IBM Watson Health

Building Cognitive Computing for Healthcare

ARCC Conference 2017

May 26th 2017

Patrick McNeillie M.D.
Clinical Lead and Architect on Watson for Genomics

IBM

Agenda

- Building Cognitive Computing
  -Defining the Importance of Natural Language Processing (NLP)
- Applying Cognitive to a Complex Problem
- Surfacing Valuable Insights in Big Data

IBM Watson Health

IBM

Moving Beyond Jeopardy: Bringing Cognitive Computing to Healthcare

Applying Cognitive Computing to Complex Problems

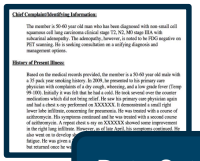
Define Attributes

Attribute Extraction

Compare to Prior Knowledge

Clinical Expert

What is the best treatment for a given patient?



Data Set

- Stage IIIA
- Squamous Cell
- Lung Cancer
- PD-L1 Receptor

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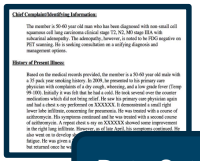

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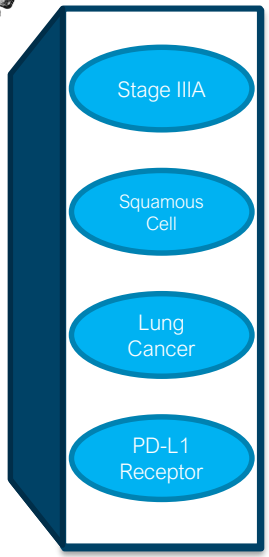
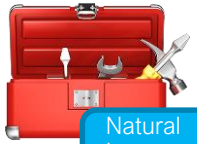
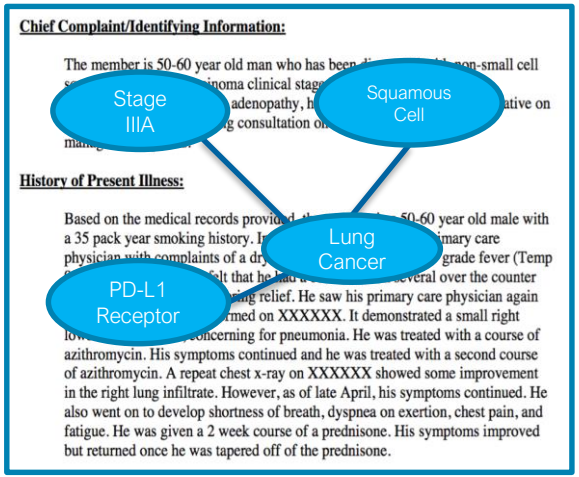




Natural Language Processing



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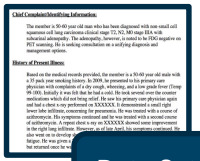

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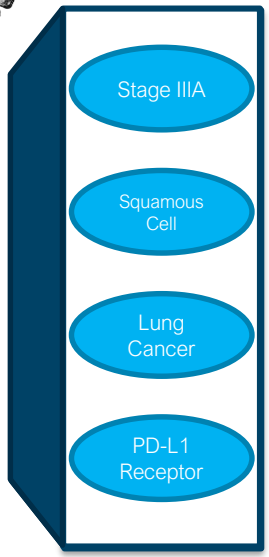
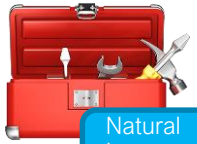
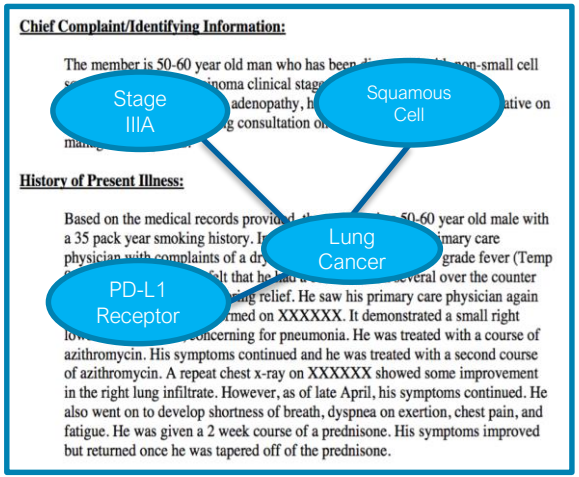
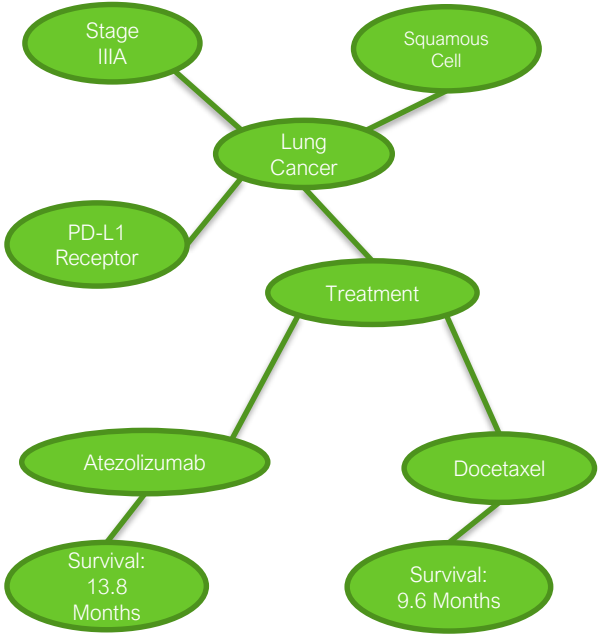




Natural Language Processing





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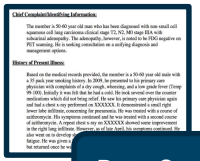

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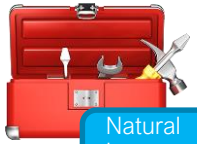

Natural Language Processing

Chief Complaint/Identifying Information:

The member is 50-60 year old man who has been [illegible] non-small cell [illegible]noma clinical stage [illegible] adenopathy, h[illegible] ative on [illegible]g consultation o[illegible]

History of Present Illness:

Based on the medical records provid[illegible] 50-60 year old male with a 35 pack year smoking history. I[illegible]imary care physician with complaints of a dr[illegible] grade fever (Temp [illegible] felt that he had a[illegible] several over the counter [illegible]ng relief. He saw his primary care physician again [illegible]rmed on XXXXXX. It demonstrated a small right [illegible] concerning for pneumonia. He was treated with a course of azithromycin. His symptoms continued and he was treated with a second course of azithromycin. A repeat chest x-ray on XXXXXX showed some improvement in the right lung infiltrate. However, as of late April, his symptoms continued. He also went on to develop shortness of breath, dyspnea on exertion, chest pain, and fatigue. He was given a 2 week course of a prednisone. His symptoms improved but returned once he was tapered off of the prednisone.

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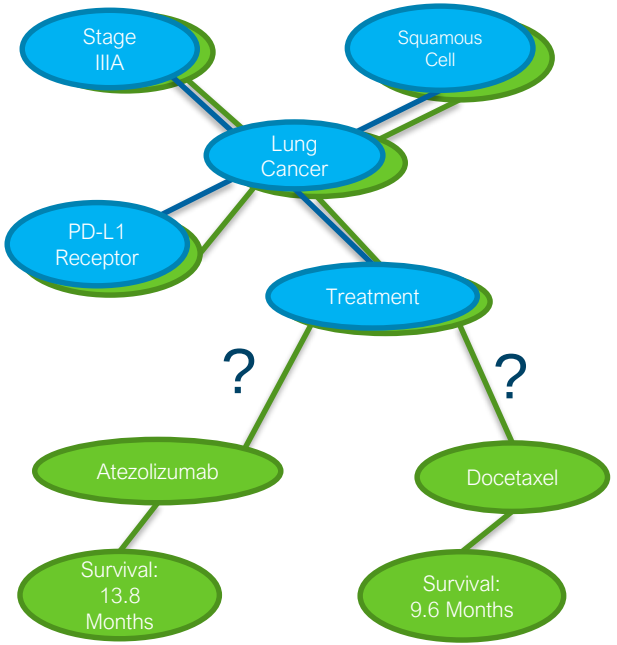
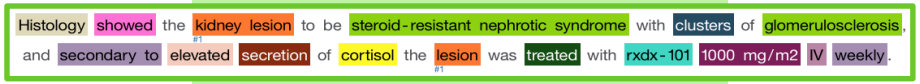
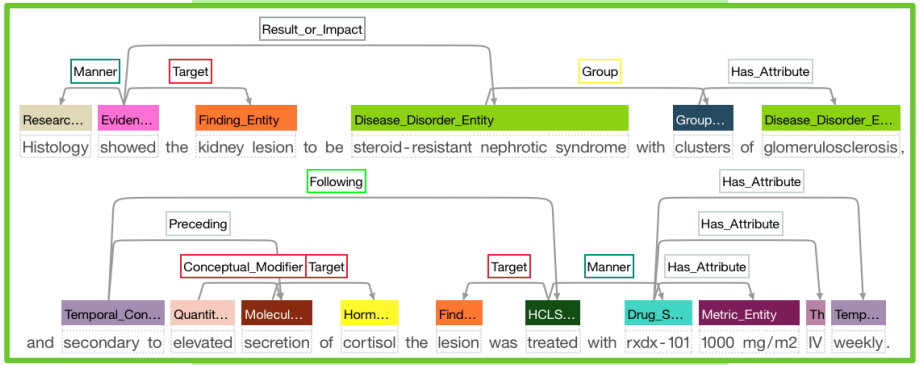


Differences in attribute extraction between Machine Learning and Rules-Based NLP

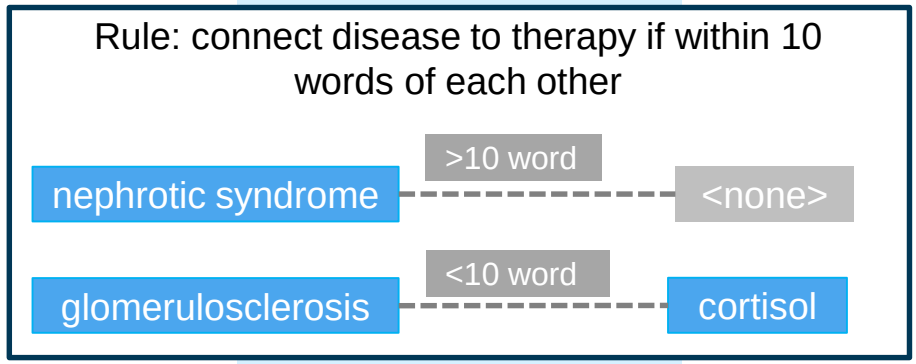
Machine Learning NLP





Disease	steroid resistant nephrotic syndrome <subtype> glomerulosclerosis
Therapy	rxdx-101

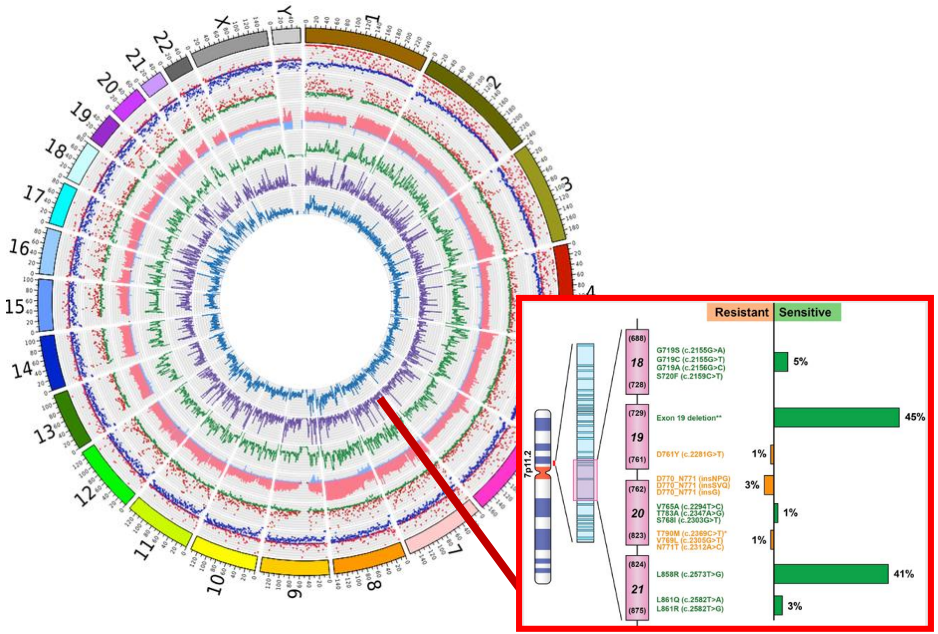
Rules-Based NLP



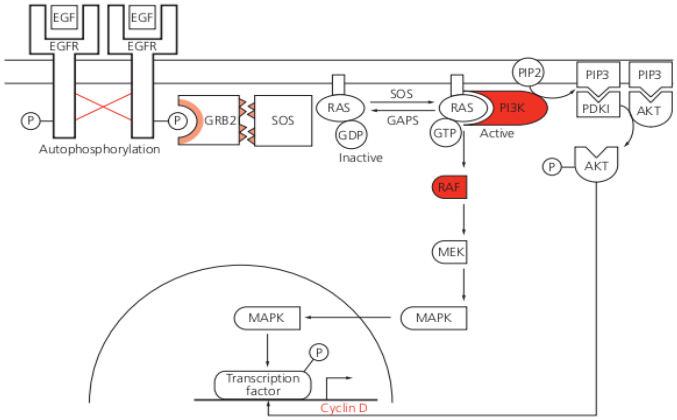
Disease	<conflict> nephrotic syndrome <conflict> glomerulosclerosis
Therapy	<incorrect> cortisol

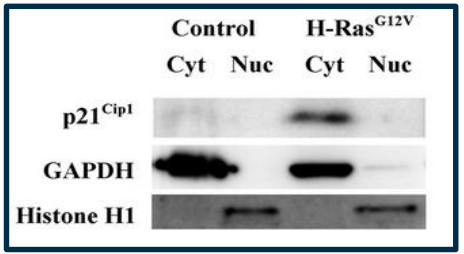
Applying Cognitive to Genomics

Impact on Medical Genomics



[COSMIC. Wellcome Trust Sanger Institute. October 2015]

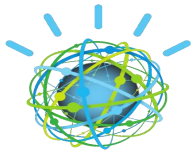




[Modern Pathology. 2012 Mar;25(3):347-69. (accessed 10/5/2015)]

What's the best treatment given a tumor sequence?

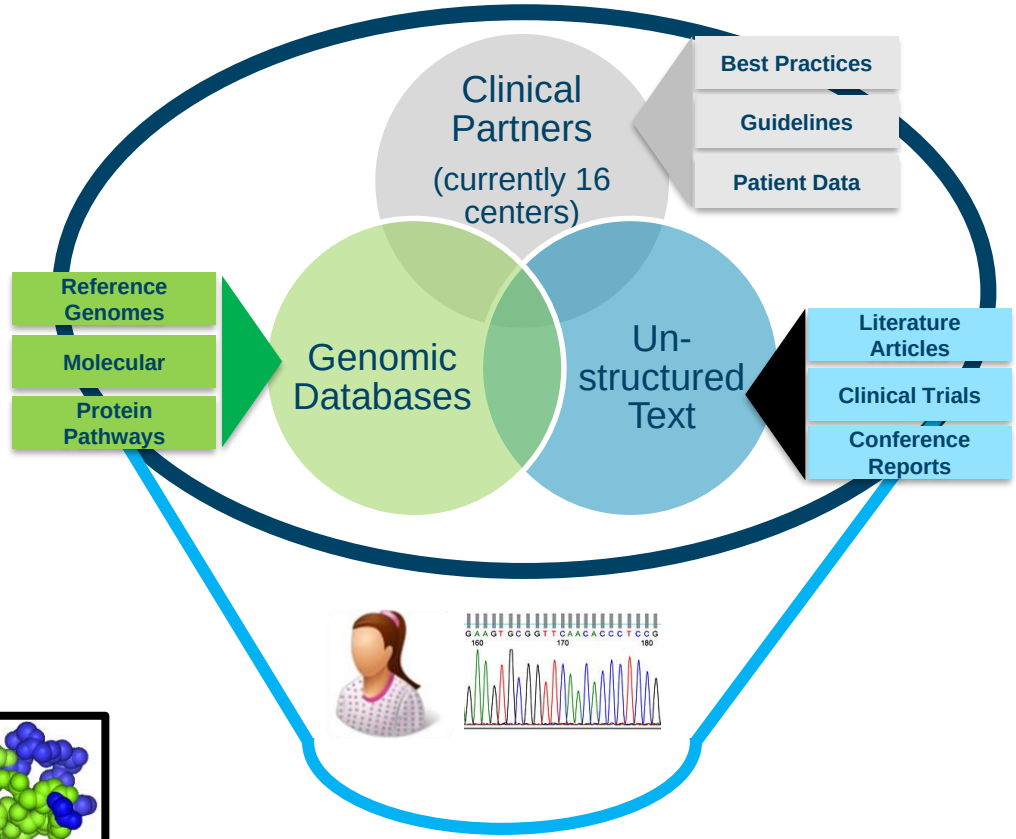
Gene	Alteration	Alteration Type	Functional Significance	Annotation	Actionable Gene	Actionable Variant
PDGFRA	Y288C	SNV				
PTEN	K163*	Trunc-ation				
FGFR2	K292M	SNV				

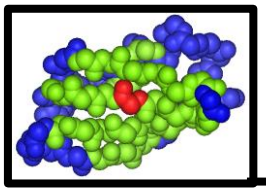


Ingest & Learn

Process Patient Data

Output Report





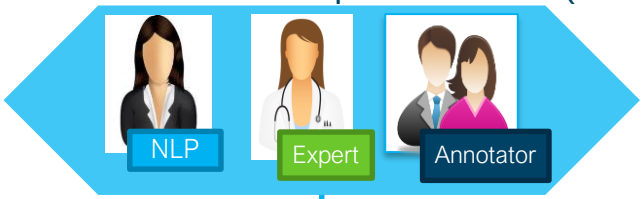
Personalized Driver Alterations and Targeted Therapies

IBM Watson Health

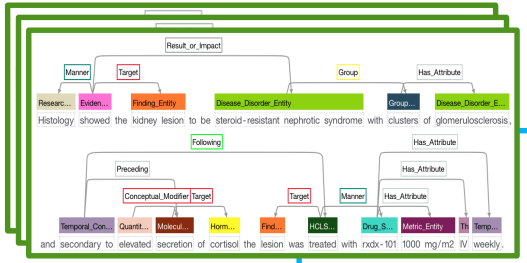
Our Approach to NLP

FAST Annotators working with Boston Children's Hospital physicians in March 2016

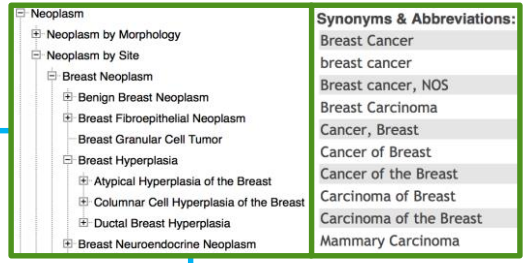
Focused Annotation Specialist Team (FAST)



Label Documents

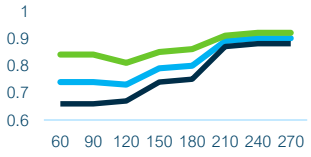


Standardize Ontologies and Dictionaries



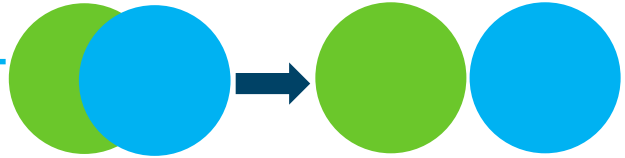
Train Machine Learning

Measure Performance



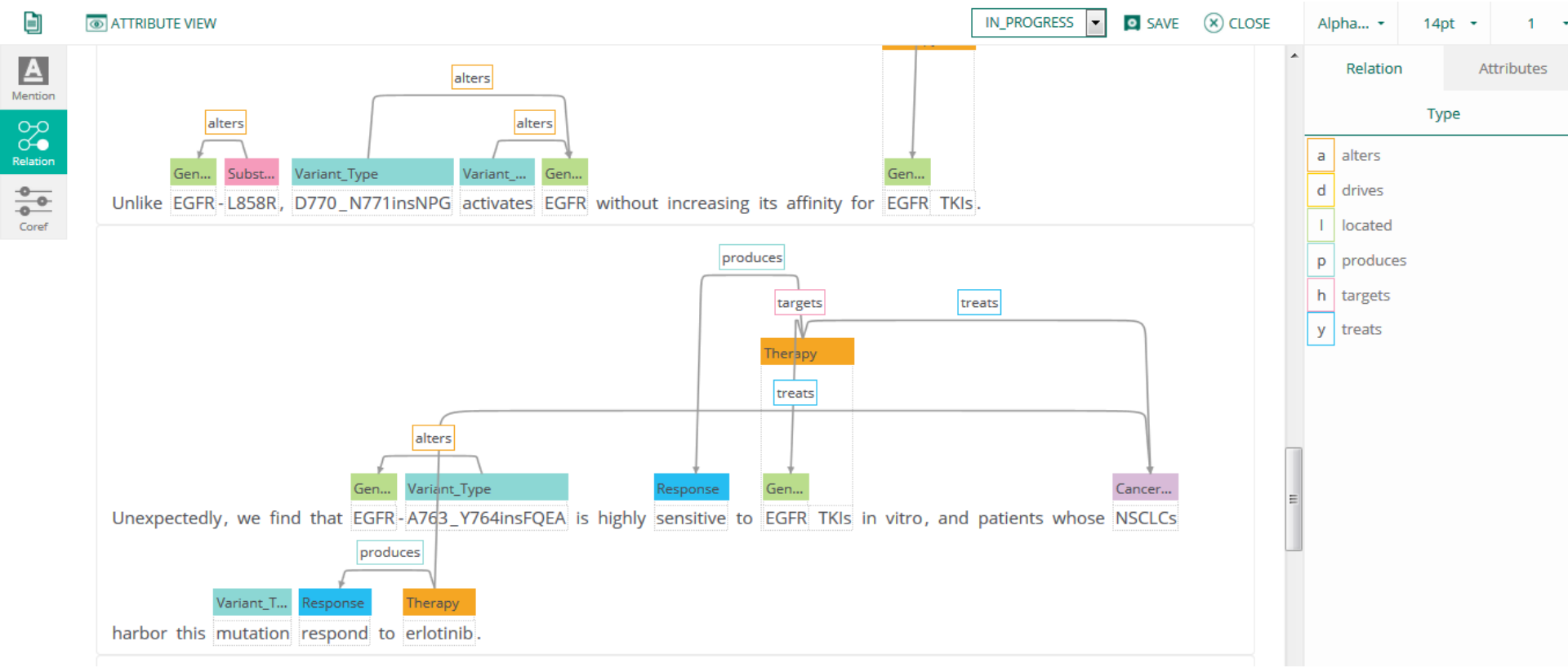
Enable Integration & Reuse

Reduce Bias

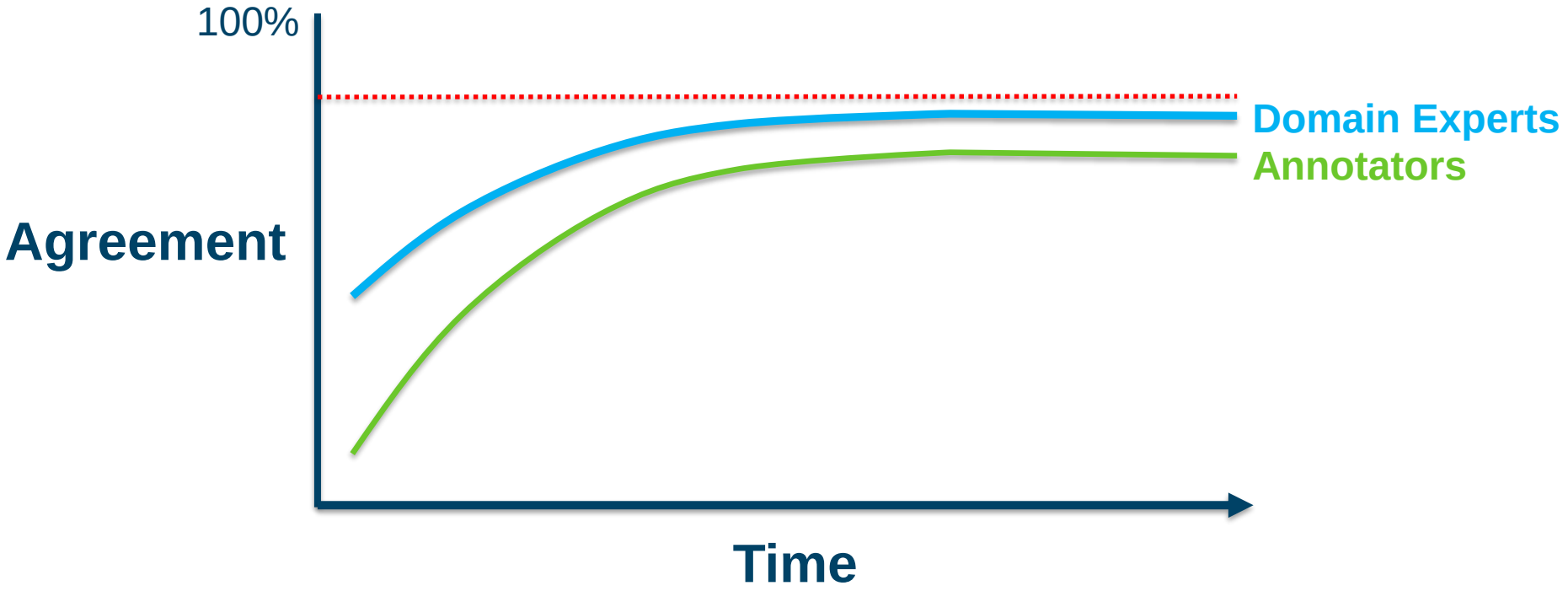


Annotating mentions

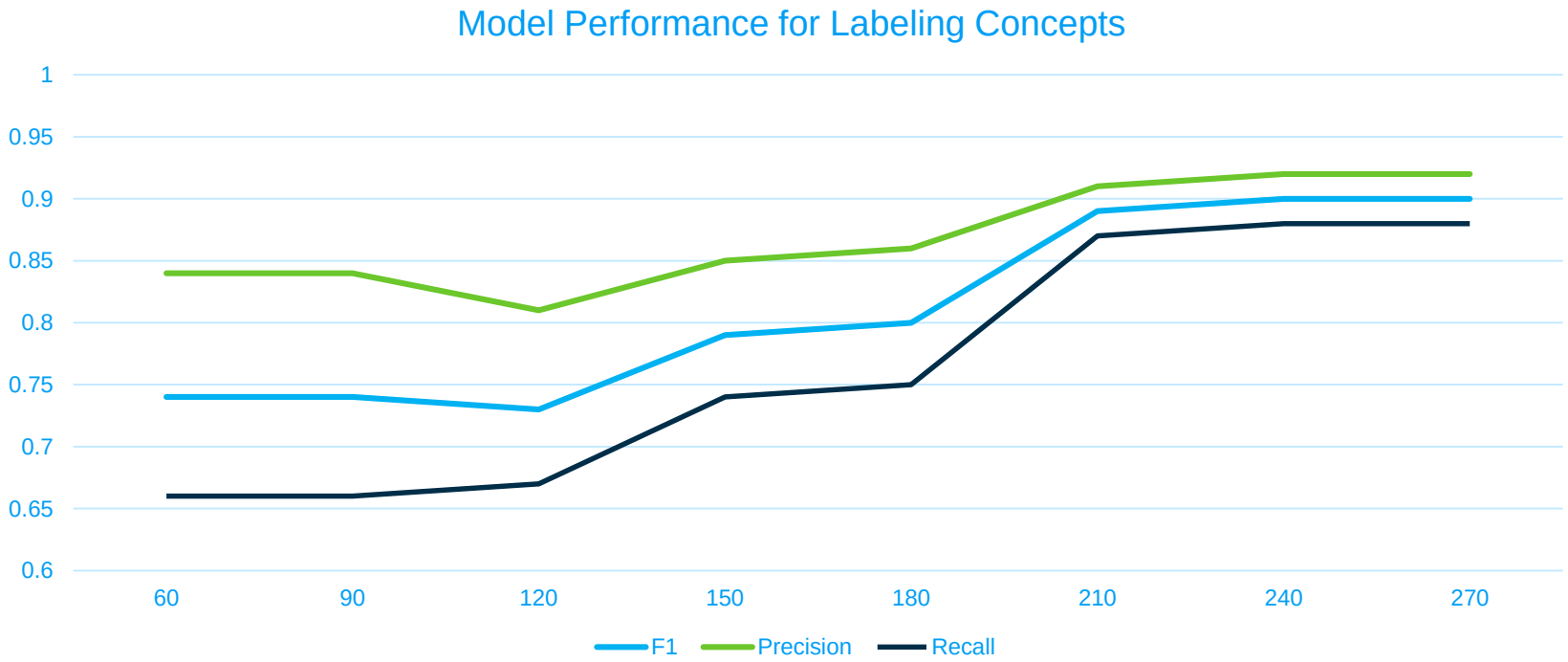
Annotating relationships



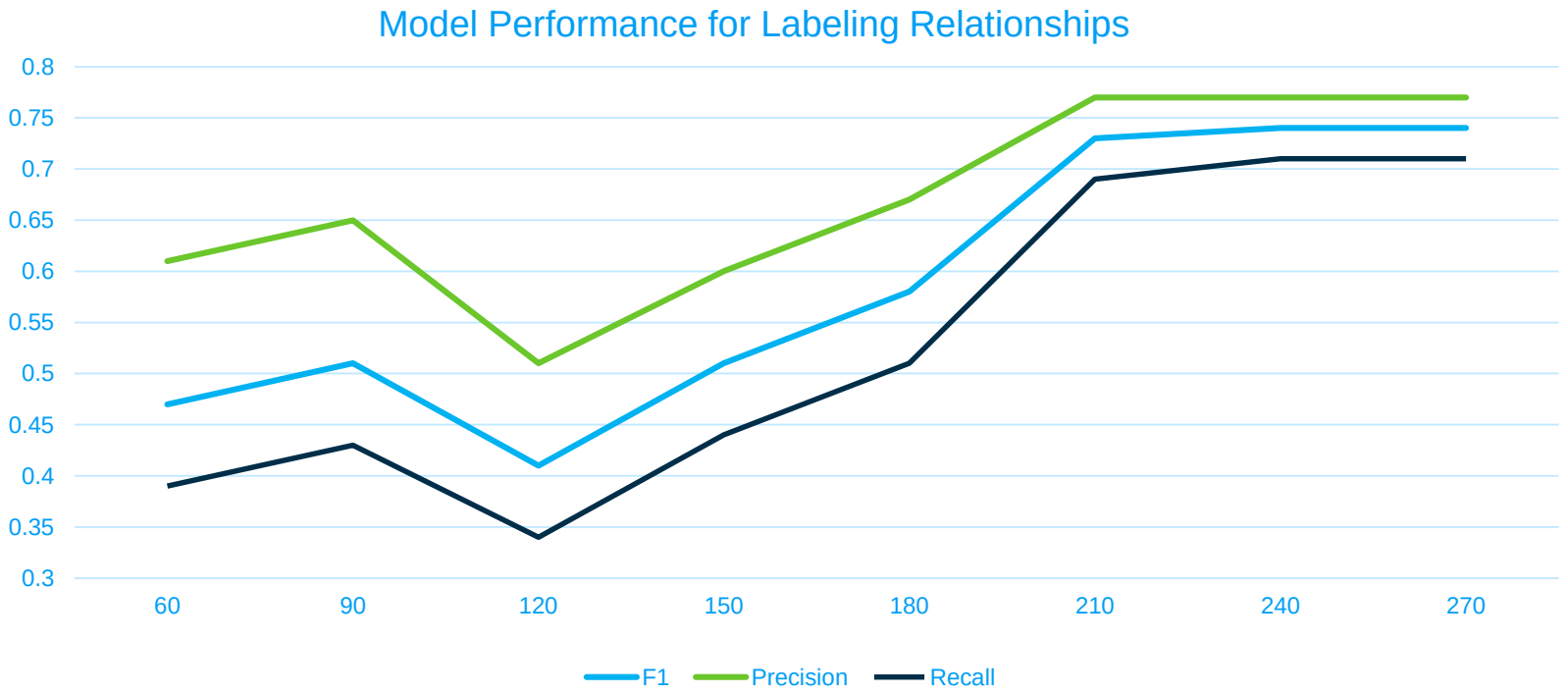
Ensuring Agreement: Measuring Kappa Scores



Concepts Detection: Compare to a standard and iterate



Relationship Detection: Compare to a standard and iterate



Maintaining Context Within and Across Documents

<text>Unexpectedly, we find that EGFR A763_Y764insFQEA is highly sensitive to EGFR TKIs in vitro, and patients whose NSCLCs harbor this mutation respond to erlotinib.</text> ="alters">

```
<relation rid="s6-r1" subtype="OTHER" type="alters">
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    <rel_entity_arg argnum="2" eid="c1"/>
    <relmentions>
      <relmention class="SPECIFIC" modality="ASSERTED" rmid="s6-r1-1" score="1" tense="UNSPECIFIED">
        <rel_mention_arg argnum="1" mid="s6-m6">A763_Y764insFQEA</rel_mention_arg>
        <rel_mention_arg argnum="2" mid="s6-m0">EGFR</rel_mention_arg>

<relation rid="s6-r5" subtype="OTHER" type="drives">
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    <rel_entity_arg argnum="2" eid="c3"/>
    <relmentions>
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        <rel_mention_arg argnum="1" mid="s6-m0">EGFR</rel_mention_arg>
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```
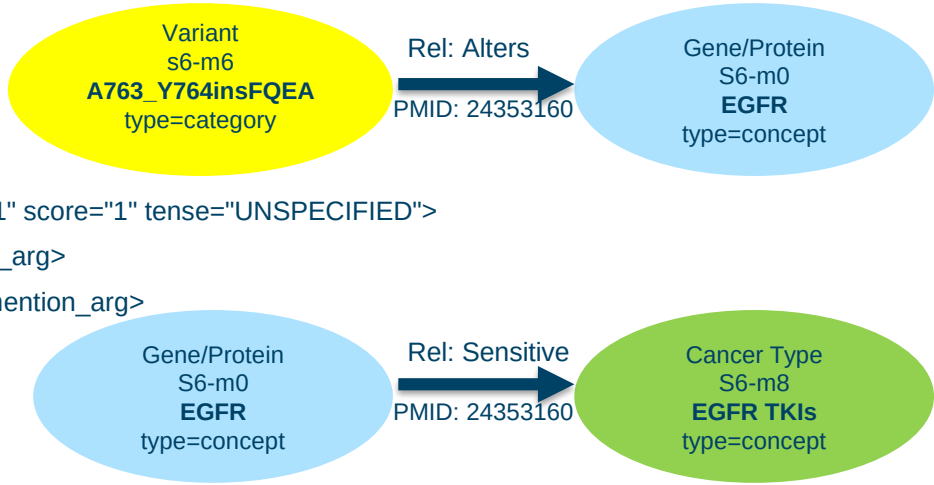
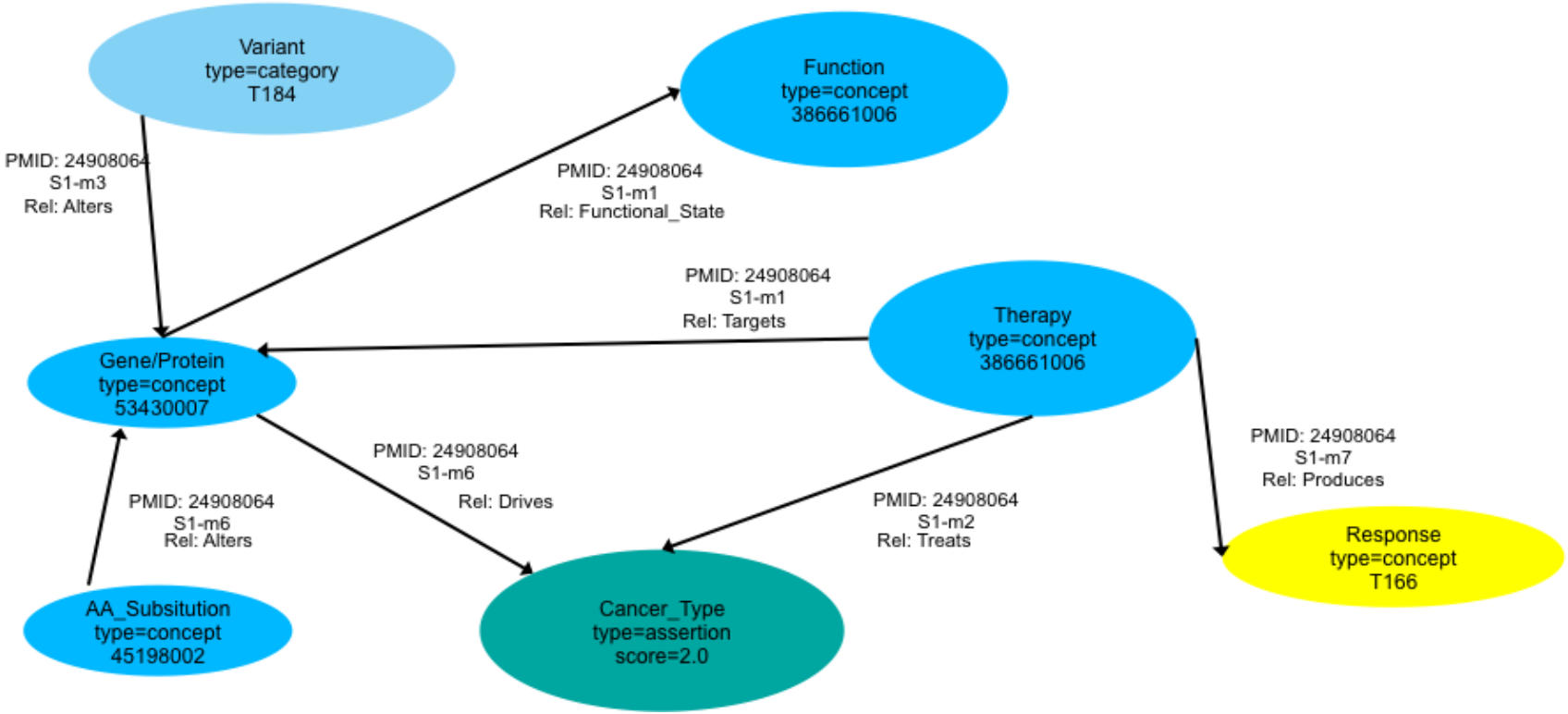
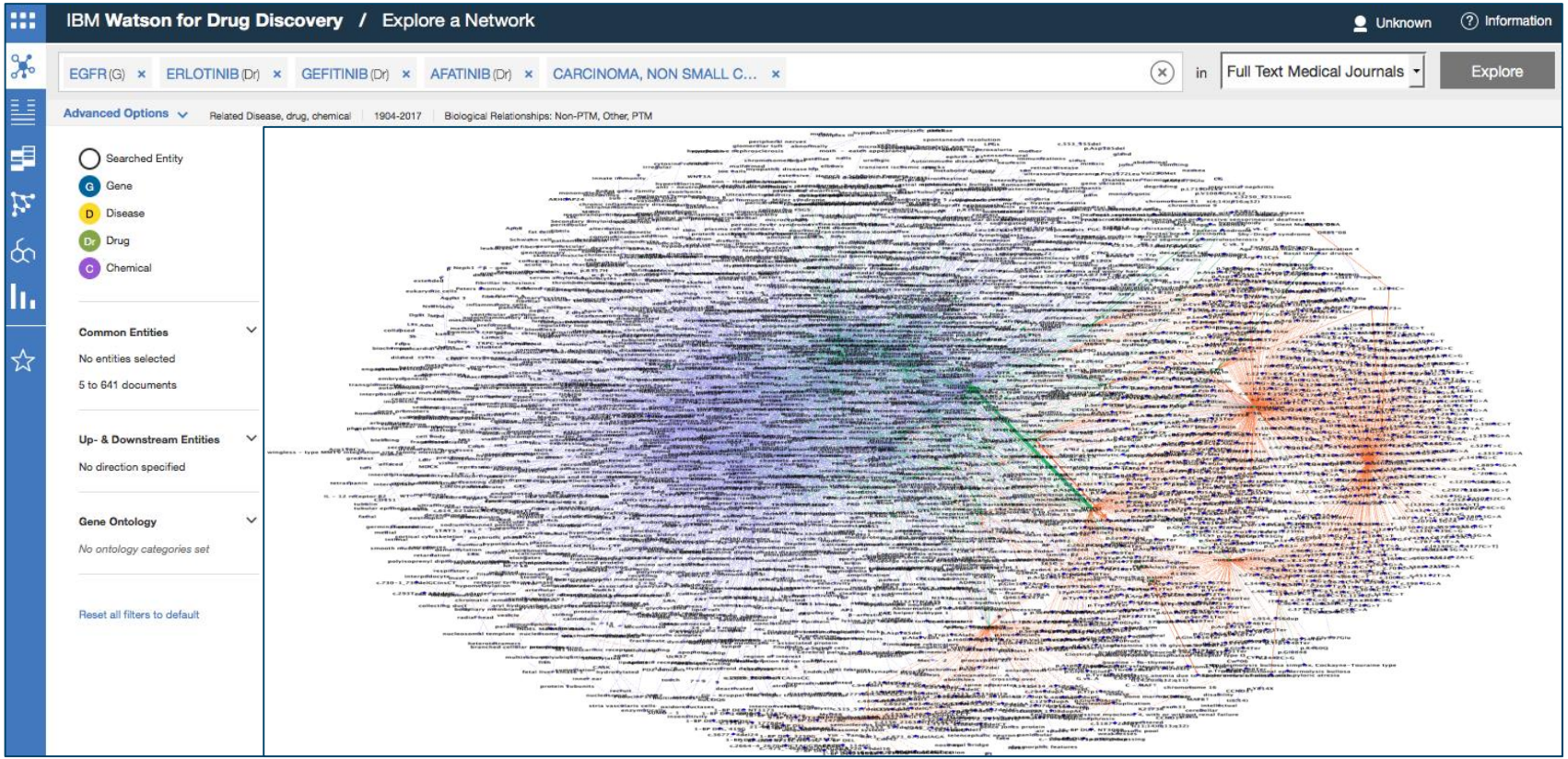



Clinical Knowledge: Example Graph



Clinical Knowledge: Extracted Data from Corpus of Documents



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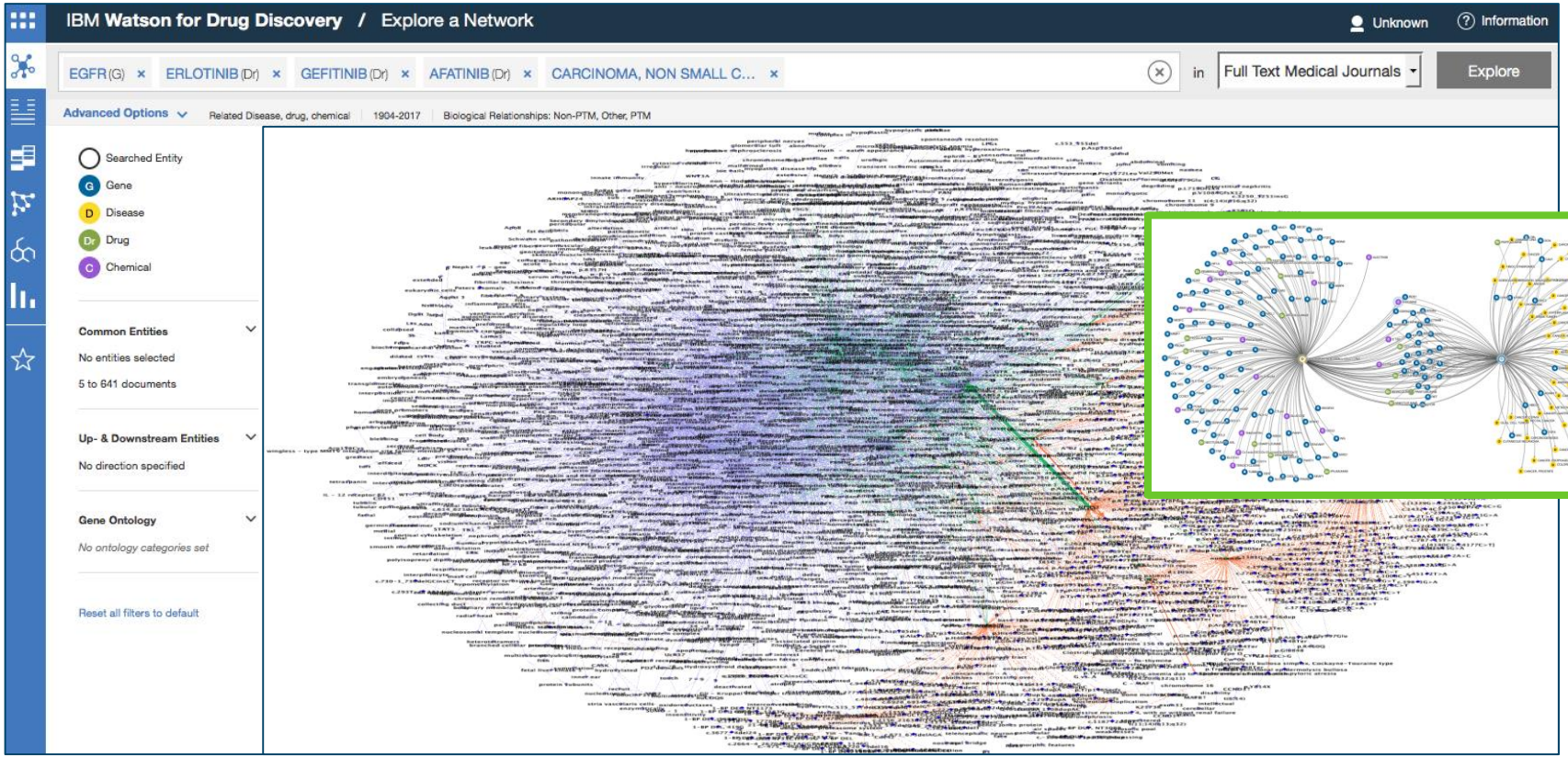


Output Sample from Knowledge Graph Query

Gene	Variant	Variant_Type	Functional_Impact	Cancer_Type	NCI Code		Therapy	Response	PMID	Evidence_Level
KIT	exon 9 p.449-514	mutation	gain-of-function	Gastrointestinal Stromal T	C3868		sorafenib	sensitivity	22270258	Level 2B
KIT	exon 11 p.550-592	mutation	gain-of-function	Gastrointestinal Stromal T	C3868		sorafenib	response	22270258	Level 2B
KIT	exon 17 p.788-828	mutation	gain-of-function	Gastrointestinal Stromal T	C3868		nilotinib	sensitivity	2119758, 214560	Level 2B
ABL1	T315I	missense mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		AURK inhibitors + BCR-ABL1 inh	response	22772060	Level 2
ABL1	T315I	missense mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		axitinib	response	25686603	Level 2
ALK	F856S	missense mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		crizotinib	sensitivity	26032424	Level 3
ALK	A348D	missense mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		crizotinib	sensitivity	26032424	Level 3
BCR-JAK2	rearrangement	fusion gene	gain-of-function	Acute Lymphoblastic Leuk	C3167		ruxolitinib	sensitivity	22897847	Level 3
CRLF2	rearrangement	fusion gene	gain-of-function	Acute Lymphoblastic Leuk	C3167		BET inhibitors	sensitivity	22904298	Level 3
CRLF2	rearrangement	fusion gene	gain-of-function	Acute Lymphoblastic Leuk	C3167		mTOR inhibitors	sensitivity	22955920	Level 3
FBXW7	any	mutation	loss-of-function	Acute Lymphoblastic Leuk	C3167		steroids in early setting	response	20861909	Level 2A
IL7R	237-255_indel or S185C	mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		ruxolitinib (in SH2B3 delete	sensitivity	2897847, 229559	Level 3
IL7R	237-255_indel or S185C	mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		mTOR inhibitors (in SH2B3 del	sensitivity	22955920	Level 3
JAK1	S646F	missense mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		ruxolitinib	sensitivity	22955920	Level 3
JAK2	rearrangement	fusion gene	gain-of-function	Acute Lymphoblastic Leuk	C3167		ruxolitinib	sensitivity	2875628, 228994	Level 3
JAK2	R683	missense mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		ruxolitinib	sensitivity	3805579, 229559	Level 3
KRAS	codon 12	missense mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		MEK inhibitors	sensitivity	18701506	Level 3
NOTCH1	rearrangement	fusion gene	gain-of-function	Acute Lymphoblastic Leuk	C3167		Gamma secretase inhibitor	sensitivity	5688224, 230339	Level 3
NOTCH1	PEST domain p.2245-2536	mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		Gamma secretase inhibitor	response	CO 2006 (abstr 65	Level 2B
NOTCH1	PEST domain p.2245-2536	mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		Gamma secretase inhibitor	sensitivity	9778842, 225108	Level 3
NOTCH1	PEST domain p.2245-2536	mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		mma secretase inhibitors + mTOR	sensitivity	19246562	Level 3
NOTCH1	PEST domain p.2245-2536	mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		mma secretase inhibitors + CDK4	sensitivity	19318552	Level 3
NOTCH1	PEST domain p.2245-2536	mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		steroids early setting	response	09, 20861920, 20	Level 2A
NOTCH1	HD p.1529-1723	mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		Gamma secretase inhibitor	response	CO 2006 (abstr 65	Level 2B
NOTCH1	HD p.1529-1723	mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		Gamma secretase inhibitor	sensitivity	778842, 225108	Level 3
NOTCH1	HD p.1529-1723	mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		mma secretase inhibitors + mTOR	sensitivity	19246562	Level 3
NOTCH1	HD p.1529-1723	mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		mma secretase inhibitors + CDK4	sensitivity	19318552	Level 3
NOTCH1	HD p.1529-1723	mutation	gain-of-function	Acute Lymphoblastic Leuk	C3167		steroids early setting	response	09, 20861920, 20	Level 2A

Leveraging Literature Articles to Support Clinical Care

Gene	Alteration	Alteration Type	Functional Significance	Annotation	Actionable Gene	Actionable Variant
PDGFRA	Y288C	SNV				
PTEN	K163*	Trunc-ation				
FGFR2	K292M	SNV				

Leveraging Literature Articles to Support Clinical Care

Gene	Alteration	Alteration Type	Functional Significance	Annotation	Actionable Gene	Actionable Variant
PDGFRA	Y288C	SNV	Activating	**Activating Mutation:** Exogenous expression of the Y288C mutant in BaF3 cells increased the number of viable cells measured an average of 5.76 fold more compared with cells expressing wildtype PDGFRA.	Yes	Yes-Functional Genomics
PTEN	K163*	Trunc-ation	Unknown	**Likely loss of function:** This mutation likely leads to loss of function due to premature stop codon in the phosphatase domain. Missense mutations in K163 resulted in an ≈80-fold reduction in its membrane affinity (Das et al., 2003)	Yes	Yes – Inferred
FGFR2	K292M	SNV	Unknown	**Potentially activating.** The functional significance of this mutation is unknown. However, it is located within the Ig-like domain type 3, and other mutations in this domain can create an autocrine, feed-forward FGF signaling loop resulting in FGFR2 activation.	Yes	Potentially

Summary

Empowering Healthcare Professionals with Cognitive Computing

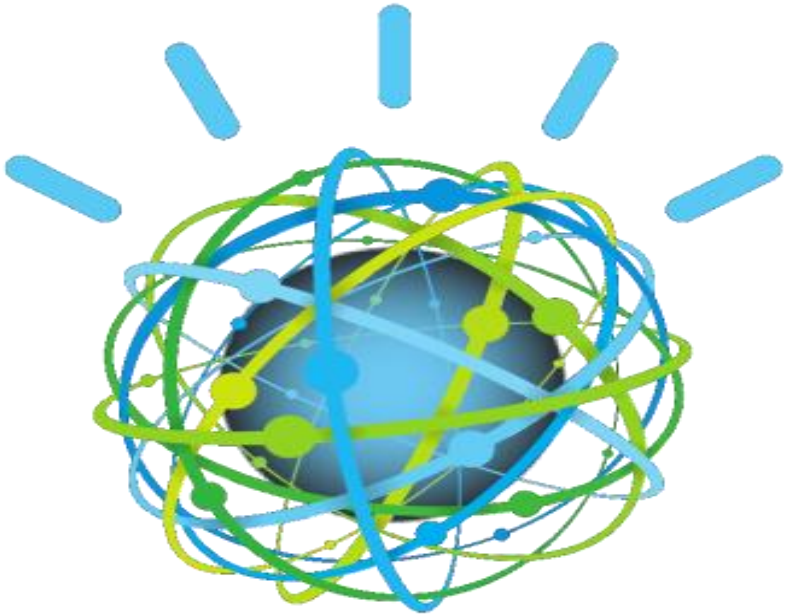
The Process of Building

- Work Closely with domain experts
- Leverage tools (like NLP) to extract unstructured concepts and their associations
- Combine unstructured and structured data to create knowledge
- Validate and iterate with domain experts

Value of Applying to Healthcare

- Increased efficiency
- Reduced bias
- Scaling expert knowledge
- Innovating across a complex domain

With Cognitive computing, the extraction of information from clinical data and published literature can empower healthcare professionals to stay up-to-date, focus on the complex problems, and spend more time with caring for patients.



Questions?
(remember, I’m not Watson..)

PRECISION ONCOLOGY FOR ALBERTA: INNOVATING HEALTH SYSTEM READINESS.

ARCC: Canadian Centre for Applied Research and Cancer Control

Toronto: May 25-26, 2017

Tania Bubela

ALMDx/PACEOMICS Team

Alberta Health Services

- Don Juzwishin

Faculty of Medicine & Dentistry

University of Alberta

- Christopher McCabe
- Judith Hugh (+AHS)
- Michael Mengel (+AHS)
- Deborah James
- Stacey Hume (+AHS)

Research staff/students:

Michael Paulden, Mark Bieber, Westerly Luth, Katherine Fu, Kiah Van der Loos, Monica Wang, Yael Mansour, Negar Razavilar

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Alberta Economic Development and Trade
Alberta.ca > Economic Development and Trade

GenomeQuébec
GenomeAlberta
GenomeCanada

PACEOMICS

BioCanRx
Biotherapeutics for Cancer Treatment
Biothérapies pour le traitement du cancer

Alberta Innovates Health Solutions

Stem Cell Network
Réseau de cellules souches

Outline

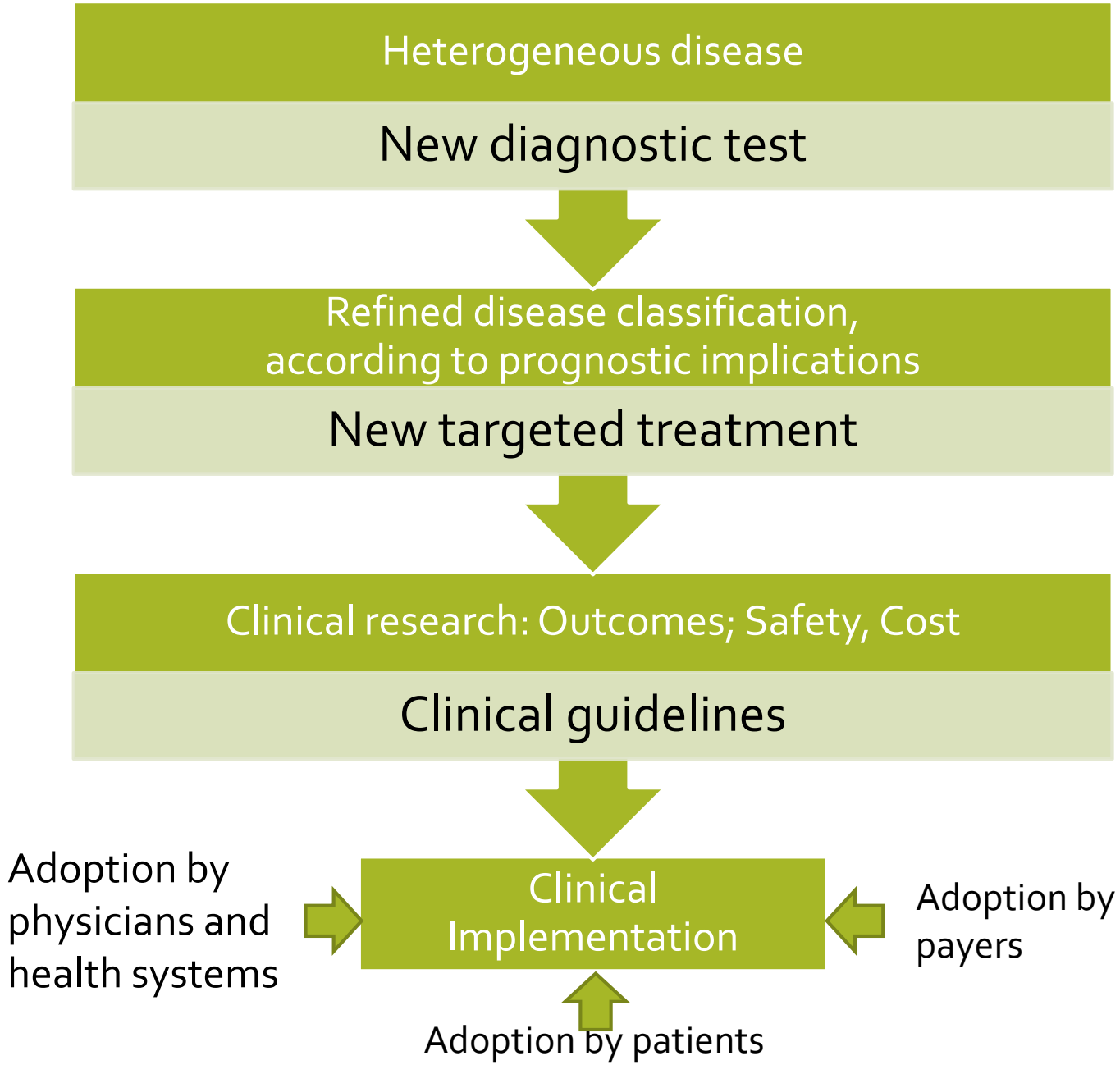
- What is precision medicine?
- Precision medicine landscape in Alberta
- Supporting precision medicine in two contexts:
  - Adoption of new technologies wherever developed
  - Local innovation
- Mike Paulden will present a case example from of Life-Cycle Technology Management in Oncology
- Conclusions and lessons learned on barriers and enablers

PRECISION MEDICINE FOR ALBERTA?

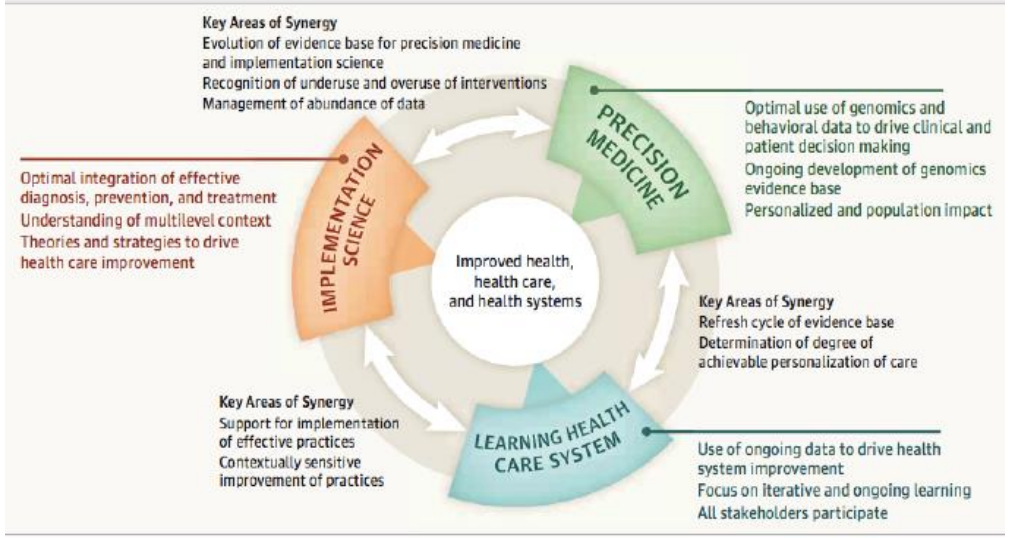
ALMDX/PACEOMICS TEAM

Precision Medicine: Personalized, Problematic & Promising

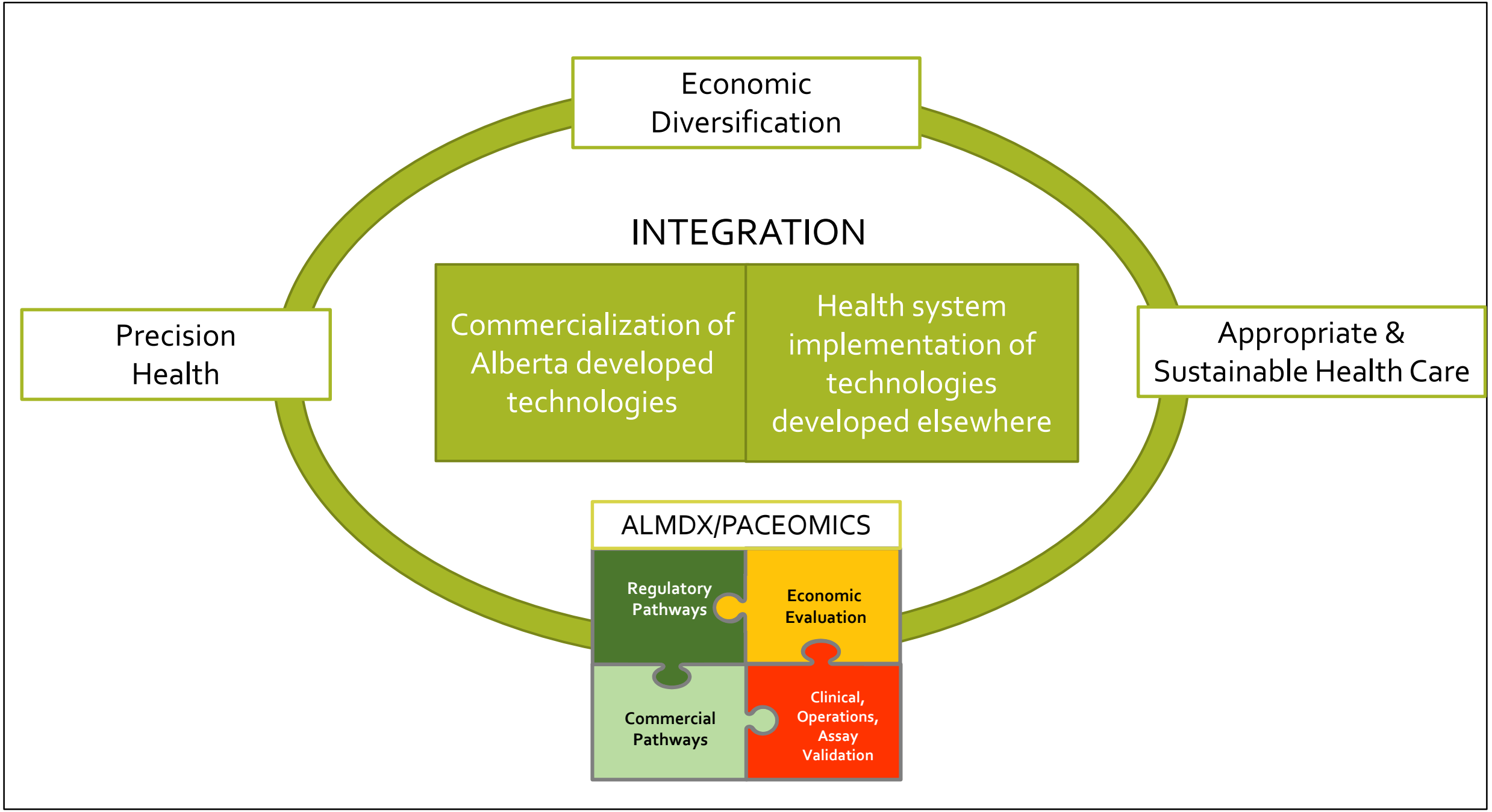
(Jameson & Longo *NEJM* 2015)

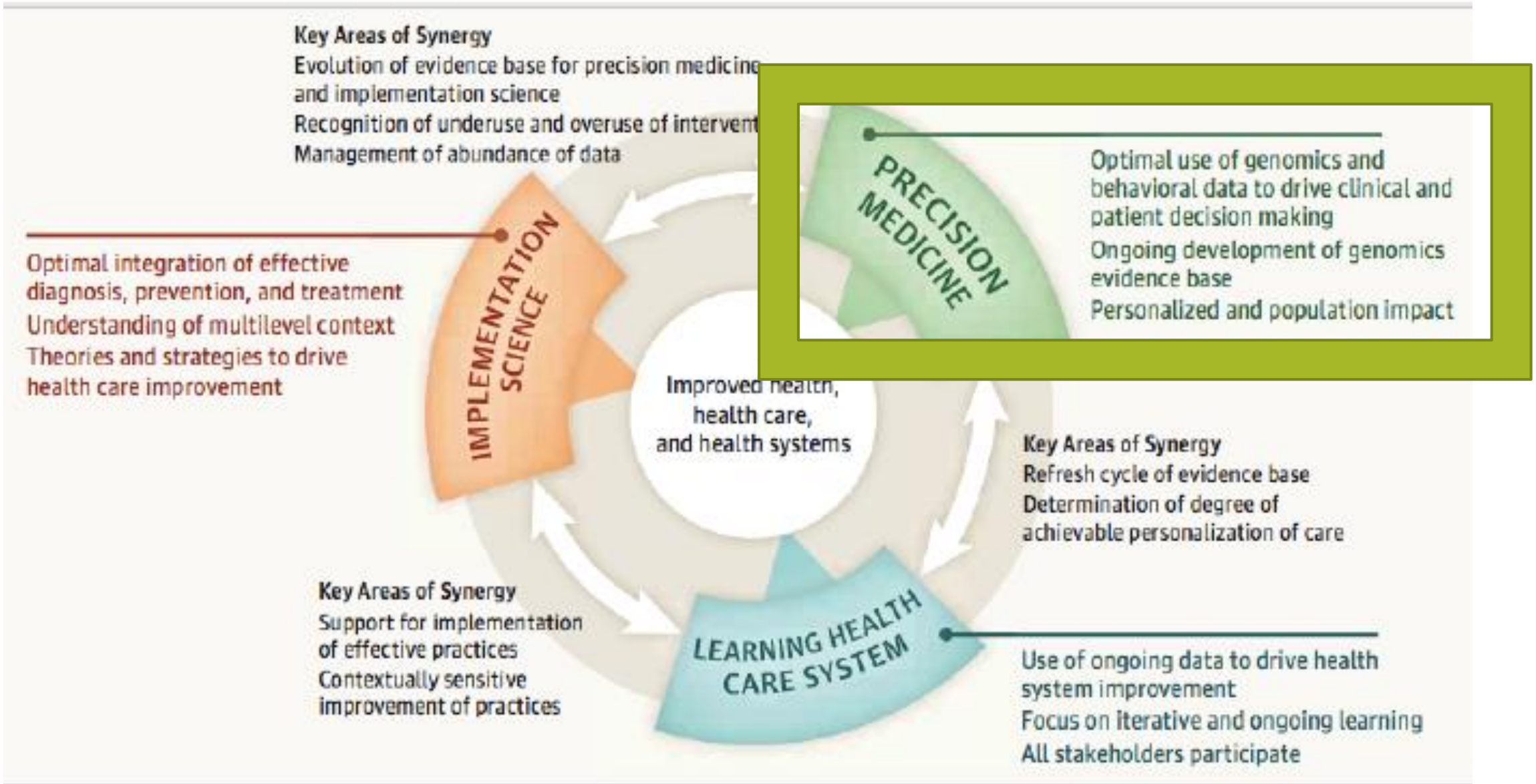


Current Challenges in Alberta



- Consensus / Joint Strategy and Vision
- Managing implementation of PM technologies
  - Ascribing 'value' to new technologies and approaches
  - Defining/implementing new funding strategies
    - 'On-ramps', decision criteria, procurement mechanisms and 'off-ramps'
    - Off-ramps for established but low value technologies – Choosing Wisely, Appropriateness of Care, Utilization management
- Changing legislation, policies, and 'behavior'
- Connecting the ecosystem
  - Re-allocating internal budgets to reward nimble portfolios


Economic Diversification
INTEGRATION
Commercialization of Alberta developed technologies
Health system implementation of technologies developed elsewhere
Precision Health
Appropriate & Sustainable Health Care
ALMDX/PACEOMICS
Regulatory Pathways
Economic Evaluation
Commercial Pathways
Clinical, Operations, Assay Validation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Determination of degree of achievable personalization of care
LEARNING HEALTH CARE SYSTEM
Use of ongoing data to drive health system improvement
Focus on iterative and ongoing learning
All stakeholders participate
Key Areas of Synergy
Support for implementation of effective practices
Contextually sensitive improvement of practices

Precision Medicine in Oncology

Courtesy of Dr. Jeffrey S. Ross, Albany Medical College
Medical Director, Foundation Medicine Inc.

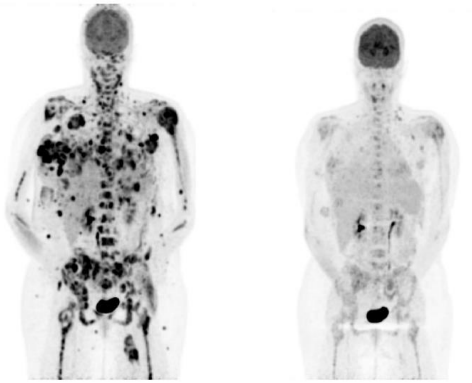
Evloution of Targeted Therapies

1970: ER testing and hormonal therapy for breast cancer
1990: cytogenetics/FISH testing and therapy for Heme malignancies
1998: *HER2* testing and Trastuzumab for breast cancer
2001: *BCR-ABL* testing and Imatinib for chronic myelogenous leukemia
2003: *EGFR* mutation testing ant Eriotinib for non-small cell lung cancer (NSCLC)
2007: *KRAS* mutation testing and Cetuximab/Panitumumab for colorectal cancer
2010: *EML4-ALK* testing and Crizotinib in NSCLC
2011: *BRAF* mutation testing and Vemurafenib in melanoma
2013: *HER2* mutation identification and anti-Her2 targeted therapy in NSCLC, breast cancer and micropapillary urothelial cancer
2013 *NTRK1* fudion testing and Crizotinib in NSCLC
2014: *PD1* and *PDL1* and immunotherapies

As of 2017: 207 Pharma pipelines for CDx – 158 in cancer

Next Generation Pathology to Precision Oncology

Patient with *BRAF* V600E mutated malignant melanoma treated with selective inhibitor of BRAF (Vemurafenib)

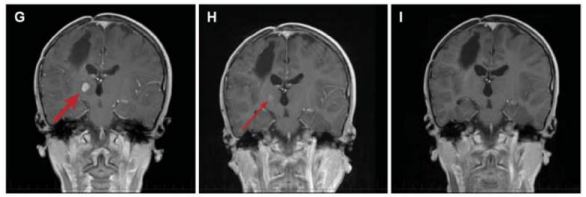


Pre-therapy 15 days Post-therapy

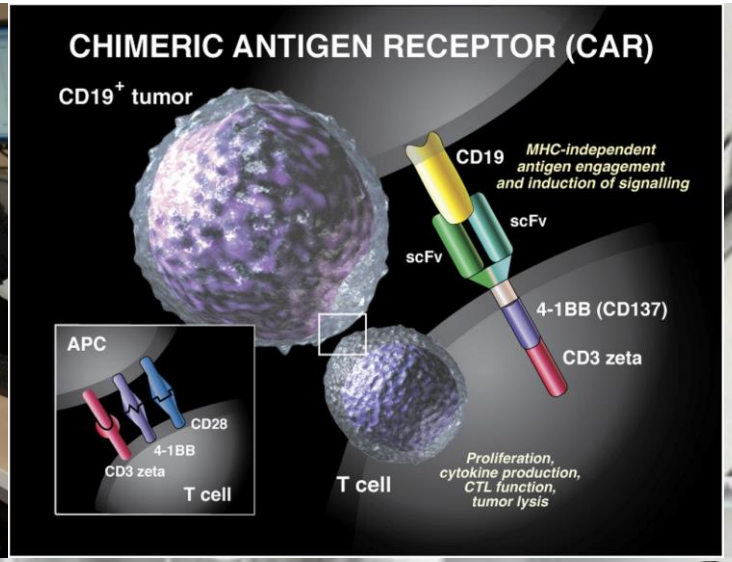
Slide courtesy of Dr. Grant McArthur

Complete Regression in Pediatric Glioblastoma

Molecularly matched targeted therapy against *BRAF* V600E



Cancer Cellular Immunotherapy



Pharma & Healthcare / #Biotech

AUG 31, 2016 @ 08:32 AM 18,697 VIEWS

Novartis Dissolves CAR-T Unit, Cutting 120 Positions

Matthew Herper, FORBES STAFF

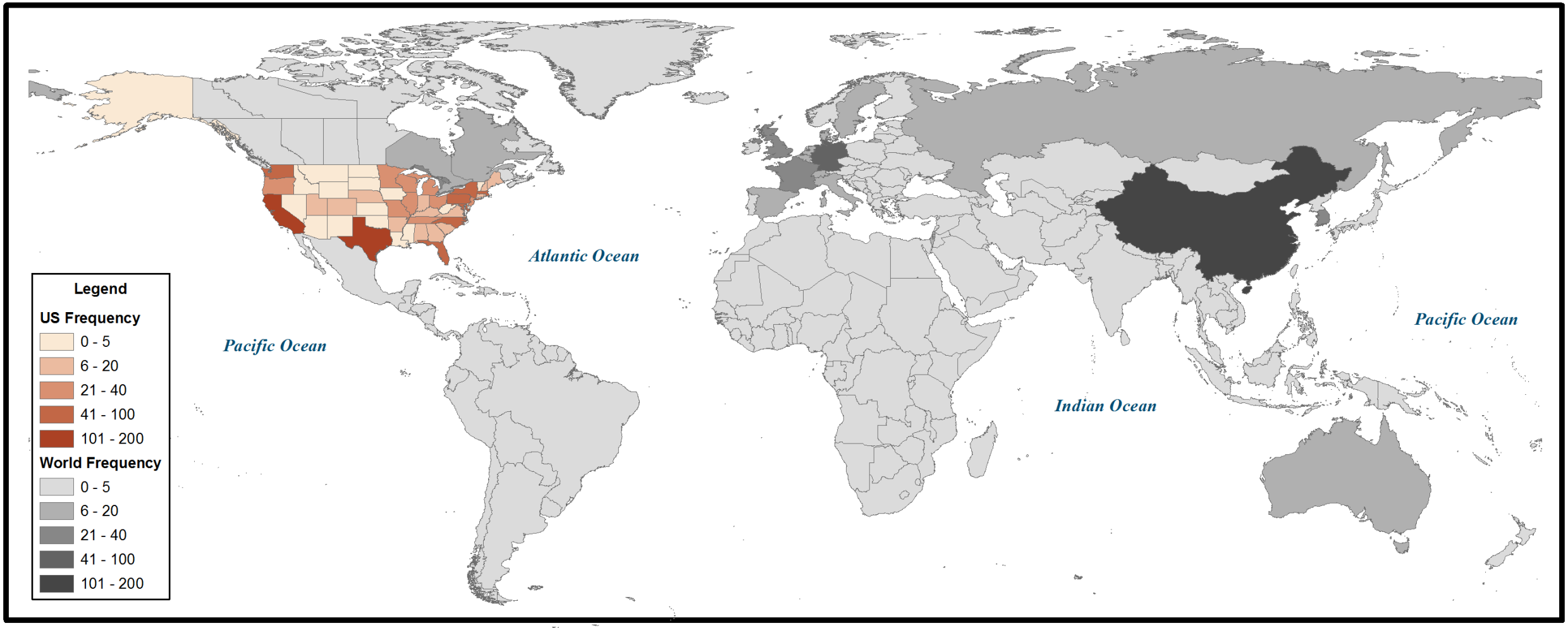
I cover science and medicine, and believe this is biology's century. FULL BIO

Novartis-Penn Center for Advanced Cellular Therapeutics

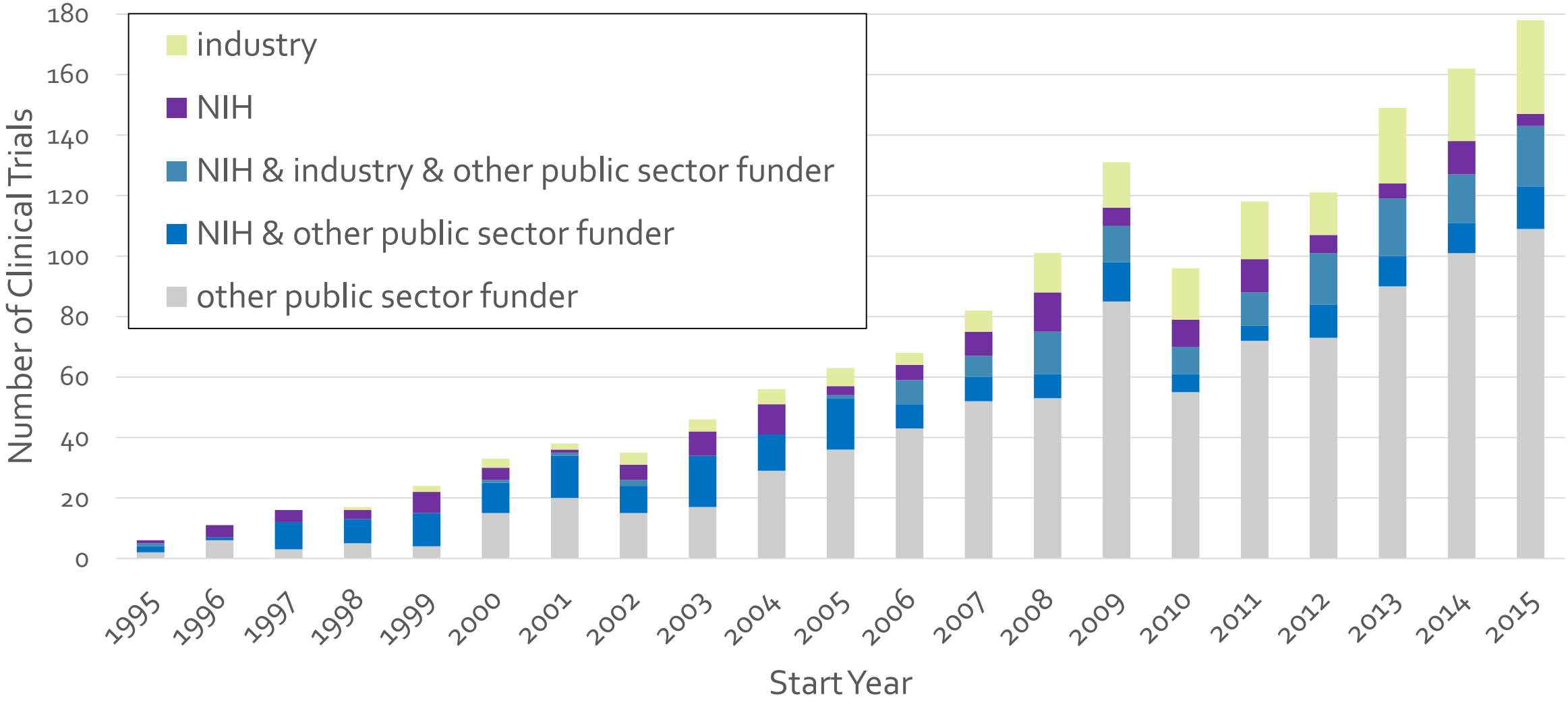
Signage is displayed in front of the Novartis AG Institutes for BioMedical Research building in Cambridge, Massachusetts, on Aug. 5, 2016. Photographer: Scott Eisen/Bloomberg

Novartis is shutting down the business unit it created to develop white blood cells that can attack certain types of cancer, but

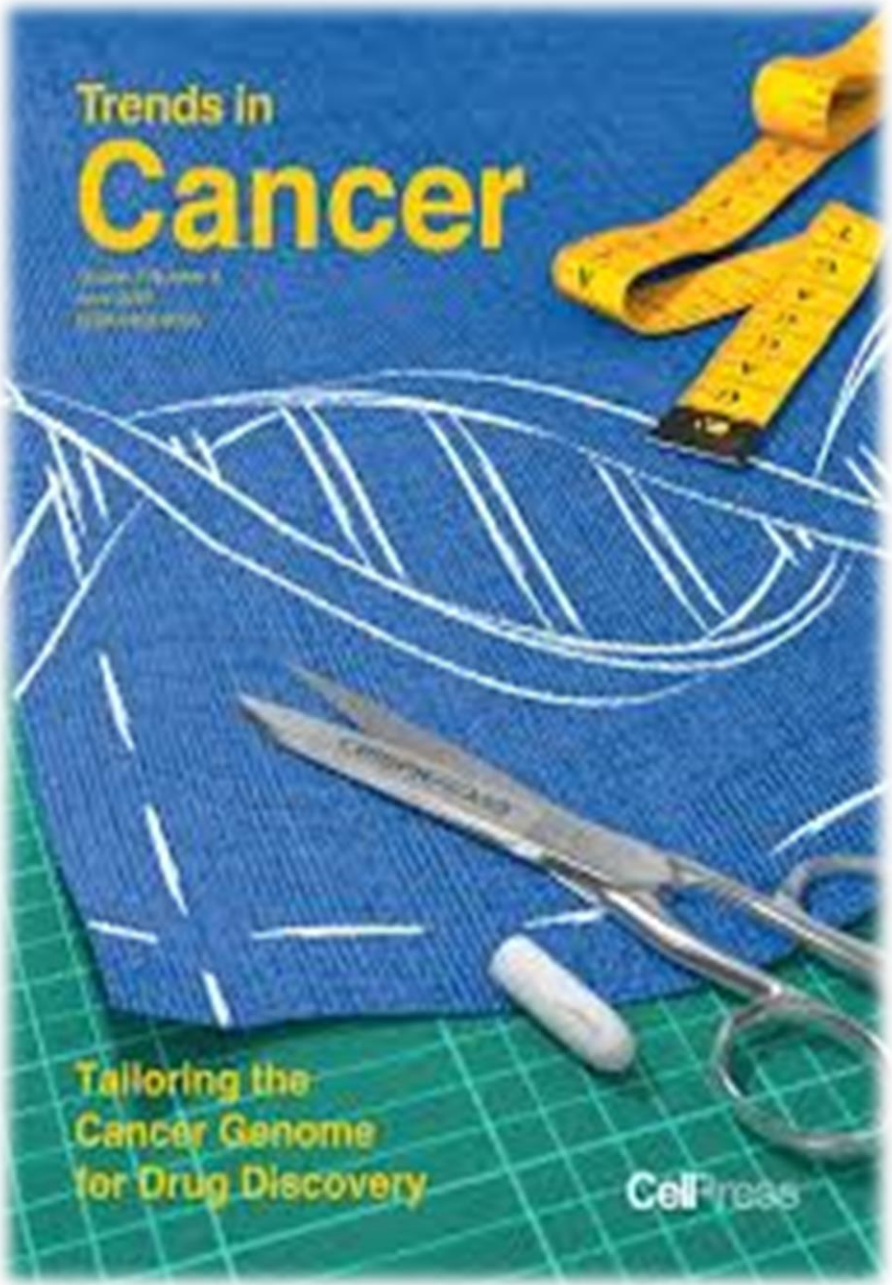
HORIZON SCANNING:
GLOBAL IMMUNOTHERAPY CLINICAL TRIALS



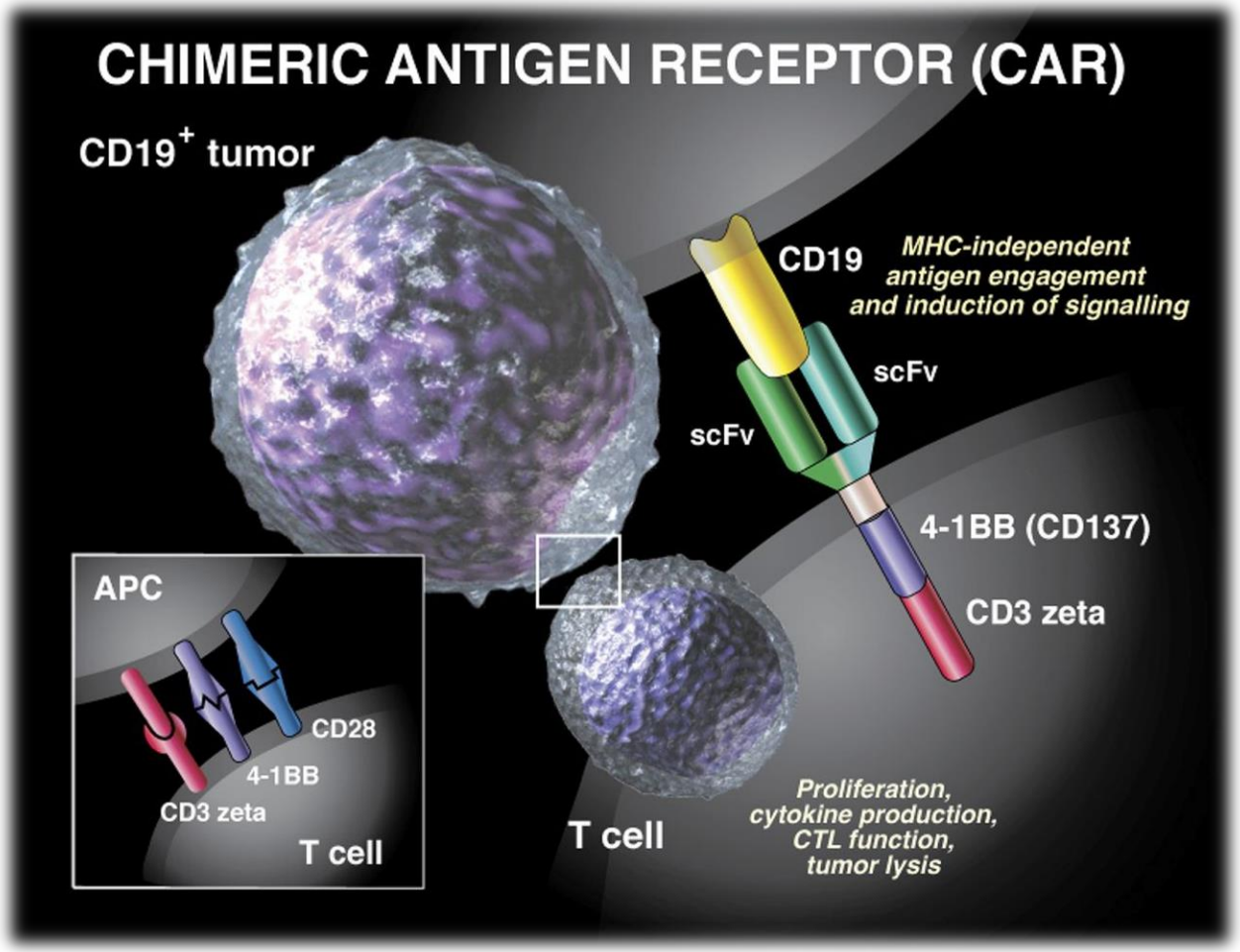
SPONSORS OF 1554 CI CLINICAL TRIALS

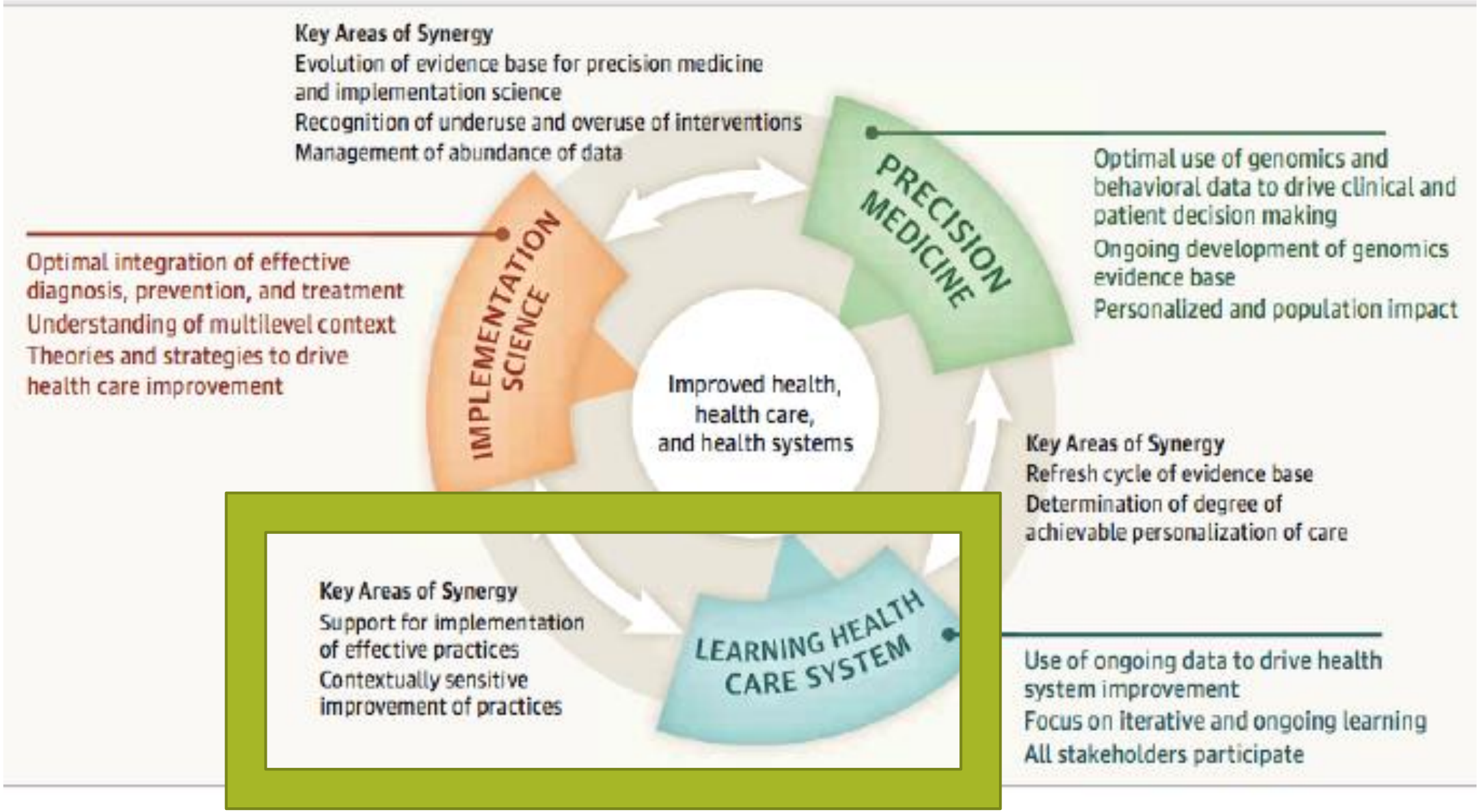



FIRST-EVER CRISPR TRIAL
POINTS TO LOOMING PROBLEMS



CRISPR and CAR-T

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International Environment

Genomics england

ExAC

the gnomAD team assembled **2.9 petabytes** of raw data... that's equal to **331 years** of movie streaming

254.2 million rare and common genomic variants, **159.8 million** of which were novel were discovered using gnomAD

gnomAD contains sequences from over **140,000 people**

gnomAD contains data from people hailing from each of the **6 inhabited continents**

Capital Investment: Beijing Genomics Institute

Complex Legislative Framework

- **Health Information**
  - *Personal Information Protection and Electronic Documents Act* R.S. 2000 c. 5 [PIPEDA]
  - *Health Information Act*, R.S.A. 2000, c. H-5. [HIA]
- **Personal Information Held by Private Sector**
  - *Personal Information Protection and Electronic Documents Act*, R.S. 2000, c. 5 [PIPEDA]
  - *Personal Information Protection Act*, S.A. 2003, c. P-6.5 [PIPA]
- **Personal Information Held by Federal Government**
  - *Privacy Act*, R.S. 2000, c. P-21.
- **Personal Information Held by the Alberta Government**
  - *Freedom of Information and Protection of Privacy Act*, R.S.A. 2000, c. F-25. [FOIP]

Custodians and the Controlled Arena

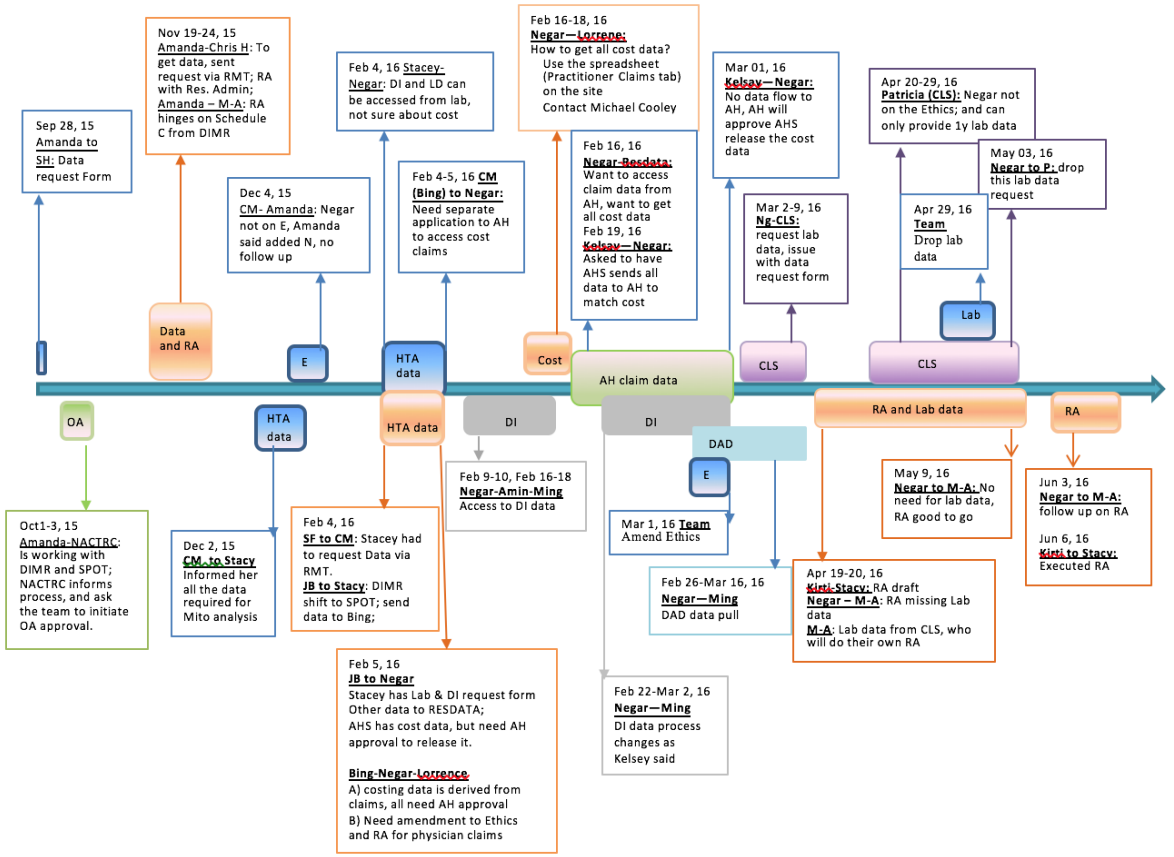
- There is a "controlled arena" around the custodians.
- Individually identifying health information can move from one custodian to another for the purposes authorized

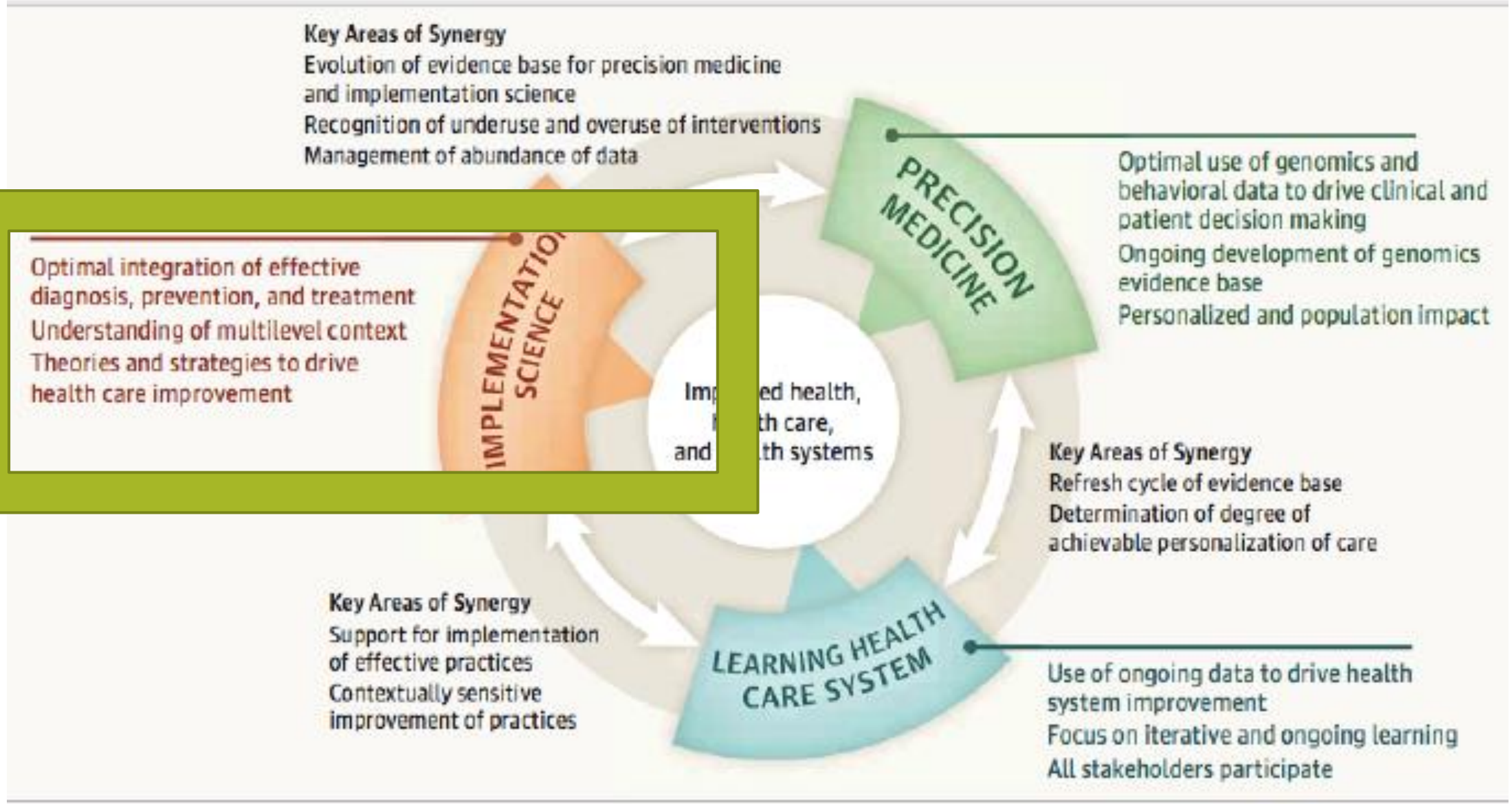
Movement of identifying health information outside of the controlled arena is more restricted

- **A researcher under certain conditions**
  - **Research agreements**
  - **Ethics**

Barriers to data access

- **Lack of process clarity**
  - Who is responsible for triggering data requests?
  - Who are the appropriate contact points?
  - What information does each database contain?
- **Role of data custodian**
- **Miscommunication**

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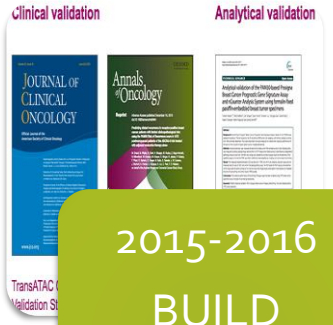
Challenges:

Moving from Oncotype Dx™ to Prosigna™

- **CFI purchase of test platform**
- **ALMDx & Cancer SCN local test**

2011
IDEA

2012-2014
ACQUIRE
TEST



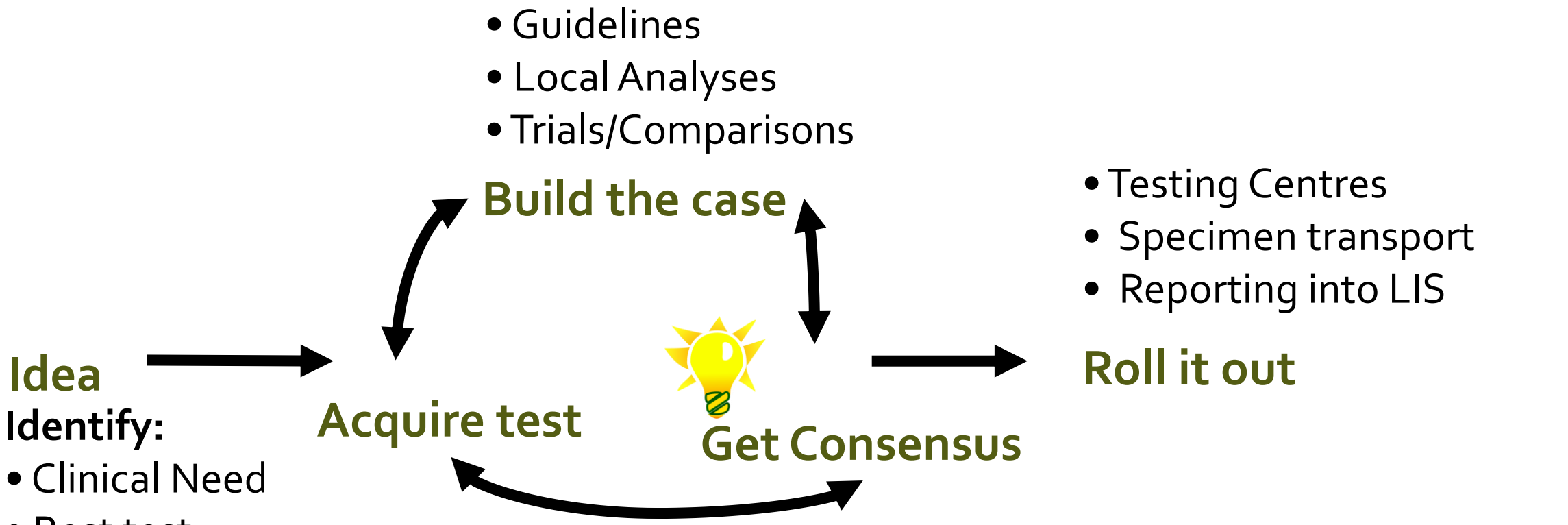
2015-2016
BUILD
THE
CASE

2016-2017
GET
CONSENSUS

2017
ROLL
IT
OUT

Guidelines
Local Analyses
Trials/
Comparisons

What is the Best way to Replace an Existing Test?



CONCLUSIONS ON PRECISION MEDICINE FOR ALBERTA

ALMDx/PACEOMICS Team

Identified challenges

- **Business models & regulatory pathways**
  - Laboratory Developed Test
  - Licensed Software
  - Distributed Kit
- **Capacity limitations**
  - Sequencing infrastructure
  - Bioinformatics capacity
- **AHS Organizational structure, lack of:**
  - Competitive billing
  - Outreach/advertising
  - Innovation incentives
  - Transparent re-investments between operational silos
- **Organizational culture**
  - Not-for-profit
  - Clinician opinion and behaviour
- **Laws and policies**
  - Procurement
  - Privacy/Health Information
- **Data access (essential for PM)**
  - Data aggregation across databases for analytics
  - Complex operational approval structures
  - Lack of procedural clarity and transparency

Opportunities

- **Life-cycle evaluation of new technologies**
  - 'Fend off' low value new diagnostics
  - Adopt through ***dynamic*** health-economic and operational evidence generation and implementation process
  - Evidence-based utilization management: 'right test at the right time in the right patient' enable adoption and decommissioning of tests/technologies
- **Support local innovators**
  - Support SME as an effective beta-site and real world incubator
  - Commercialization and regulatory affairs
  - Provincial procurement policies
- **Impact on the Alberta Economy**
  - Jobs in Alberta through repatriation of high-complexity diagnostics
  - Build expertise in implementation sciences i.e. knowledge-based jobs
  - Become competitive in the global diagnostic testing market: research & innovation
  - Attractive partner to industry


THANK YOU

Innovation in Cancer Care: The Promise and the Peril

Mike Paulden, Assistant Professor,
School of Public Health, University of Alberta

@mikepaulden paulden@ualberta.ca mikepaulden.com

Overview

---

1. How might **economists** define **“innovation”** in cancer care?
2. What are some of the “**promises**” associated with this approach to defining “innovation”?
3. What are some of the “**perils**”?
4. Case study: **Oncotype DX** vs **Prosigna** for guiding adjuvant chemotherapy decisions in early breast cancer

How might economists define “innovation”?

Defining “innovation” requires a clear objective

Typically, economists make **two key assumptions:**

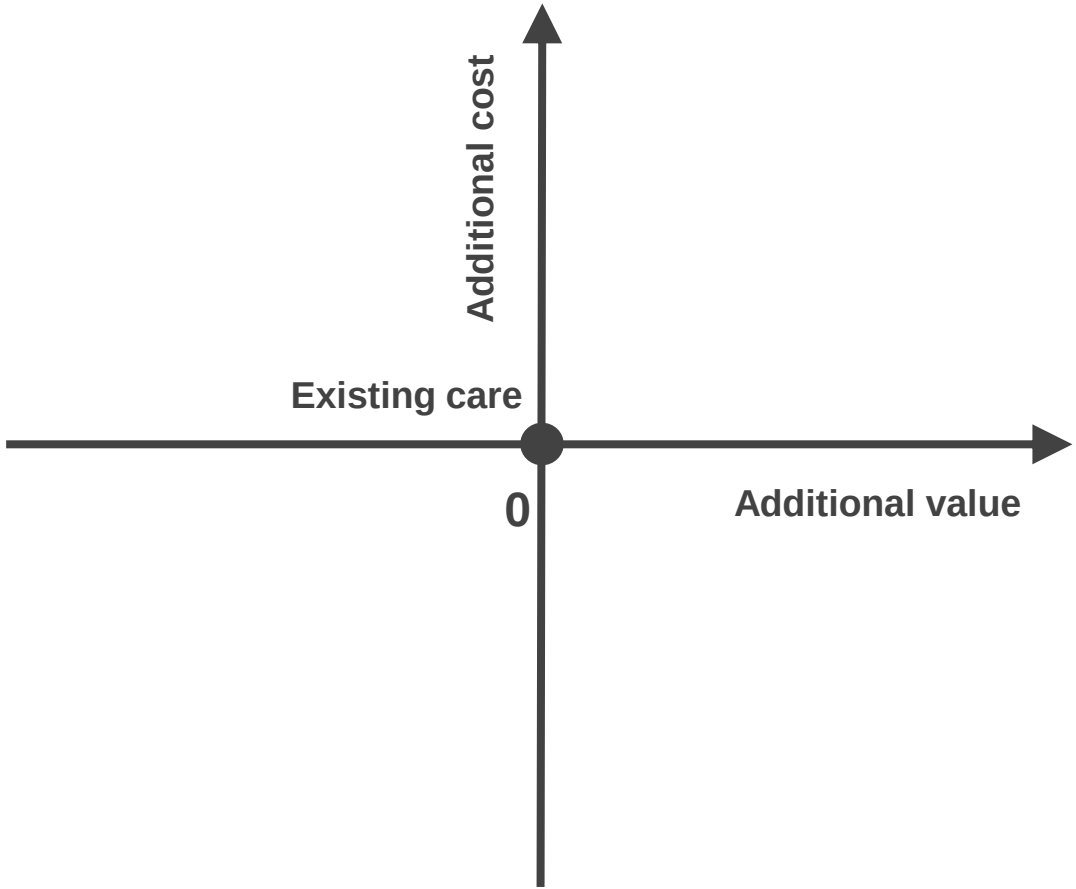
- Health system has a **constrained budget** - we can’t afford everything
- Given this, resources are allocated to **satisfy some objective**

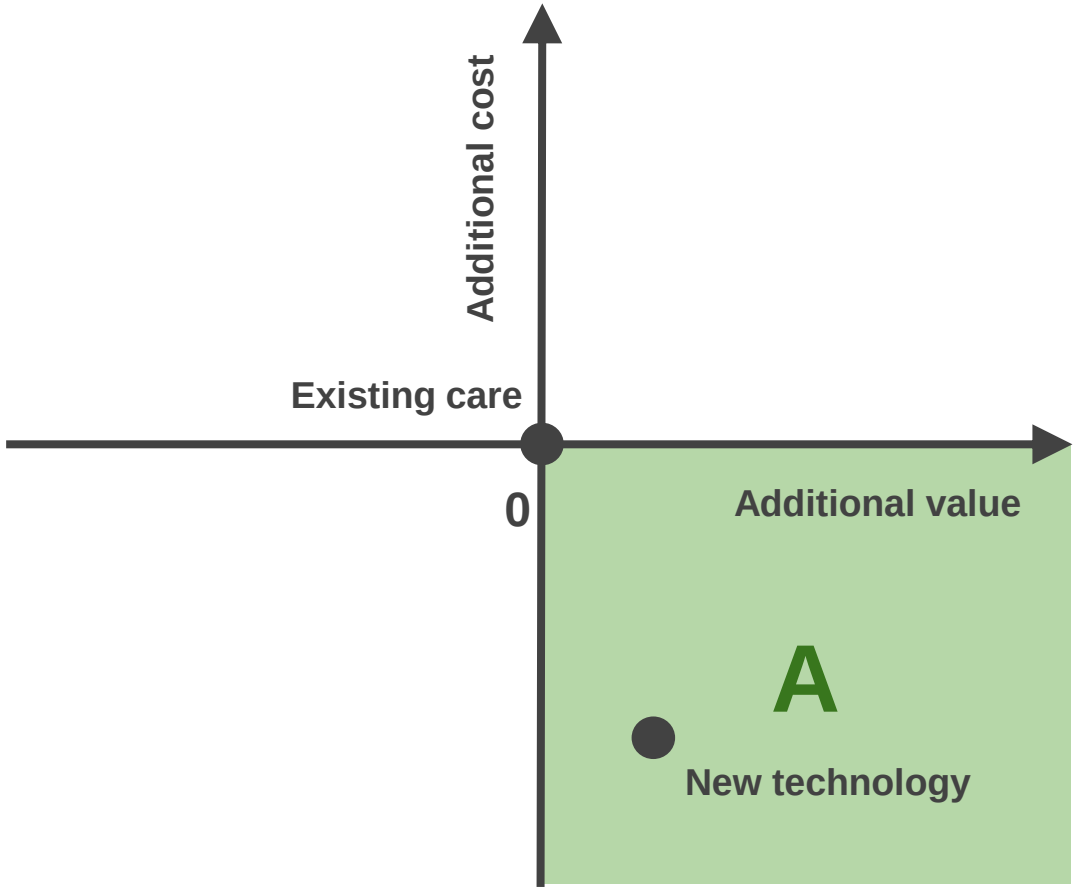
Conventional objective is to “**maximize population health**”

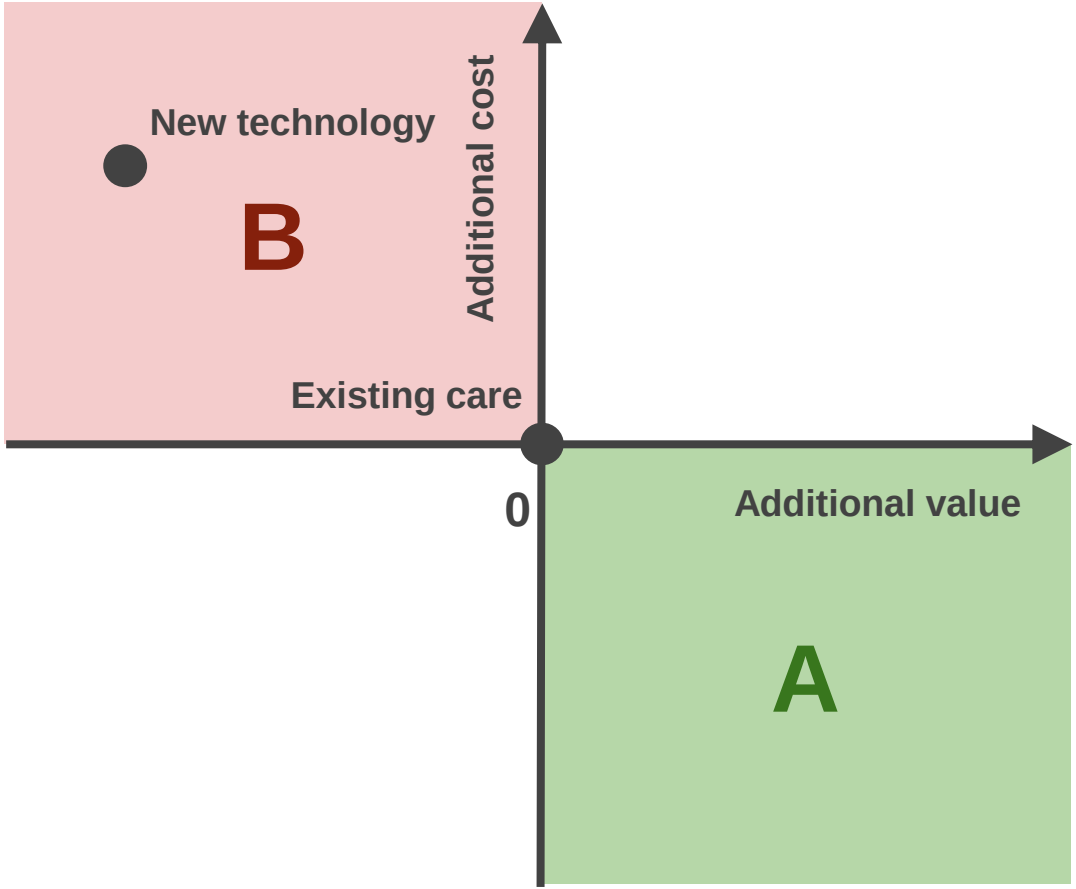
- Often measured using **quality-adjusted life years (QALYs)**
- But **other measures** of health can be used

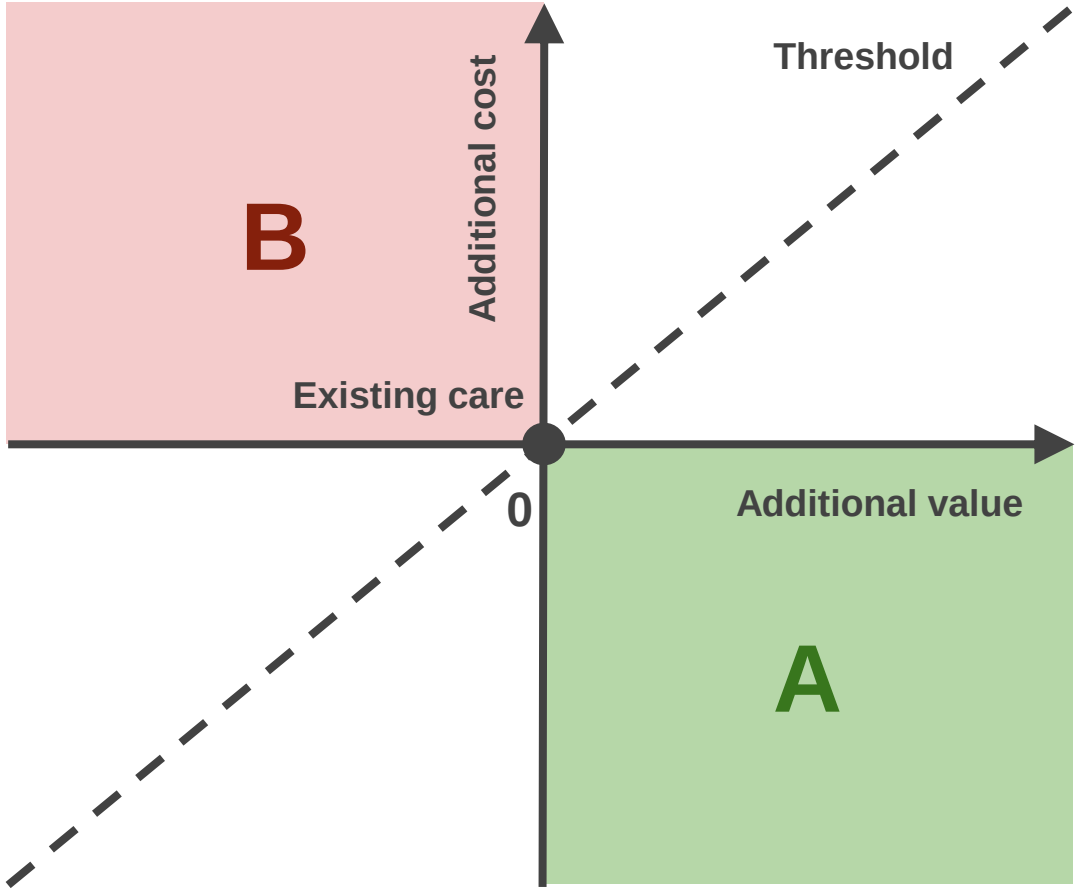
Alternative objectives may include **non-health outcomes**

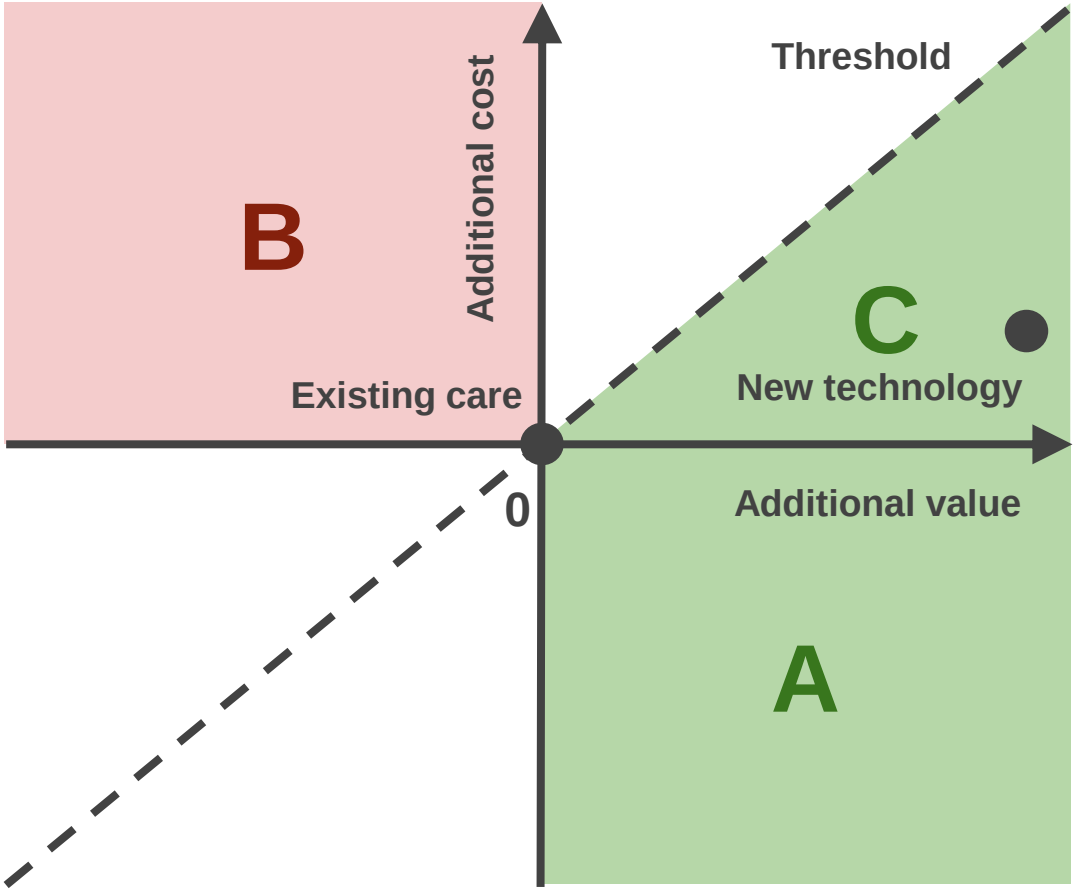
Can consider generic objective of “**maximizing value**”

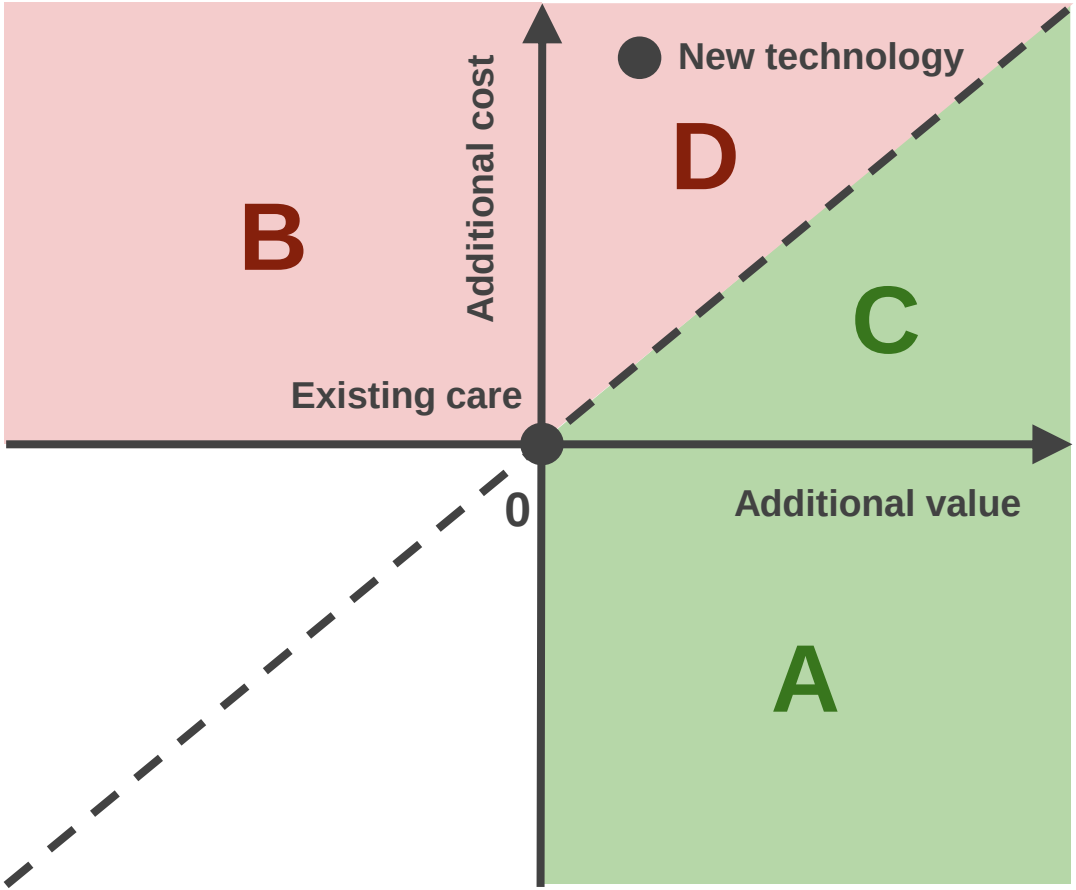

Additional cost
Existing care
0
Additional value

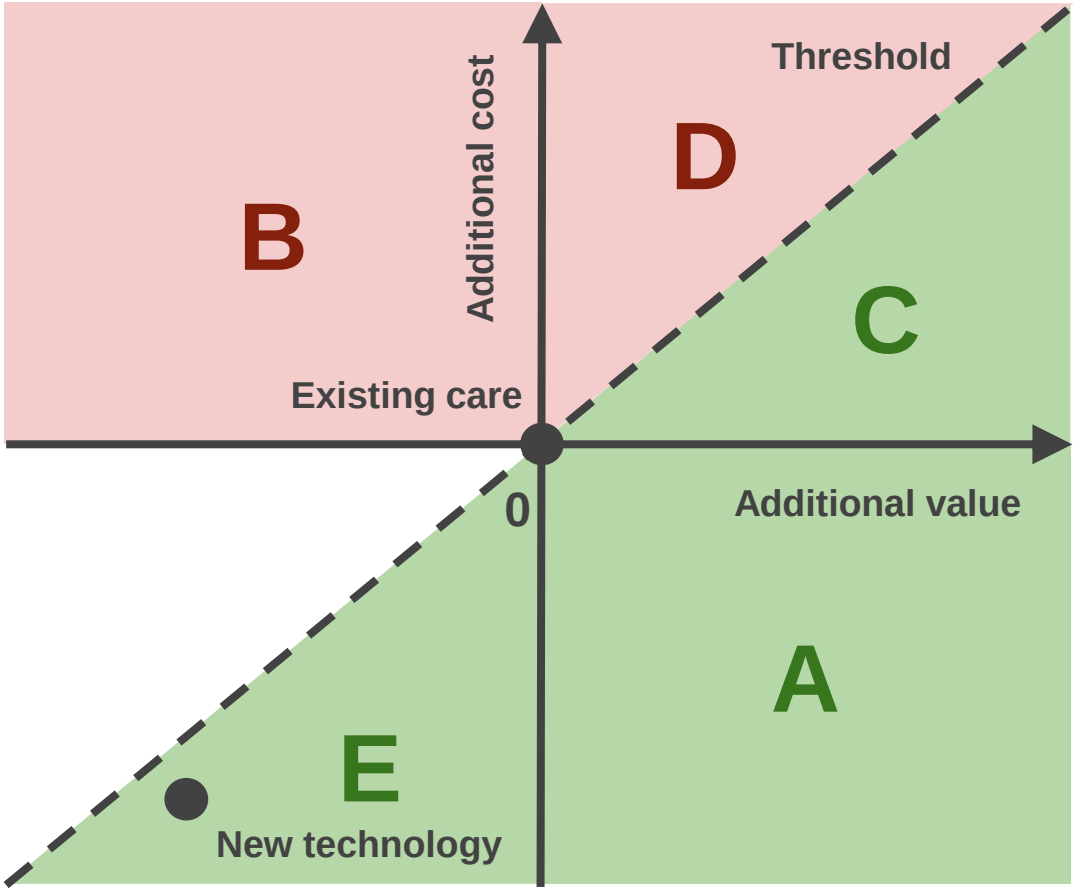

Additional cost
Existing care
0
Additional value
A
New technology

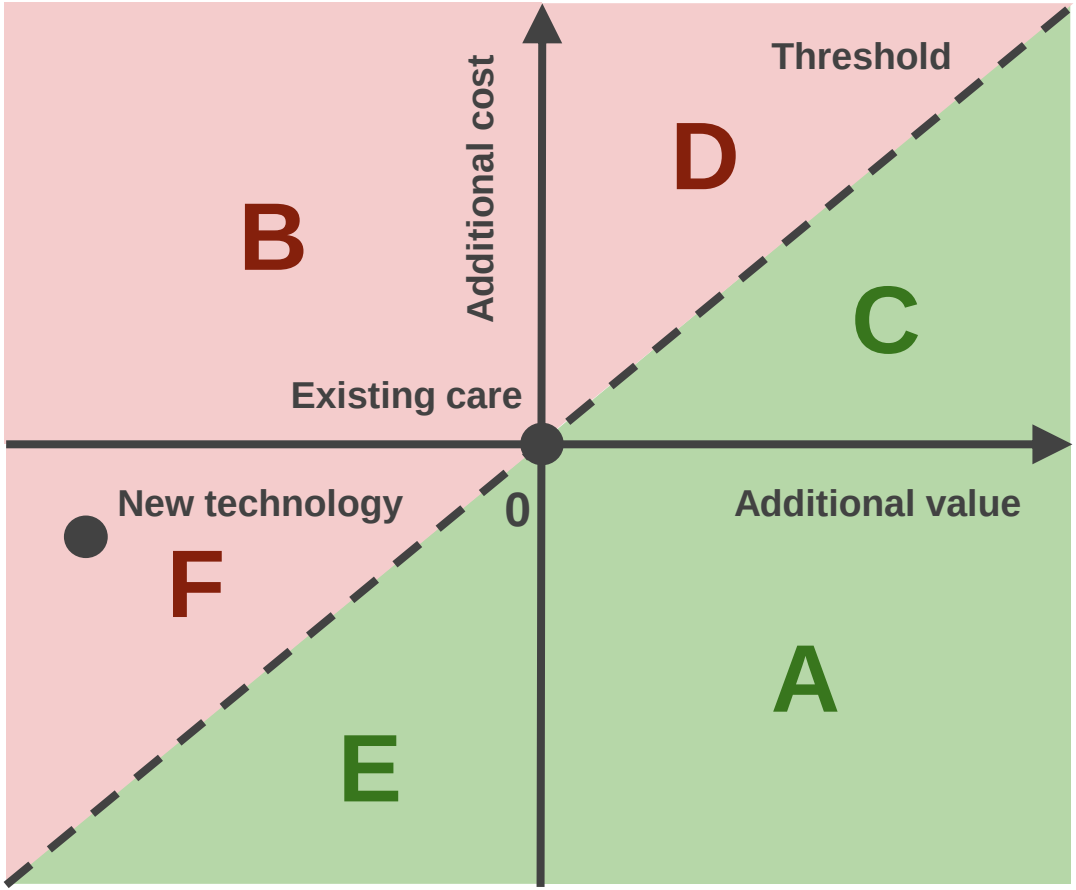

New technology
B
Additional cost
Existing care
0
Additional value
A


B
Additional cost
Threshold
Existing care
0
Additional value
A

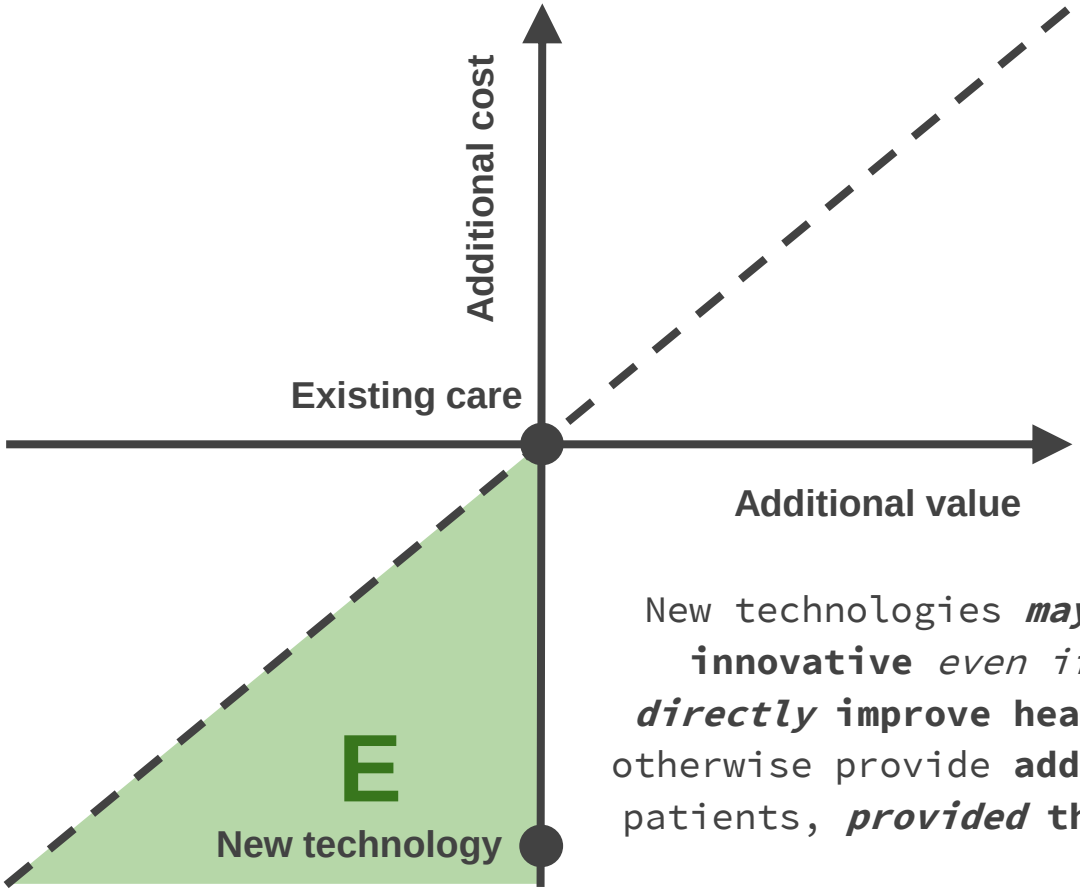

Threshold
Additional cost
B
C
New technology
Existing care
0
Additional value
A


New technology
Additional cost
D
B
C
Existing care
0
Additional value
A

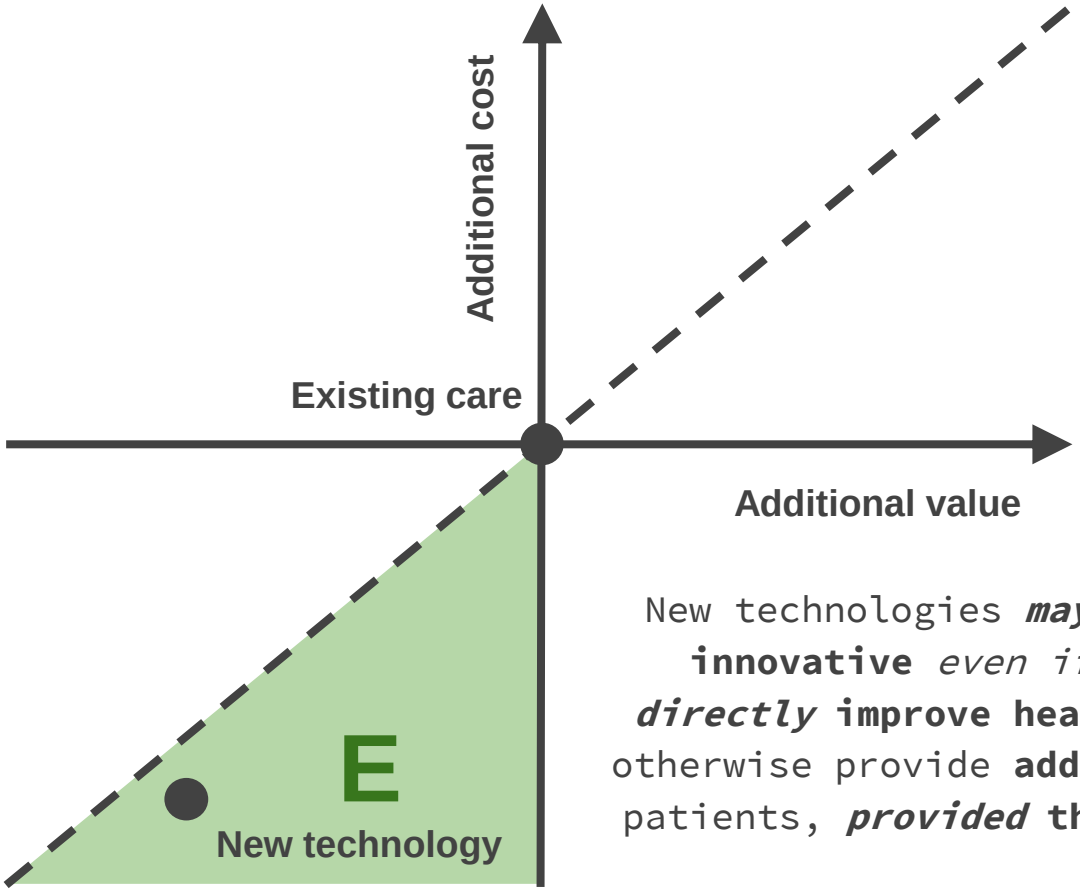

Threshold
Additional cost
D
B
C
Existing care
0
Additional value
A
E
New technology


Threshold
Additional cost
B
D
C
Existing care
New technology
0
Additional value
F
A
E

What are some of the “promises”?



New technologies ***may*** **be considered innovative** *even if* they **do not *directly* improve health outcomes** or otherwise provide **additional value** to patients, ***provided*** **they reduce costs**



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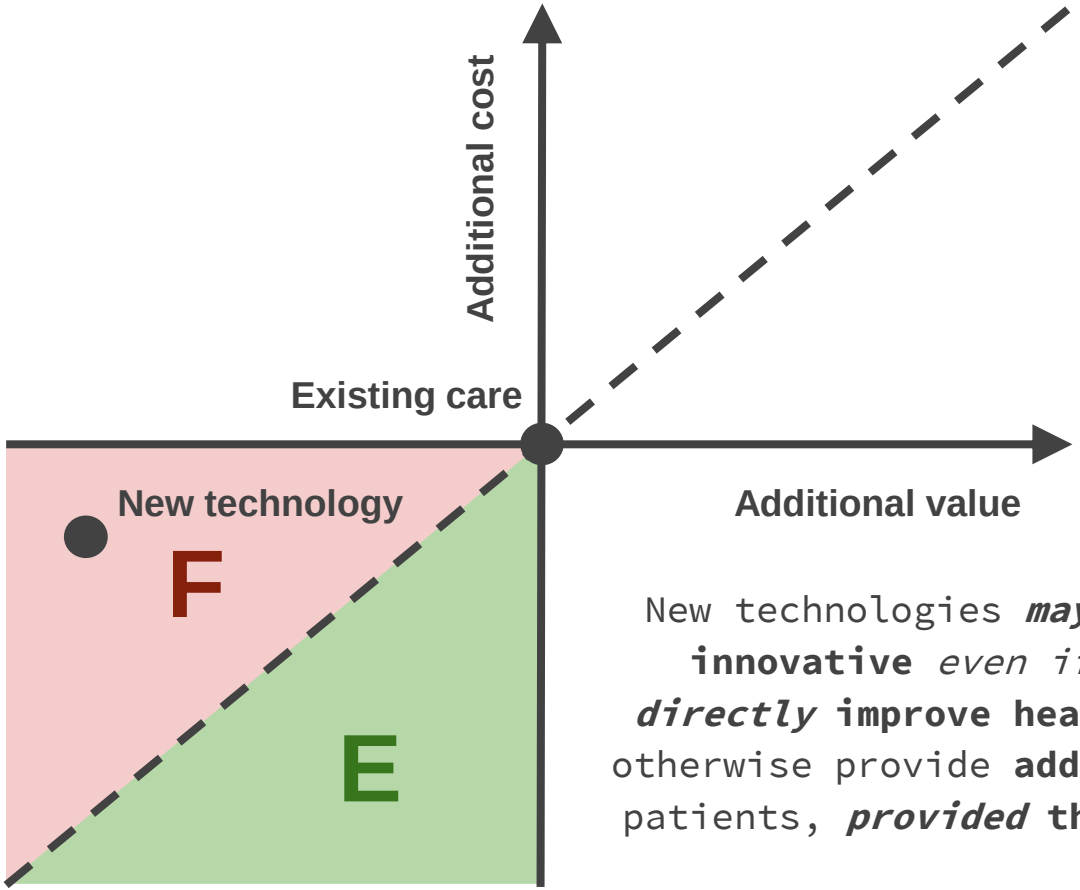

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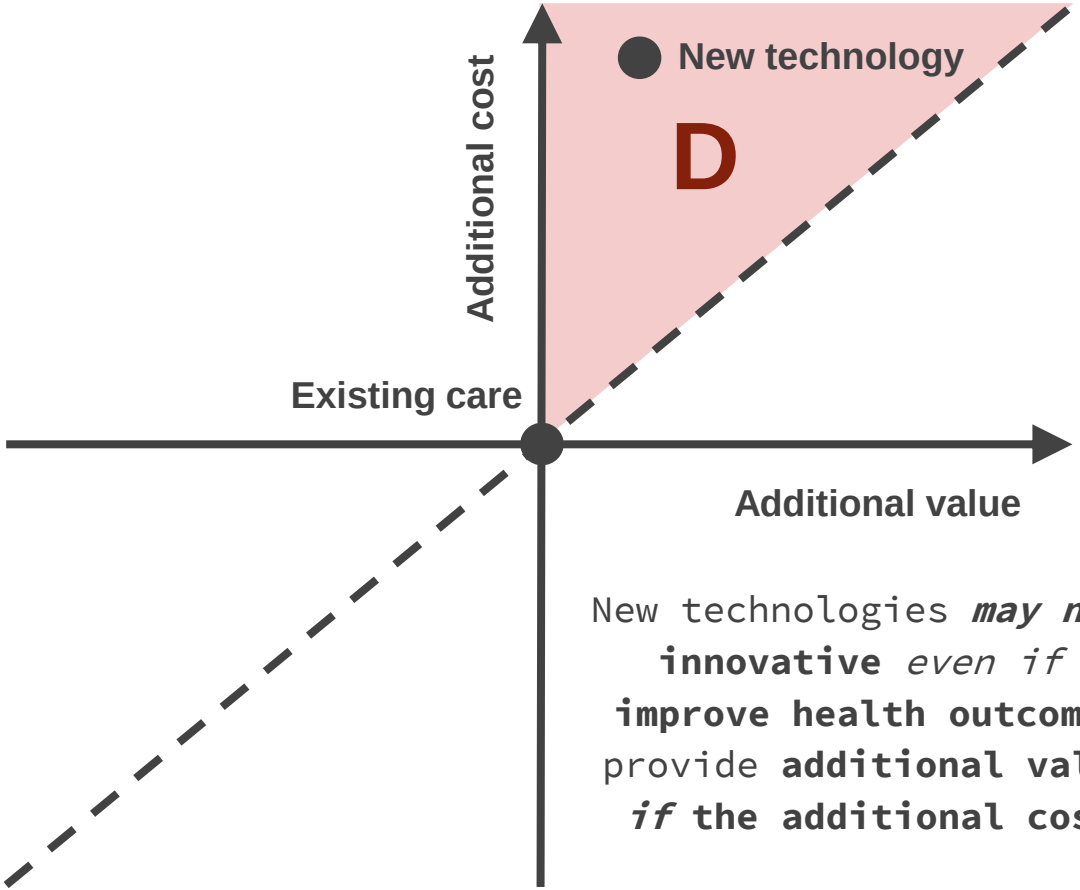
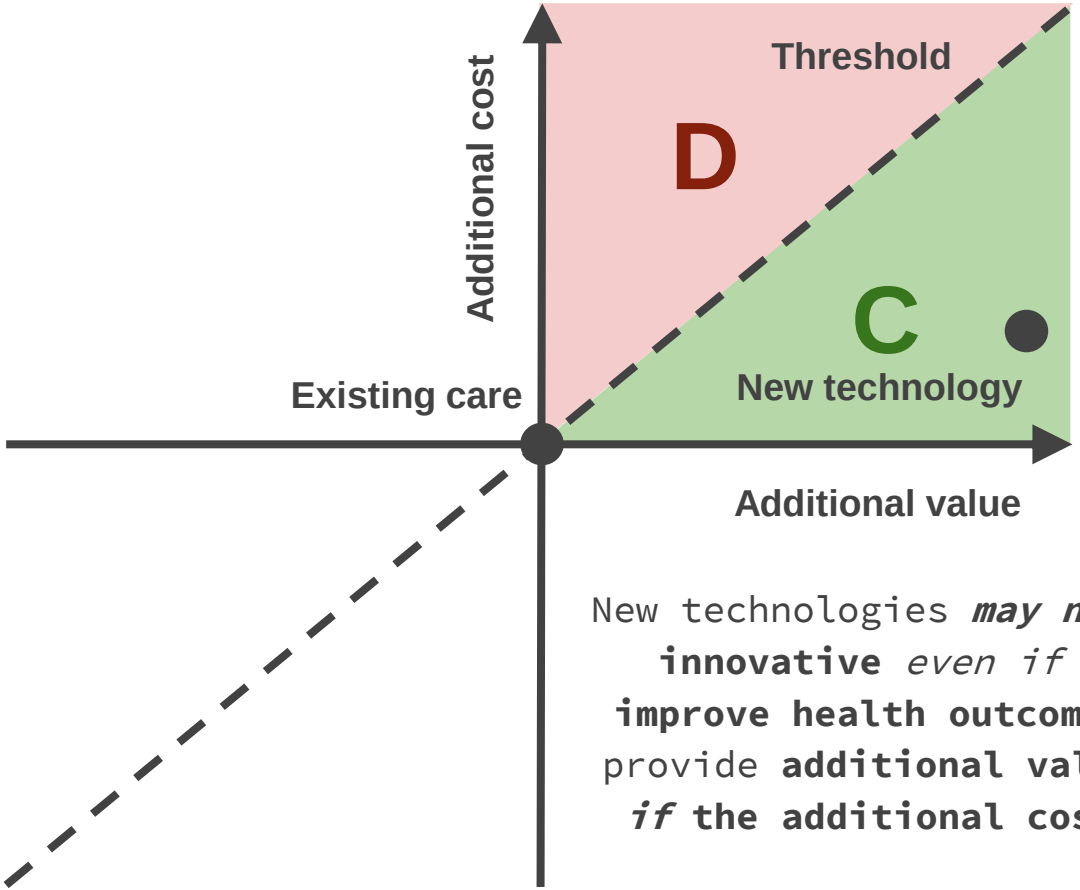
What are some of the “perils”?



New technologies ***may not*** **be considered innovative** *even if* they ***directly*** **improve health outcomes** or otherwise provide **additional value** to patients, ***if*** **the additional cost is too great**



New technologies ***may not*** **be considered innovative** *even if* they ***directly*** **improve health outcomes** or otherwise provide **additional value** to patients, ***if*** **the additional cost is too great**

Political and ethical issues

If policy makers wish to **incentivise development of innovative technologies** and **improve population health**, they must be **willing to reject technologies in region D** - those which provide **added value**, but which **cost so much** that they **displace *even more* value** elsewhere

Politically and ethically **difficult**, since **beneficiaries** of new technologies are generally **known**, but the **patients who bear the cost of their adoption** are generally **unknown**

Dynamic issues

For technologies to be considered **innovative**, they must provide **sufficient additional value**, at a **sufficiently low additional cost**, compared to all other **comparators**

But the set of comparators can **change over time**

New technologies may result in technologies *previously* considered innovative **no longer** considered innovative

Over time, policy makers need to **reassess** whether technologies are **still innovative** and be **prepared to disinvest in existing technologies** when necessary

Case study: Oncotype DX vs Prosigna

VALUE IN HEALTH 16 (2013) 729–739

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

ELSEVIER

Cost-Effectiveness of the 21-Gene Assay for Guiding Adjuvant Chemotherapy Decisions in Early Breast Cancer

Mike Paulden, MSc[1,*], Jacob Franek, MHSc[2], Ba' Pham, MSc[1], Philippe L. Bedard, MD[3,4], Maureen Trudeau, MD[5,6], Murray Krahn, MD[1]

[1]Toronto Health Economics and Technology Assessment (THETA) Collaborative, University of Toronto, Toronto, ON, Canada; [2]Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care, Toronto, ON, Canada (previous affiliation); Health Quality Ontario, Toronto, ON, Canada (current affiliation); [3]Division of Medical Oncology and Hematology, University Health Network – Princess Margaret Cancer Centre, Toronto, ON, Canada; [4]Department of Medicine, University of Toronto, Toronto, ON, Canada; [5]Division of Medical Oncology and Hematology, Sunnybrook Health Sciences Centre – Odette Cancer Centre, Toronto, ON, Canada; [6]Department of Medicine, University of Toronto, Toronto, ON, Canada

ABSTRACT

Objectives: Adjuvant chemotherapy decisions in early breast cancer are complex. The 21-gene assay can potentially aid such decisions, but costs US $4175 per patient. Adjuvant! Online is a freely available decision aid. We evaluate the cost-effectiveness of using the 21-gene assay in conjunction with Adjuvant! Online, and of providing adjuvant chemotherapy conditional upon risk classification. **Methods:** A probabilistic Markov decision model simulated risk classification, treatment, and the natural history of breast cancer in a hypothetical cohort of 50-year-old women with lymph node–negative, estrogen receptor– and/or progesterone receptor–positive, human epidermal growth factor receptor 2/neu-negative early breast cancer. Cost-effectiveness was considered from an Ontario public-payer perspective by deriving the lifetime incremental cost (2012 Canadian dollars) per quality-adjusted life-year (QALY) for each strategy, and the probability each strategy is cost-effective, assuming a willingness-to-pay of $50,000 per QALY. **Results:** The 21-gene assay has an incremental cost per QALY in patients at low, intermediate, or high Adjuvant Online! risk of $22,440 (probability cost-effective 78.46%), $2,526 (99.40%), or $1,111 (99.82%), respectively. In patients at low (high) 21-gene assay risk, adjuvant chemotherapy increases (reduces) costs and worsens (improves) health outcomes. For patients at intermediate 21-gene assay risk and low, intermediate, or high Adjuvant! Online risk, chemotherapy has an incremental cost per QALY of $44,088 (10.59%), $1,776 (77.65%), or $1,778 (82.31%), respectively. **Conclusions:** The 21-gene assay appears cost-effective, regardless of Adjuvant! Online risk. Adjuvant chemotherapy appears cost-effective for patients at intermediate or high 21-gene assay risk, although this finding is uncertain in patients at intermediate 21-gene assay and low Adjuvant! Online risk.

Keywords: breast cancer, chemotherapy, cost-effectiveness analysis, decision making, pharmacogenetics.

Introduction

Adjuvant chemotherapy decisions for women with early stage breast cancer are complex. At present, decisions are informed by clinical judgment, often supplemented through the use of Adjuvant! Online [1]. Adjuvant! Online is a free online diagnostic tool that estimates a woman's risk of breast cancer–specific mortality (BCSM) or relapse on the basis of information entered by the physician, including the woman's age, comorbidities, tumor size, estrogen receptor status, number of involved lymph nodes, and proposed course of treatment [2]. Results can be categorized as "low" (BCSM < 9%), "intermediate" (9% < BCSM < 17%), or "high" (BCSM ≥ 17%) risk [3]. A validation study of Adjuvant! Online has found a high degree of correlation between predicted and observed survival [4].

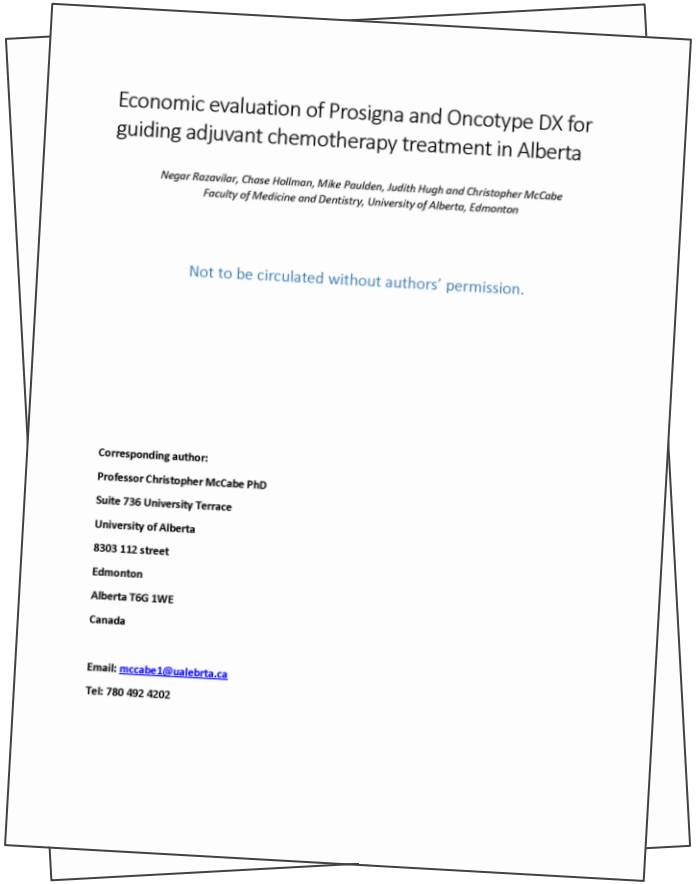
An alternative predictive tool has recently become available. The 21-gene assay (Oncotype DX, Genomic Health, Redwood City, CA) quantifies the expression of 21 genes in breast cancer tissue by performing reverse transcription polymerase chain reaction on formalin-fixed paraffin-embedded tumor blocks that are obtained during initial surgery. Results are summarized by a "Recurrence Score" (RS) between 0 and 100, with scores categorized as "low" (RS < 18), "intermediate" (18 ≤ RS < 30), or "high" (RS ≥ 30) risk [5]. It has been validated both in women with estrogen receptor–positive early stage breast cancer that is lymph node–negative, and in women with estrogen receptor–positive breast cancer that is lymph node–positive, as a means to predict the risk of distant recurrence and magnitude of chemotherapy benefit when added to endocrine therapy [6–9].

As of April 2012, the 21-gene assay cost US $4175 per patient [10]. Its cost-effectiveness is therefore a matter of considerable policy interest. There is also uncertainty as to the clinical- and cost-effectiveness of providing adjuvant chemotherapy, particularly to patients at intermediate risk [11,12]. We present a cost-effectiveness analysis that comprehensively addresses both these issues. An earlier version of our analysis formed part of a

* Address correspondence to: Mike Paulden, THETA Collaborative, University of Toronto, 144 College Street, Toronto, ON M5S 3M2, Canada.
E-mail: mike.paulden@theta.utoronto.ca.

1098-3015/$36.00 – see front matter
Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.jval.2013.03.1625

Paulden M, Franek J, Pham B, Bedard PL, Trudeau M, Krahn M. Cost-effectiveness of the 21-gene assay for guiding adjuvant chemotherapy decisions in early breast cancer. Value Health. 2013;16: 729–739. doi:10.1016/j.jval.2013.03.1625



Economic evaluation of Prosigna and Oncotype DX for guiding adjuvant chemotherapy treatment in Alberta

Negar Razavilar, Chase Hollman, Mike Paulden, Judith Hugh and Christopher McCabe
Faculty of Medicine and Dentistry, University of Alberta, Edmonton

Corresponding author:
Professor Christopher McCabe PhD
Suite 736 University Terrace
University of Alberta
8303 112 street
Edmonton
Alberta T6G 1WE
Canada

Email: mccabe1@ualebrta.ca
Tel: 780 492 4202

Razavilar N, Hollman C, Paulden M, Hugh J, McCabe C. Economic evaluation of Prosigna and Oncotype DX for guiding adjuvant chemotherapy treatment in Alberta. Report produced for Alberta Health Services by McCabe Research Group, Faculty of Medicine and Dentistry, University of Alberta. May 2016.

Oncotype DX appeared cost-effective vs usual care...

Ontario-based economic analysis published in 2013

Compared to **usual care** (adjuvant chemotherapy guided using Adjuvant! Online or clinical judgement) **Oncotype DX** was found to **increase costs** ($3,505 per patient) and **improve health outcomes** (0.22 QALYs per patient), resulting in an incremental cost-effectiveness ratio (ICER) of **$15,932 per QALY**

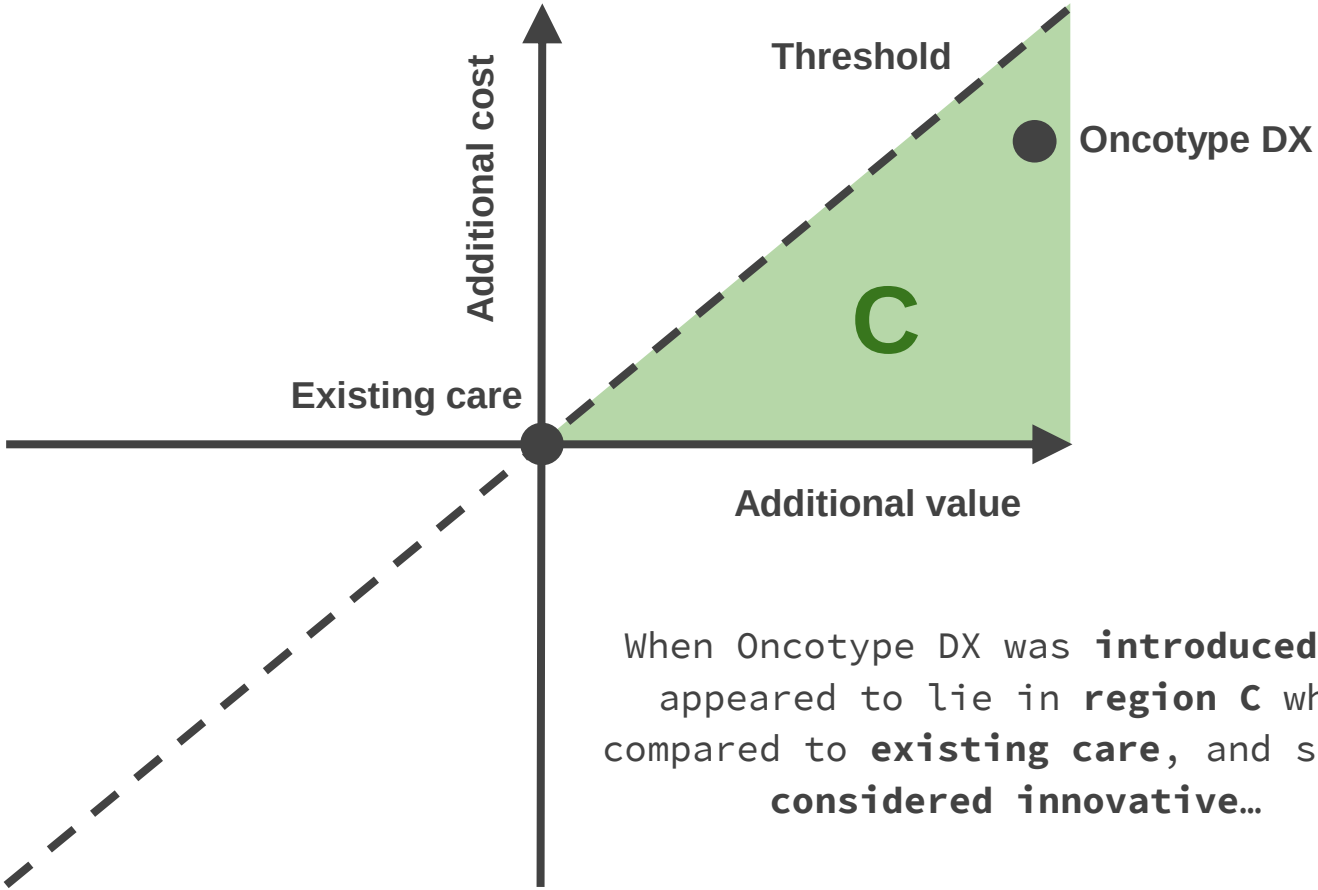
Compared to a conventional cost-effectiveness **threshold** of $50,000 per QALY, **Oncotype DX appeared cost-effective**

… but Oncotype DX did not appear cost-effective vs Prosigna

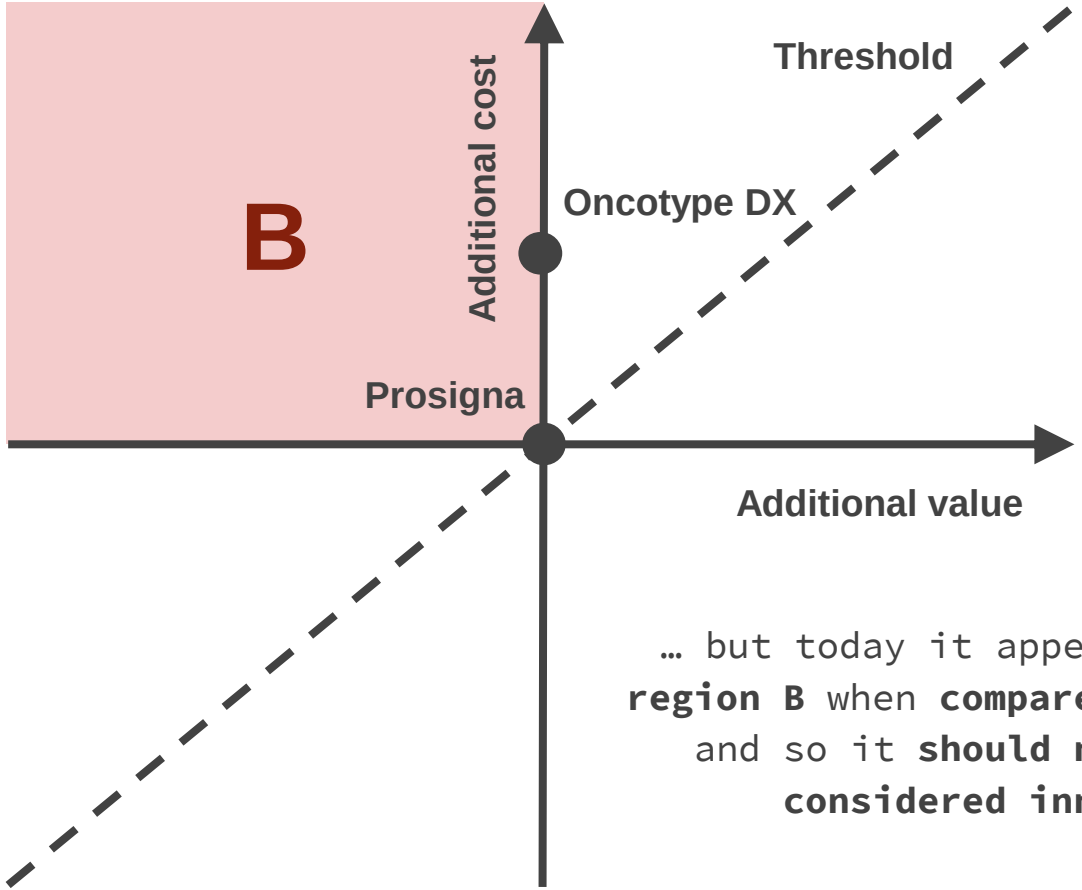
Alberta-based economic analysis reported in 2016

Compared to **Prosigna**, **Oncotype DX** was found to **increase costs** ($1,240 per patient) and **worsen health outcomes** (0.003629 QALYs per patient), resulting in Oncotype DX appearing **dominated** (higher costs and worse outcomes)

It follows that **Oncotype DX is not cost-effective** compared to Prosigna



When Oncotype DX was **introduced**, it appeared to lie in **region C** when compared to **existing care**, and so was **considered innovative…**



… but today it appears to lie in **region B** when **compared to Prosigna**, and so it **should no longer be considered innovative**

Policy response

Prosigna has **further benefits** compared to Oncotype DX:

- Fewer intermediate (**indeterminate**) results
- Superior prediction of **long-term treatment benefit** (TransATAC study)
- Repatriation of **out-of-province testing** (in-house vs shipped to US)

Yet **barriers exist** to its implementation in practice

- Lack of **life-cycle HTA processes** (Oncotype DX not re-assessed)
- Appropriate utilization and **physician compliance** (reluctance to disinvest in Oncotype DX and adopt Prosigna in its place)

Conclusion

Conclusions

Health interventions or technologies might be considered **“innovative”** if they **improve population health outcomes**

If any **additional costs** are borne by the health system, this results in **forgone health care** for other patients

It follows that an **expensive** new technology *might* **not be considered innovative** - *even if it* ***adds value*** - since it *may* **displace more population health than it provides**

A technology that **reduces health expenditures** *might* be **considered innovative**, *even if it* ***has no additional value***

Conclusions

It also follows that technologies ***previously*** **considered innovative** may **no longer appear innovative** once cheaper and/or more valuable **comparators** become available

Continuing to use older technologies when **more innovative alternatives** are available may **diminish population health**

Policy makers should adopt a **life-cycle approach to HTA** and be **willing to disinvest in existing technologies**

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Any questions?