Cancer Precision Medicine at LLNL

May 17, 2017

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Outline

- LLNL’s stake in precision oncology
- Collaboration with the National Cancer Institute
  - Aim, challenges, and current work
- Collaboration with the Cancer Registry of Norway
  - Current work: Cervical cancer screening
  - Nascent work: Cancer patient outcome prediction
Precision medicine can be fully enabled by the convergence of advanced supercomputing, life sciences, and big data.
Advancing Precision Medicine and Computing

Data and HPC capabilities enable advances in precision medicine

Bio data and complexity help guide evolution of computing through co-design
Country-Scale Data

- ~318 million people
- Federated healthcare
- No unique PIN across all databases

- ~5.2 million people
- Universal healthcare
- Unique PIN links all registries

- LLNL has established strong partnerships with both NCI and CRN
NCI-DOE Pilot 3
Population Information Integration, Analysis and Modeling

Improve the effectiveness of cancer treatment in the “real world” through computing
Report ID............................9-
Patient ID............................

[Report de-identified (Safe-harbor compliant) by De-ID v.6.24.5.]

<<PROTECTED[begin]>>

<PATIENT_DISPLAY_ID>
PAT-4816149
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1
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<TUMOR_RECORD_NUMBER>
1
</TUMOR_RECORD_NUMBER>

<CLINICAL_HISTORY>
Calcification right breast posterior.
</CLINICAL_HISTORY>

</TEXT_PATH_CLINICAL_HISTORY>

</TEXT_PATH_COMMENTS>

</TEXT_PATH_FORMAT_ID>

Final Diagnosis:
1. Breast, Right Breast with Calcifications Posterior, Core Biopsy:
Lobular Carcinoma in Situ (LCIS); See Comment.
Atypical Ductal Hyperplasia (ADH) Noted; No DCIS Identified.
Background of Blunt Duct Adenosis, Columnar Cell Change and Dilatation of Ducts.
Calcifications Seen in Benign Ducts.
No Evidence of Invasive Carcinoma.
2. Breast, Right Breast without Calcifications Posterior, Core Biopsy:
Benign Fatty Breast Tissue; Few Ductal Elements Identified.
No Evidence of Malignancy.

Comment:
An E Cadherin stain is performed on part 1. No DCIS is identified. The lobular carcinoma appears both classic and pleomorphic type. There is no evidence of invasive carcinoma.

This is reviewed at the daily Departmental Conference.

<GROSS_DESCRIPTION>

Container 1: Received in formalin labeled right breast biopsy with calcifications posterior are four cylindrical portions of tan to yellow, soft and delicate tissue ranging from 1.8 x 0.2cm to 3.8 x 0.2cm. The specimen is submitted in toto as 1A.

Container 2: Received in formalin labeled right breast without calcifications posterior are six cylindrical portions of tan to yellow, soft and delicate tissue ranging from 0.8 x 0.2cm to 3.8 x 0.2cm. The specimen is submitted in toto as 2A and 2B.

Fixation of specimens reviewed and assured to be 6 to 48 hours.

<<DATE[Dec 29 2031]>>

Microscopic Description:
Slides Reviewed.

1: Right breast core biopsy: Right breast core biopsy

2: Right breast core biopsy

3: Right breast core biopsy

4: Right breast core biopsy

5: Right breast core biopsy

6: Right breast core biopsy

<<PROTECTED[end]>>
### Colorectal Cancer

#### Pathology Reports
- Single or Fragment
- Pedunculated or sessile
- Lymph nodes

#### Pharmacy
- FOLFOX
- CAPEOX
- FOLFIRI
- FLOX
- Capecitabine Fluorouracil + Leucovorin

#### Radiology
- CT scan
- Other scan

#### Radiation Oncology
- IORT

#### Genomic/Lab
- CBC
- CEA
- RAS (KRAS and NRAS)
- BRAF
- MMR/MSI

#### Electronic Health Records
- Diagnosis
- Recurrence
- Progression
- Clinical Features
- Treatment plan

#### Claims
- Colonoscopy
- Surgery (colectomy, resection, diversion stent)

### Specific Variable Elements

#### Pathology Reports
- Text Fields
- Numeric Fields
- Genomic Tests

#### Pharmacy
- Drug Name
- Date of Fill
- Qty Dispensed

#### Radiology
- Text Fields
- Numeric Fields
- Image Data

#### Radiation Oncology
- Dosimetry
- Types
- Quantity

#### Genomic
- Biomarkers
- WGS
- Predictive Testing

#### Electronic Health Records
- Unstructured Text Fields
- Structured Text Fields
- Attachments
- Clinical Codes

#### Claims
- Treatment
- Procedures
- Clinical Codes
- Other
Surveillance data captured/planned on each cancer patient for the entire population

Diagnosis → Pathology → Molecular Characterization → Initial Treatment → Subsequent Treatment → Progression Recurrence → Survival Cause of Death

Understand treatment and improve outcomes in the “real world”

Prospectively support development of new diagnostics and treatments

SEER Cancer Information Resource

Exposome

Genome
Norway Cervical Cancer Screening Dataset

- National database of **1,728,336** unique Norwegian women’s cervical cancer screening results
- Records cover **1991–2015**
- **10,753,752** individual records (rows)
- Current dataset has 10 columns:
  - Patient ID, birthdate, diagnosis date, test type, diagnosis1, diagnosis2, stage, lab number, region, censor date
Diagnostic Test Dependent, Mixture HMM

$Z$ : Latent Class (*frailty*)

$S_t$ : Disease State (*healthy*, *sick*)

$D_t$ : Diagnosis Test (*cytology*, *histology*)

$X_t$ : Observed Test Result (*severity*)
Histogram of Personalized Screening Intervals

Frequency

Screening Intervals in Years
Personalized Cervical Cancer Screening

- Define a policy to guide individualized screening
  - Optimal resources allocation
    - Low risk women should be screened seldomly
    - High risk women should be screened frequently

When to screen for cervical cancer

Age 21 y
Begin screening for cervical cancer

Age 21-30 y
Pap test every 3 years if results normal

Age 31-64 y
Pap test every 3 years or Pap test + HPV test every 5 years

Age 65 y and older
Stop routine screening if results normal for the previous 10 years

Maximize screening interval when at low risk
Reduce screening interval when at higher risk

Develop a data-guided individualized cervical cancer screening protocols
What’s Next for the LLNL-CRN Collaboration?

Goal: To accurately predict cancer patient outcome

- Recurrence
- Survival probability given time window
- Response to specific treatment

How will different interventions affect the course of the patient’s health trajectory?

- Disease burden/symptoms
- Time
- Cancer therapy
- Hospitalization
- Diagnostics test
Norway clinical registries – Patient trajectory

### Diagnose
- Start of primary treatment
- End of primary treatment

### Local relapse
- Time of relapse
- Time of metastatic disease

### Metastases
- Diagnosis
- Start of primary treatment
- End of primary treatment
- Time of metastatic disease

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D: Diagnostic report
S: Surgery report
R: Radiotherapy
C: Chemotherapy report
H: Hormone therapy report
P: Pathology report
D: Death certificate
N: Patient registry report
Q: Patient questionnaire

Slide generously provided by Jan Nygard (CRN)
Underlying Commonalities Example

**HPV**

- HPV is the cause of
  - ~99% of cervical cancers
  - ~70% of oropharyngeal cancers

- Evidence linking HPV to lung cancers
  - 15–20% of lung-cancer cases in men and 50% in women are in people who have never smoked. One hypothesis is that a virus might be the culprit.


[Diagram: Cancer probably caused by HPV type

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>HPV types 16/18</th>
<th>HPV types 31/33/45/52/58</th>
<th>Other HPV types</th>
<th>HPV-negative*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>can be prevented by bivalent and quadrivalent vaccines</td>
<td>can be prevented by 9-valent vaccine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Graph: Sex / Cancer Site]

- **Female**
  - Cervix
  - Vagina
  - Vulva
  - Anus
  - Rectum
  - Oropharynx

- **Male**
  - Penis
  - Anus
  - Rectum
  - Oropharynx

[Graph: Average number of cases per year]

[Website: CDC: https://www.cdc.gov/cancer/hpv/statistics/cases.htm]
Underlying Commonalities Example Ras

Schubbert et al. (2007) Nature Reviews Cancer

https://www.cancer.gov/research/key-initiatives/ras
In Summary...

- LLNL is invested in leveraging HPC to advance precision oncology
- Partnership with CRN and NCI are uniquely positioned to address challenges in precision medicine
- Work on personalizing cervical cancer screening is underway with promising initial results
- Nascent project on prediction of cancer patient outcome

Going forward

- HMMs:
  - Continue screening time optimization
  - Go beyond diagnostics and extend models to predict patient outcome
- Deep multitask learning
  - Late network fusion
Our team

- **LLNL**
  - Ghaleb Abdulla
  - Braden Soper
  - Priyadip Ray

- **NCI-DOE Pilot 3 team led by Lynne Penberthy (NCI) and Gina Tourassi (ORNL)**

- **Cancer Registry of Norway**
  - Jan Nygard
  - Mari Nygard
  - Giske Ursin
Thanks!