

Cancer Precision Medicine at LLNL

May 17, 2017

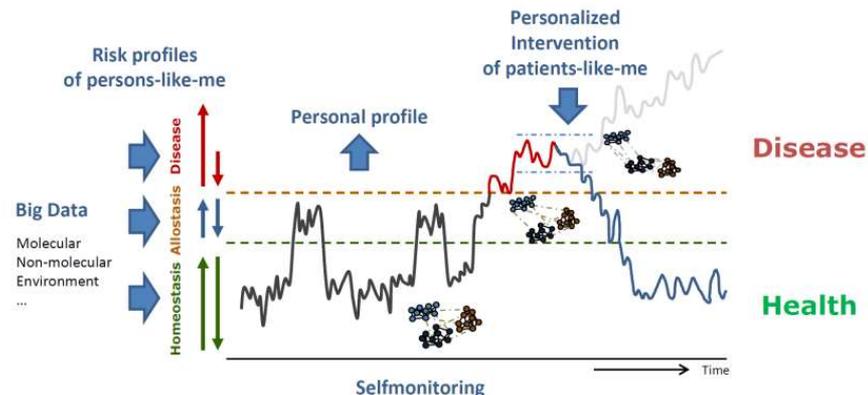
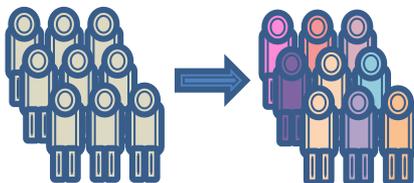
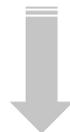
Ana Paula Sales



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



Prapat Suriyaphol (2016) Precision Medicine – the future of healthcare

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

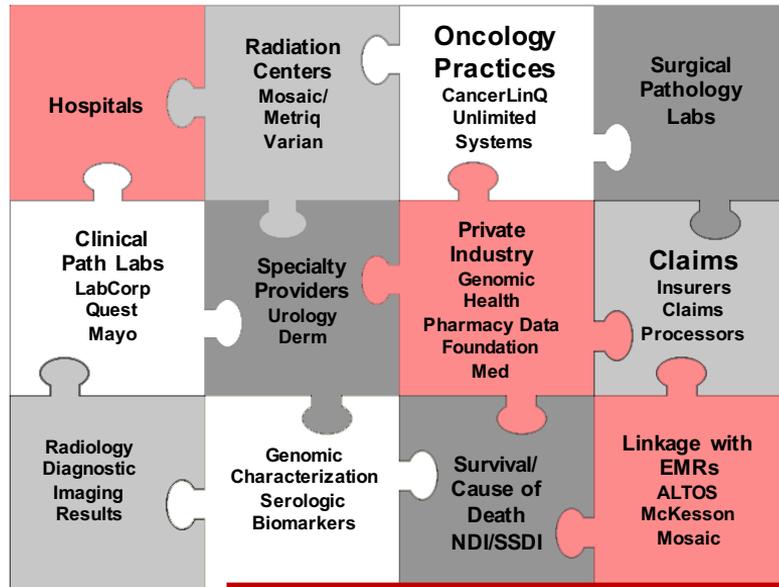


Bio data and complexity help guide evolution of computing through co-design

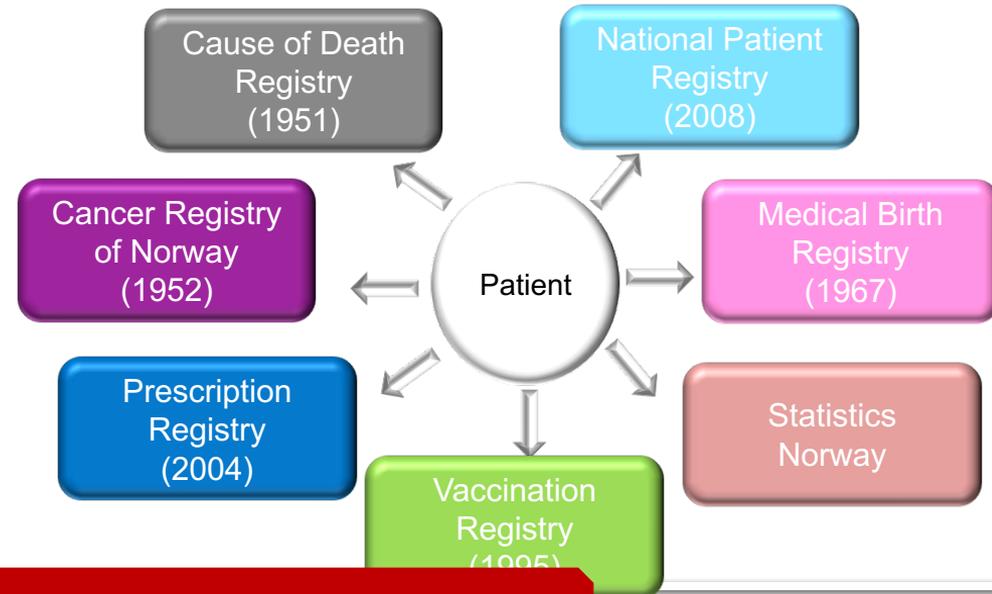


Country-Scale Data

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



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

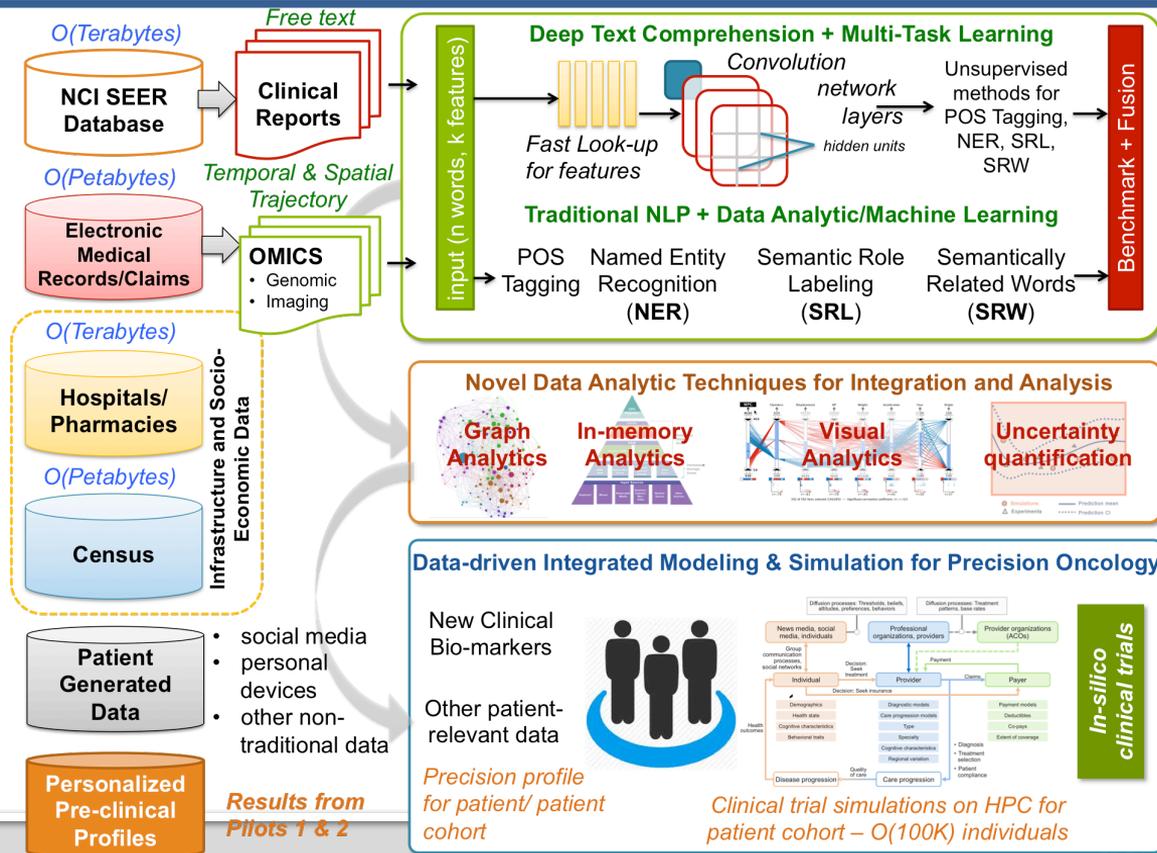


LLNL has established strong partnerships with both NCI and CRN

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.6.24.5.2]

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ClinicalHistory:
  Calcification right breast posterior.
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FinalDiagnosis:
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.

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2. Breast, Right Breast without Calcifications Posterior, Core Biopsy:
  Benign Fatty Breast Tissue; Few Ductal Elements Identified.
  No Evidence of Malignancy.

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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 case is reviewed at the Daily Departmental Conference.

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<TEXT_PATH_GROSS_PATHOLOGY>

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GrossDescription:
 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 1.0 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 3.0 x 0.2cm. The specimen is submitted in toto as 2A and 2B.

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

```

AC:left **DATE[Oct 29 2013].
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MicroscopicDescription:
  Slides Reviewed.
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1: Right breast core biopsy2: Right breast core biopsy
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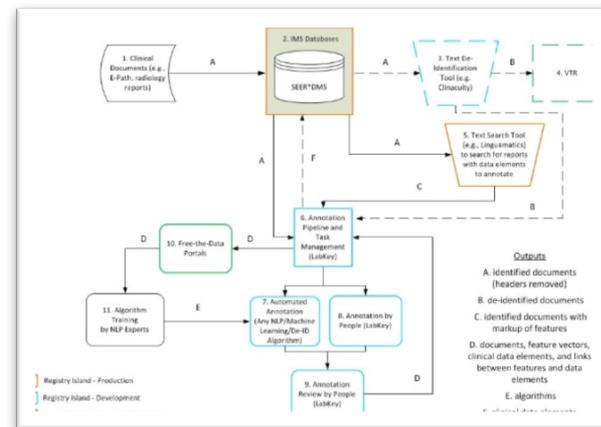
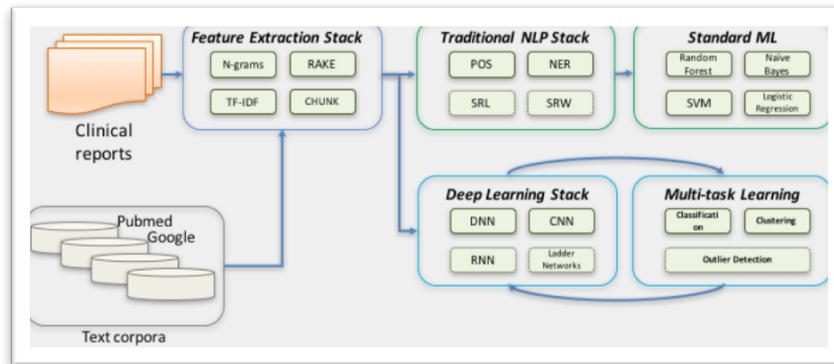
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E_O_R



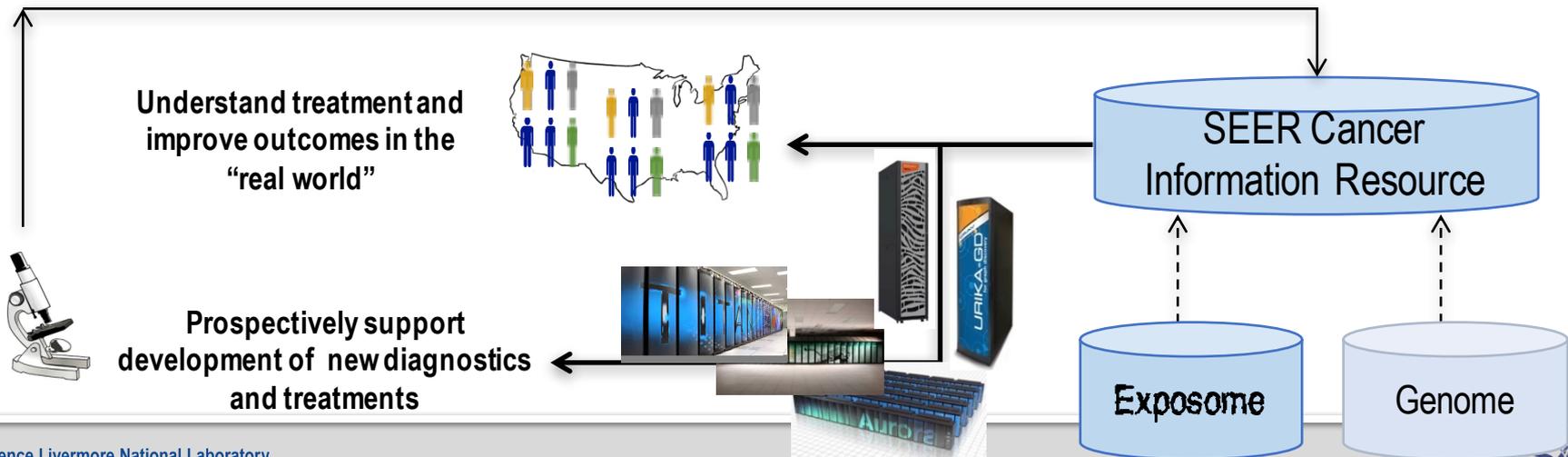
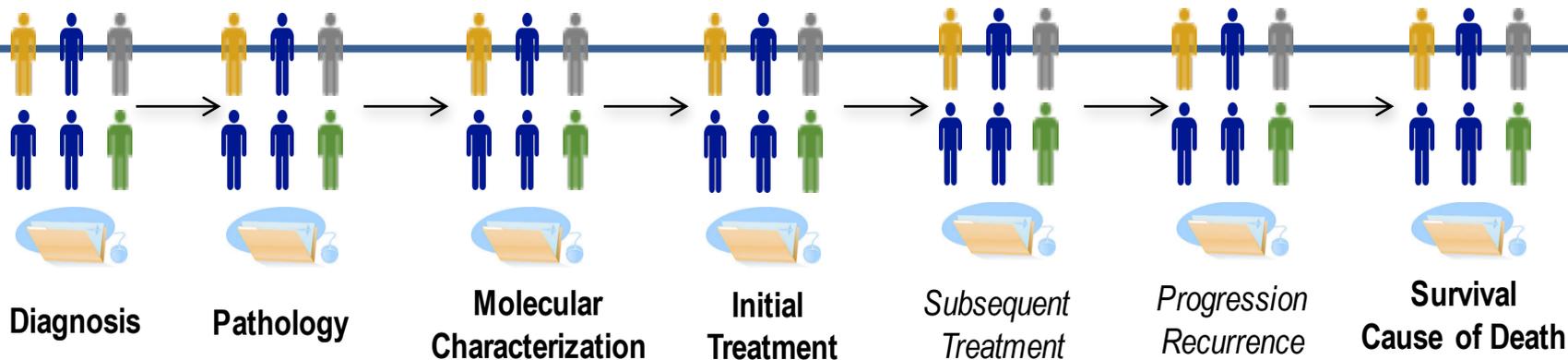
Colorectal Cancer

Pathology Reports	Pharmacy	Radiology	Radiation Oncology	Genomic/Lab	Electronic Health Records	Claims
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Single or Fragment	<input type="checkbox"/> FOLFOX	<input type="checkbox"/> CT scan	<input type="checkbox"/> IORT	<input type="checkbox"/> CBC	<input type="checkbox"/> Diagnosis	<input type="checkbox"/> Colonoscopy
<input type="checkbox"/> Pedunculated or sessile	<input type="checkbox"/> CAPEOX	<input type="checkbox"/> Other scan	<input type="checkbox"/>	<input type="checkbox"/> CEA	<input type="checkbox"/> Recurrence	<input type="checkbox"/> Surgery (colectomy, resection, diversion stent)
<input type="checkbox"/> Lymph nodes	<input type="checkbox"/> FOLFIRI		<input type="checkbox"/>	<input type="checkbox"/> RAS (KRAS and NRAS)	<input type="checkbox"/> Progression	
	<input type="checkbox"/> FLOX			<input type="checkbox"/> BRAF	<input type="checkbox"/> Clinical Features	
	<input type="checkbox"/> Capecitabine			<input type="checkbox"/> MMR/MSI	<input type="checkbox"/> Treatment plan	
	<input type="checkbox"/> Fluorouracil + Leucovorin					

Specific Variable Elements

Pathology Reports	Pharmacy	Radiology	Radiation Oncology	Genomic	Electronic Health Records	Claims
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Text Fields	<input type="checkbox"/> Drug Name	<input type="checkbox"/> Text Fields	<input type="checkbox"/> Dosimetry	<input type="checkbox"/> Biomarkers	<input type="checkbox"/> Unstructured Text Fields	<input type="checkbox"/> Treatment
<input type="checkbox"/> Numeric Fields	<input type="checkbox"/> Date of Fill	<input type="checkbox"/> Numeric Fields	<input type="checkbox"/> Types	<input type="checkbox"/> WGS	<input type="checkbox"/> Structured Text Fields	<input type="checkbox"/> Procedures
<input type="checkbox"/> Genomic Tests	<input type="checkbox"/> Qty Dispensed	<input type="checkbox"/> Image Data	<input type="checkbox"/> Quantity	<input type="checkbox"/> Predictive Testing	<input type="checkbox"/> Attachments	<input type="checkbox"/> Clinical Codes
					<input type="checkbox"/> Other	

Surveillance data captured/ planned on each cancer patient for the entire population



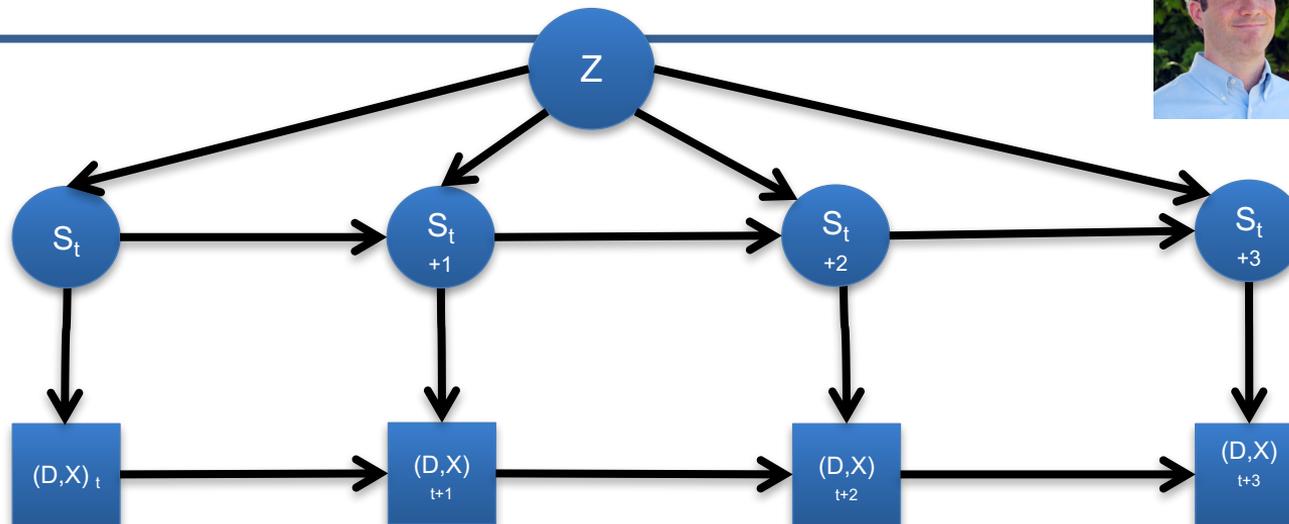
Norway Cervical Cancer Screening Dataset

- 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

Patient ID	Birthdate	Diagnosis date	Test type	Diagnosis 1	Region	...
1	12/15/1978	2/15/1998	Cyt	11	North	...
1	12/15/1978	4/15/2010	Cyt	11	North	...
2	11/15/1990	11/15/2008	Cyt	11	South-East	...
3	5/15/1956	5/15/1999	Cyt	12	West	...
3	5/15/1956	6/15/1999	Cyt	11	West	...
3	5/15/1956	6/15/1999	Hist	20	West	...
3	5/15/1956	9/15/1999	HPV	1	West	...
...

Diagnostic Test Dependent, Mixture HMM

Braden Soper Ghaleb Abdulla

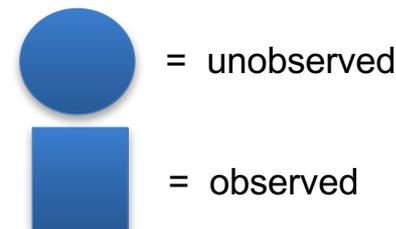


Z : Latent Class (*frailty*)

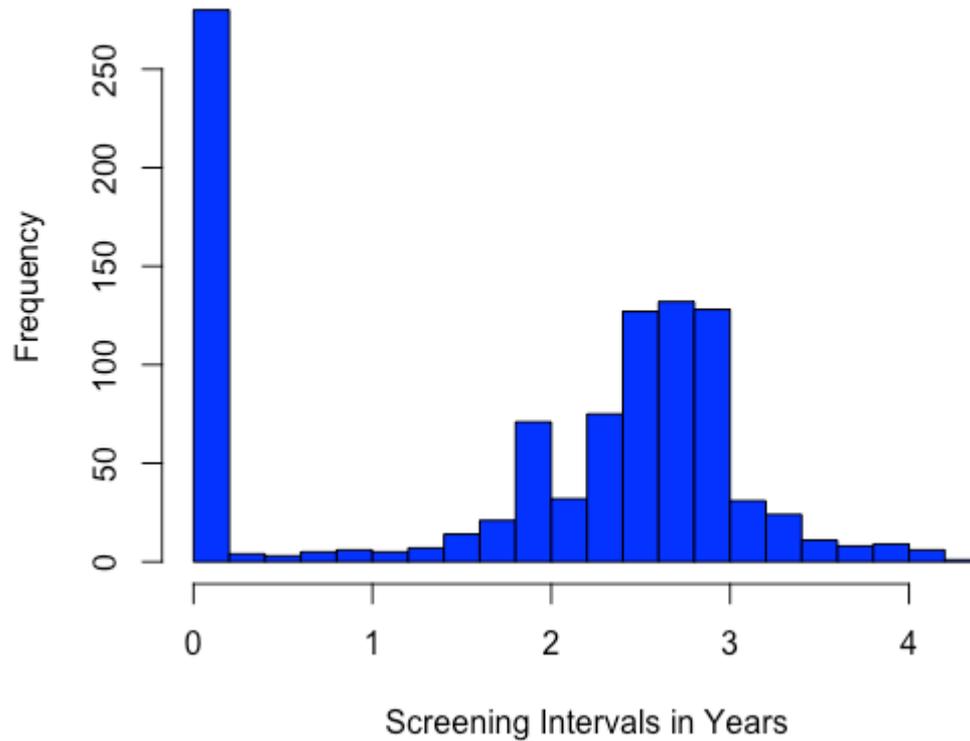
S_t : Disease State (*healthy, sick*)

D_t : Diagnosis Test (*cytology, histology*)

X_t : Observed Test Result (*severity*)



Histogram of Personalized Screening Intervals

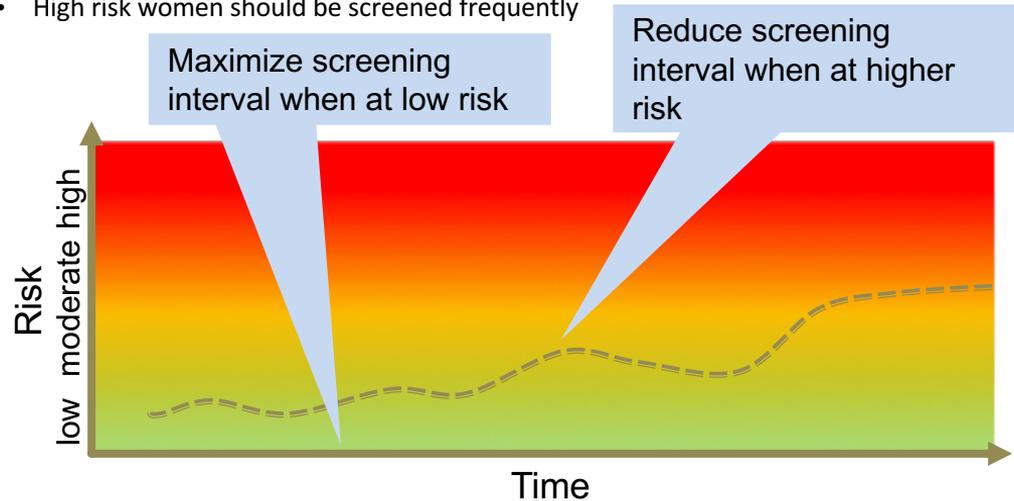
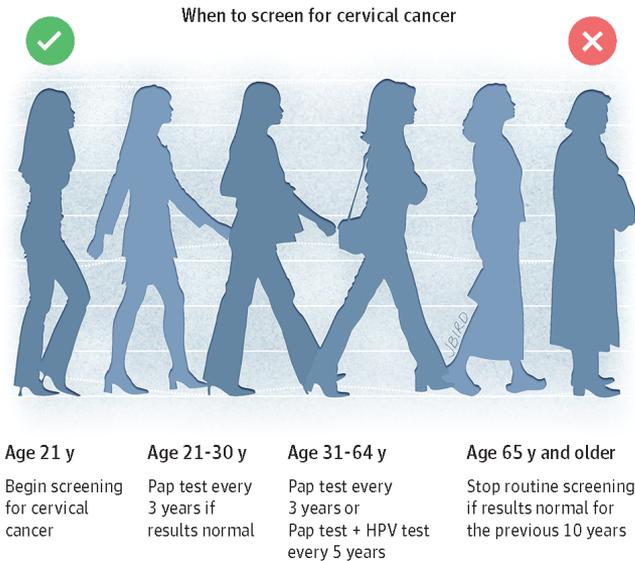


Personalized Cervical Cancer Screening

- Define a policy to guide individualized screening

- Optimal resources allocation

- Low risk women should be screened seldomly
 - High risk women should be screened frequently



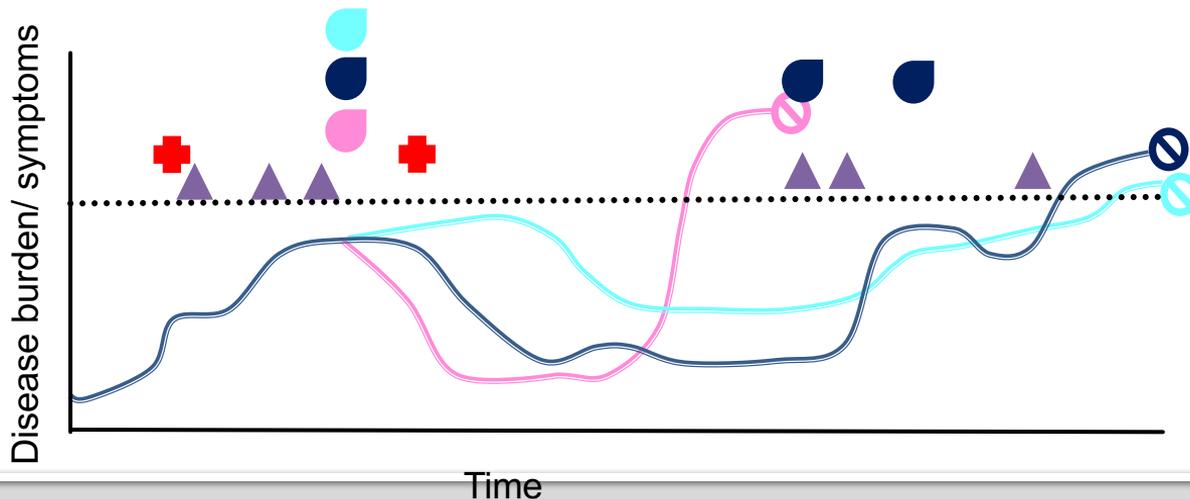
Develop a data-guided individualized cervical cancer screening protocols

What's Next for the LLNL-CRN Collaboration?

Goal: To accurately predict cancer patient outcome

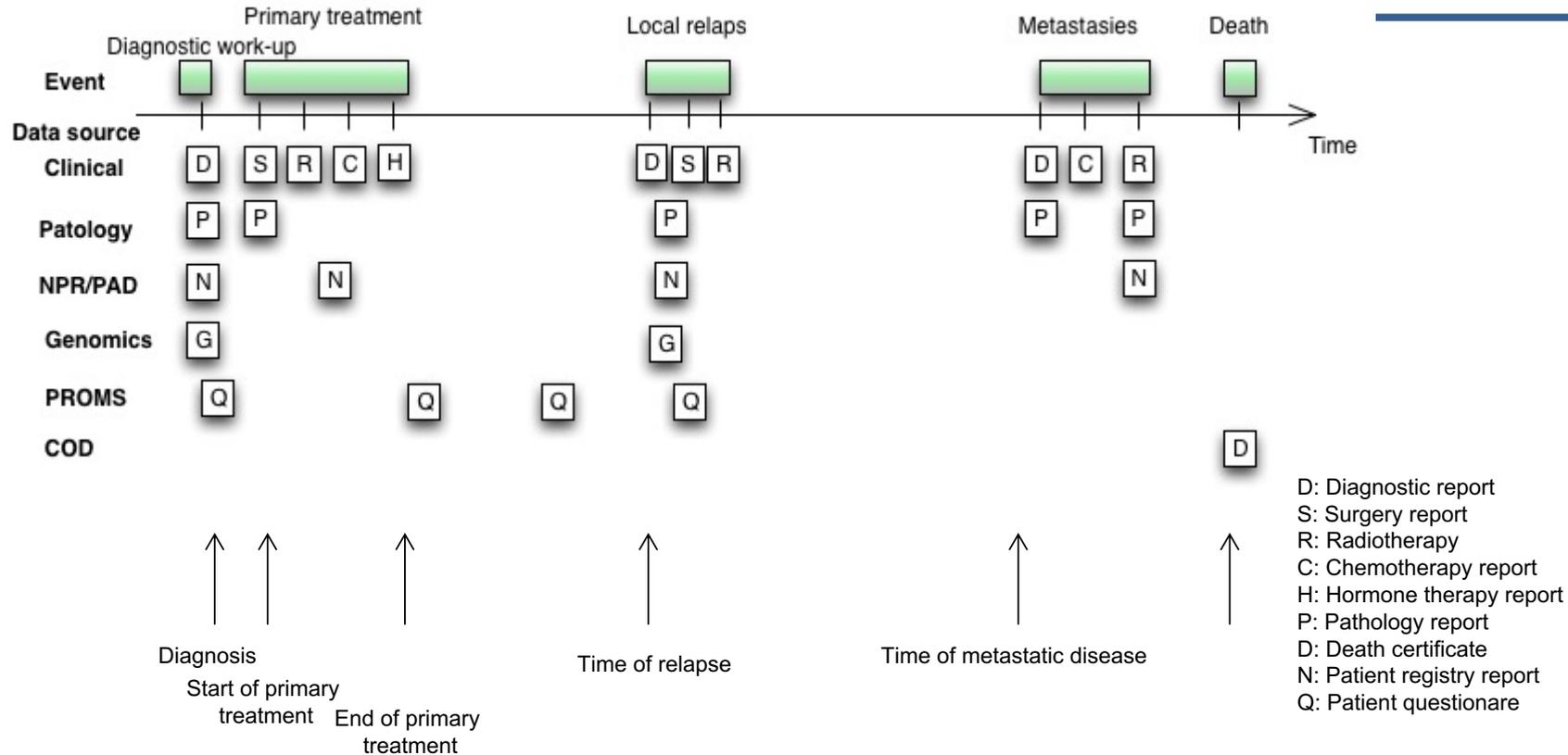
How will different interventions affect the course of the patient's health trajectory?

Recurrence
Survival probability
Response to specific treatment



- Cancer therapy
- ✝ Hospitalization
- ▲ Diagnostics test

Norway clinical registries – Patient trajectory

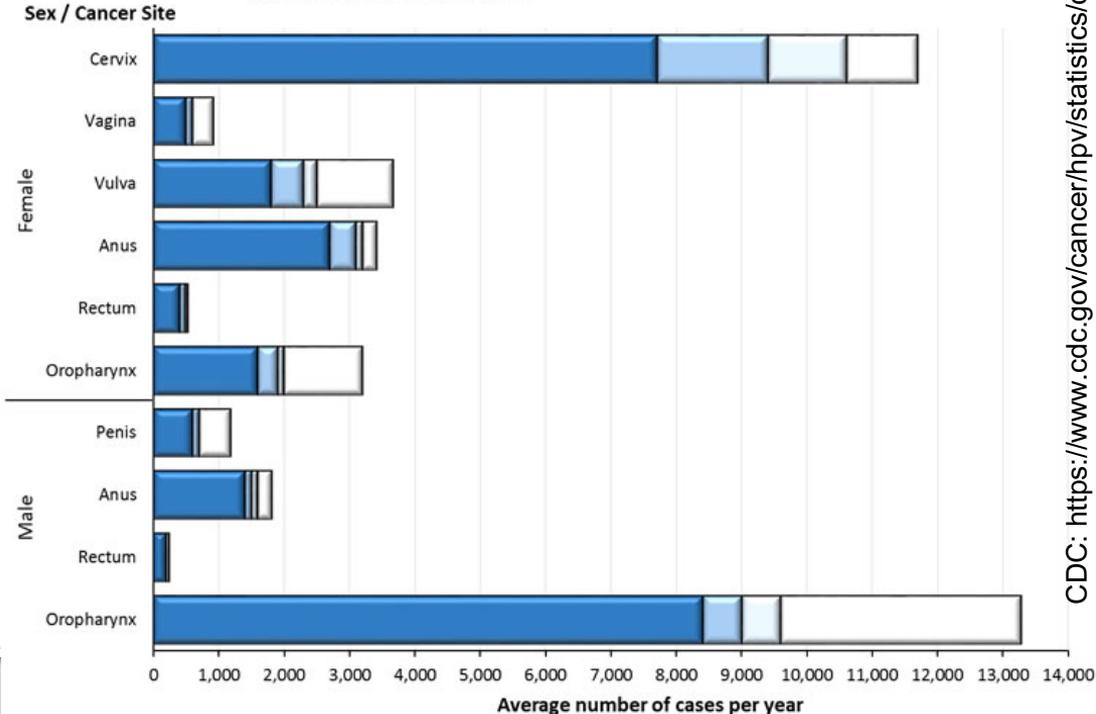
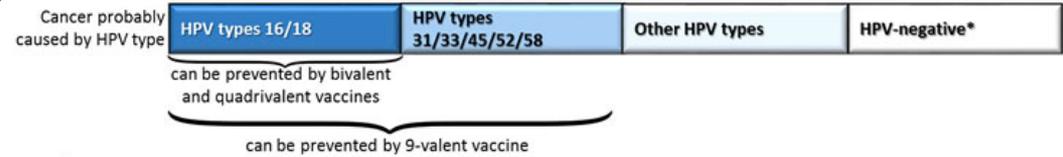
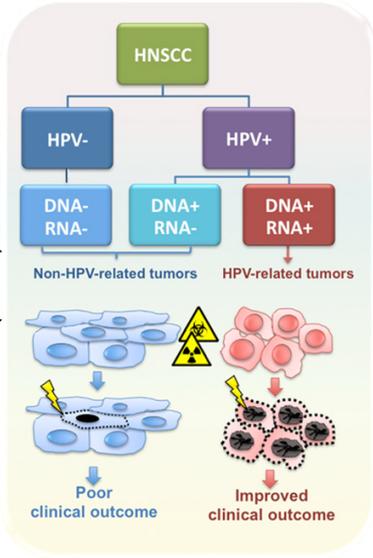


Underlying Commonalities Example

HPV

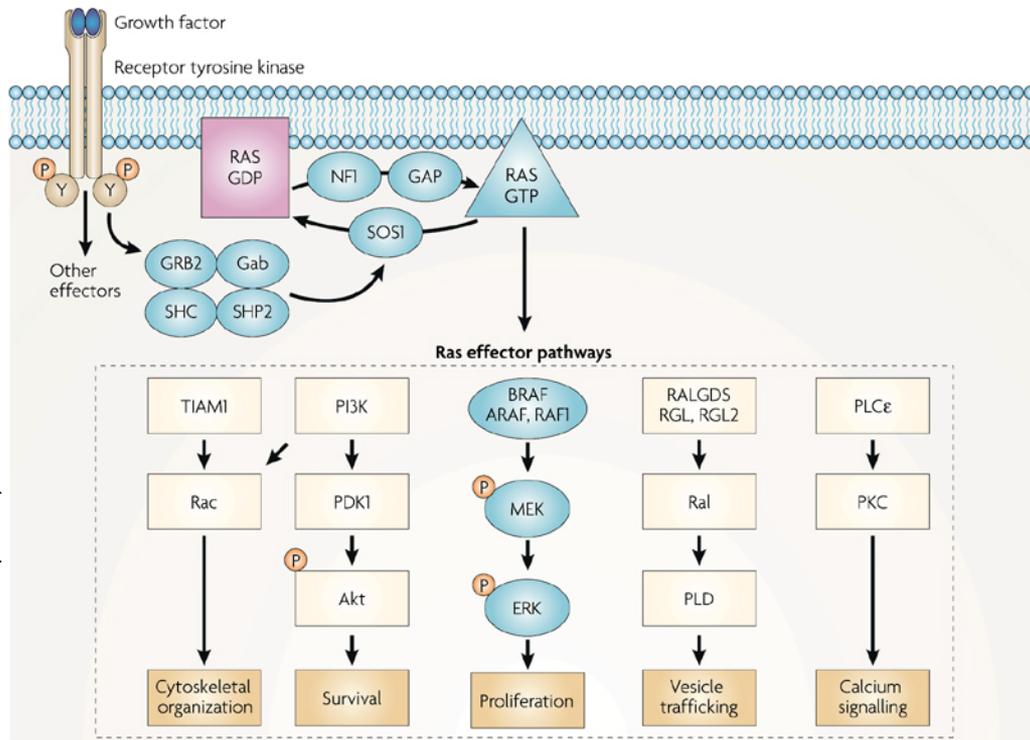
- HPV is the cause of
 - ~99% of cervical cancers
 - ~70% of oropharyngeal cancers
- Evidence linking HPV to lung cancers
 - 15–20% of lung-cancer cases in men and 50% in women are in people who have never smoked. One hypothesis is that a virus might be the culprit.

Kostareli et al (2012) Front. Oncol.



CDC: <https://www.cdc.gov/cancer/hpv/statistics/cases.htm>

Underlying Commonalities Example Ras



Nature Reviews | Cancer

<https://www.cancer.gov/research/key-initiatives/ras>

MORE THAN
30%

OF ALL HUMAN CANCERS
ARE DRIVEN BY MUTATIONS OF

RAS GENES

RAS MUTATIONS

IN HUMAN CANCERS

	PANCREAS – KRAS	95%
	COLORECTAL – KRAS	45%
	LUNG – KRAS	35%
	AML – NRAS	15%
	MELANOMA – NRAS	15%
	BLADDER CANCER – HRAS	10%

“RAS ONCOGENES ARE
THE **WORST** ONCOGENES.”

– Dr. Frank McCormick,
RAS National Program Advisor

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
- Cancer Registry of Norway
 - Jan Nygard
 - Mari Nygard
 - Giske Ursin
- NCI-DOE Pilot 3 team led by Lynne Penberthy (NCI) and Gina Tourassi (ORNL)

Thanks!

