matching code can alert clinicians to actionable mutations and potential clinical trials.

<table>
<thead>
<tr>
<th>Report de-Id</th>
<th>Organization</th>
<th>Performed On</th>
<th>Collected On</th>
<th>Diagnosis</th>
<th>Variant</th>
<th>Variant Type</th>
<th>Pathogenicity</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>e975ed94-331b-4086-b342-9d3160871465 (FoundationOne CDX (v3.1.3))</td>
<td>DUHS</td>
<td>2019</td>
<td>2018</td>
<td>appendix adenocarcinoma source: soft tissue</td>
<td>SETD2(NM_014159)c.4187delA(p.N1396fs*16)</td>
<td>insertion/deletion, frameshift</td>
<td>Likely Pathogenic</td>
<td>SETD2</td>
</tr>
<tr>
<td>4a637127-577a-4bd5-a7a9-d9a2e48c53b (FoundationOneDX (QSR_F1DX_v1.0.5))</td>
<td>DUHS</td>
<td>2018</td>
<td>2016</td>
<td>skin melanoma source: skin</td>
<td>SETD2(NM_014159)c.4861G&gt;A(p.G1621R)</td>
<td>substitution, missense</td>
<td>Pathogenic</td>
<td>SETD2</td>
</tr>
<tr>
<td>b7a32a9d-00cf-4561-999b-a1ff0f087a54 (FoundationOne CDX (v3.1.3))</td>
<td>DUHS</td>
<td>2018</td>
<td>2018</td>
<td>esophagus adenocarcinoma source: esophagus</td>
<td>SETD2(NM_014159)c.6179C&gt;A(p.S2060*)</td>
<td>substitution, nonsense</td>
<td>Likely Pathogenic</td>
<td>SETD2</td>
</tr>
<tr>
<td>bd29c4ad-dabb-41f1-b4e4-ccae6ef344d7 (FoundationOneDX (QSR_F1DX_v1.0.4))</td>
<td>DUHS</td>
<td>2018</td>
<td>2018</td>
<td>prostate acinar adenocarcinoma source: prostate</td>
<td>SETD2(NM_014159)c.2752delT(p.S918fs*4)</td>
<td>insertion/deletion, frameshift</td>
<td>Likely Pathogenic</td>
<td>SETD2</td>
</tr>
<tr>
<td>0395202d-eacd-43ce-9d45-4e719ac17037</td>
<td>DUHS</td>
<td>2018</td>
<td>2018</td>
<td>brain glioblastoma (gmb)</td>
<td>SETD2(NM_014159)c.5290C&gt;T(p.Q1764*)</td>
<td>substitution, frameshift</td>
<td>Likely Pathogenic</td>
<td>SETD2</td>
</tr>
</tbody>
</table>
WEE1/dNTP depletion and synthetic lethality with SETD2 loss

UM1 group study of AZD 1775 in SETD2 advanced malignancies

Locally advanced or metastatic solid tumor malignancy other than ccRCC

Bi-allelic loss of SETD2 based on NGS Panel (fresh or archived tissue analysis)

Locally advanced or metastatic ccRCC

Loss of SETD2 based on NGS Panel (fresh or archived tissue analysis)

AZD1775 300 mg PO daily days 1-5, 8-12 of 21 day cycle

Enroll Stage 1 (N = 9 pts)

No Responses

≥ 1 Responses

Close Cohort

Enroll Stage 2 (N = 21 pts)

No Responses

≥ 1 Responses

Close Cohort

Enroll Stage 2 (N = 21 pts)
Other research initiatives

1. BRPC Alignment
   - Mr. T born in Pathology with Clinical Laboratory Data
   - Genomic data links to BRPC blood, tissues, cell lines and PDX models
   - Many ongoing projects requiring biospecimen cohorts with specific molecular variants, 2 published 2019
Research Initiatives

2. AACR (American Association for Cancer Research) GENIE (Genomics Evidence Neoplasia Information Exchange) Project
AACR GENIE Overview

• International pan-cancer registry built through data sharing
  – Driven by openness, transparency, and inclusion

□ GOAL: improve clinical decision making
  • Linking clinical genotype to clinical outcomes

□ Eight founding participants, now 19
  • North America & Europe
  • Plans for future expansion

□ Sponsored research
□ Collaborative projects

AACR GENIE Dataset (January 2019) contains 60,000 records!
AACR GENIE, 19 Participants
How the Registry Operates

The AACR Project GENIE Consortium, Cancer Discovery, 2017

A
- DFCI
- DUKE
- JHU
- MDA
- MSK
- CHOP
- WFU
- VICC

Clinical Sequencing
- regular data uploads

B
- clinical queries are posed based on registry content

Synapse
- Data mapped to common ontology and harmonized
- Limited PHI removed
- Data governance, provenance, and versioning in a secure, HIPAA-compliant environment.

www.aacr.org/genie/data

The AACR Project GENIE Consortium, Cancer Discovery, 2017

B
- clinical data required to answer the question are manually abstracted

genomic and clinical data linked

C
- Consortium/sponsor-only access 6 months to time of publication

www.aacr.org/genie/data
Define Virtual Cohorts of Interest
Important clinical dates (metastatic Dx, XRT, etc.)
Research Initiatives

3. “NGS Experience” IRB Protocol; QA projects in Pathology
   – Multiplatform QA correlation study for MSI testing (PCR vs. IHC vs. NGS tumor vs. NGS cfDNA)
   – Correlations with TMB and PD-L1
Future Initiatives

• Integrating NGS data as discrete elements in Epic, continued development of innovative Pathology tools
• Launching GenomOncology for enhanced bioinformatics, decision-making support and clinical trials matching
• Improving clinical annotation of molecular results
• We are looking for collaborators in the space of AI/EMR data extraction
Early research projects

- Assess negative predictive value of multiplexed genomic testing on cancer biopsies for germline alterations

- “Real world” analysis of use of myeloid targeted sequencing panels in acute myeloid leukemia patients

- Explore genomic predictors of primary/ acquired treatment resistance in patients with MSI-H cancers treated with anti-PD-1 antibodies
Conclusions

• Comprehensive genomic profiling vastly improves our ability to detect cancer alterations.

• We are already significantly impacting patient care.

• We are piloting systems to better characterize cancers with genomics and assign molecularly directed therapies (& trials).

• We have made substantial progress and we are learning more all the time!