PRECISION MEDICINE: APPLYING THEORY TO PRACTICE FOR VALUE WITH COMPANION DIAGNOSTICS

CADTH Panel Presentation, Ottawa, Ontario.

*Precision Medicine: Applying Theory to Practice for Value with CDx*

April 24, 2017

Don Juzwishin, Tania Bubela, Judith Hugh, Christopher McCabe

Alberta Health Services and University of Alberta
Presenters

Alberta Health Services
• Don Juzwishin
Faculty of Medicine & Dentistry University of Alberta
• Christopher McCabe
• Judith Hugh (+AHS)

SCHOOL OF PUBLIC HEALTH
• Tania Bubela

OTHER TEAM MEMBERS
• Michael Mengel (+AHS)
• Deborah James
• Stacey Hume

Research staff/students:
Michael Paulden, Mark Bieber, Westerly Luth, Katherine Fu, Kiah Van der Loos, Monica Wang, Yael Mansour, Negar Razavilar
Panel Outline

- **Bubela:** Introduction to the ALMDx/PACEOMICS Platform to support precision medicine landscape in Alberta in two contexts:
  - Adoption of new technologies wherever developed
  - Local innovation

- **Hugh:** Case example of adoption of new breast cancer companion diagnostic by Alberta’s health system

- **McCabe:** Local innovation context, conclusions and lessons learned on barriers and enablers for the adoption and implementation of Precision Medicine in Alberta
Precision Medicine: Personalized, Problematic & Promising

(Jameson & Longo NEJM 2015)
Key Areas of Synergy
Evolution of evidence base for precision medicine and implementation science
Recognition of underuse and overuse of interventions
Management of abundance of data

Optimal integration of effective diagnosis, prevention, and treatment
Understanding of multilevel context
Theories and strategies to drive health care improvement

Improved health, health care, and health systems

Optimal use of genomics and behavioral data to drive clinical and patient decision making
Ongoing development of genomics evidence base
Personalized and population impact

Key Areas of Synergy
Refresh cycle of evidence base
Determination of degree of achievable personalization of care

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
Evolutions 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 and Erbitux 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 fusion testing and Crizotinib in NSCLC
2014: PD1 and PDL1 and immunotherapies

As of 2017: 207 Pharma pipelines for CDx – 158 in cancer
Cancer Cellular Immunotherapy
SPONSORS OF 1554 CI CLINICAL TRIALS

- industry
- NIH
- NIH & industry & other public sector funder
- NIH & other public sector funder
- other public sector funder

Number of Clinical Trials vs. Start Year
FIRST-EVER CRISPR TRIAL POINTS TO LOOMING PROBLEMS
CRISPR and CAR-T
Leber Congenital Amaurosis Gene Therapy Timeline

1997
- RPE65 gene mutation that causes Type 2 LCA identified

2001
- Pre-clinical research

2007
- Phase I or I/II gene therapy clinical trials begin

2012
- Phase III RPE65 gene therapy clinical trial begins

2015
- Phase III clinical trial expected to report in late 2015 (NCT00999609)

Next Steps
- Regulatory approvals in key markets
- Positive coverage decisions by public and private payers
- Clinical adoption of gene therapy in treatment centers

Leber Congenital Amaurosis Gene Therapy Timeline
Implementation of Precision Medicine

- Population-based guidelines for screening and prevention
- Specific diagnostic tests
- Decision support from health system
- Unique interventions based on precision diagnostics
- Use of clinical research to inform best practices

Most effective health care for the individual patient and the population

(Jameson & Longo NEJM 2015)
International Environment

ExAC

- the gnomAD team assembled 2.9 petabytes of raw data... that's equal to 331 years of movie streaming.
- gnomAD contains sequences from over 140,000 people.
- gnomAD contains data from people hailing from each of the 6 inhabited continents.
- 254.2 million rare and common genomic variants, 159.8 million of which were novel, were discovered using gnomAD.

THE PRECISION MEDICINE INITIATIVE

LONGER-TERM GOALS
Create a research cohort of >1 million American volunteers who will share genetic data, biological samples, and diet/lifestyle information, all linked to their electronic health records if they choose.

NEAR-TERM GOALS
Intensify efforts to apply precision medicine to cancer.
- Innovative clinical trials of targeted drugs for adult, pediatric cancers
- Use of combination therapies
- Knowledge to overcome drug resistance
Capital Investment: Beijing Genomics Institute
PRECISION MEDICINE FOR ALBERTA?

ALMDX/PACEOMICS TEAM
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
Goals

1. Accelerate development, adoption and implementation of new valuable tests and test-directed treatments.
2. Identify and eliminate low value tests and test utilization.
3. Optimize translational research and clinical infrastructure across the province.
4. Enable provincial collaboration at the public-private and research-clinical interfaces.
5. Expand the highly qualified workforce of the future.
6. Diversify the economy.
7. Successfully compete for large federal and international funding.
Demonstration Projects ALMDX/PACEOMICS

• ALMDx funded by Alberta Economic Development and Trade, 2014-16

• PACEOMICS funded bGenome Canada, CIHR, AI-HS, 2013-2018

• Four demonstration projects
  • Breast Cancer diagnostics
  • Mitochondrial diseases gene panel
  • Thyroid cancer diagnostics
  • DVT gene panel for pediatric cancer patients
PRACTICAL CHALLENGES TO IMPLEMENTING A NEW COMPANION DIAGNOSTIC:

Moving from Oncotype Dx to Prosigna

Dr. Judith Hugh
Objectives

- Clinical and Testing Background
- General algorithm for replacing an existing test
- Overview of the processes and challenges we faced
- Some specific challenges around “Building our case”
- The sordid story of reaching consensus
- Lessons learned
Treatment According to ER+ Subtypes

- **Triple Neg**
- **HER2**
- **Luminal A**
- **Luminal B**

**Disease Free Survival (%)**

- **YES ChemoRx**
- **NO ChemoRx**

**Years**

ER Positive:

- Low-grade Carcinomas: Ductal and Lobular
Commercial Tests to Separate ER+ Breast Cancers

2000 Perou CM Nature
Molecular portraits…

2002 van’t Veer LJ Nature
Gene-expression profiling predicts…

2004 Paik S NEJM
A multi-gene assay…

A. Intrinsic Subtype

B. 70 - gene profile

C. Recurrence Score

PAM50 → Prosigna™

MammaPrint™ ($4200 USD) Agendia

Oncotype Dx™ ($4200 USD) Genomic Health

2009+

2007

2004

Approved by Health Canada April 2014

Offered as a funded test in AB March 2014

Fan C. et al. NEJM 2006;355:560-9
## Comparison of Oncotype Dx and Prosigna

<table>
<thead>
<tr>
<th></th>
<th>Oncotype Dx™</th>
<th>Prosigna™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Centre</td>
<td>USA</td>
<td>Local Lab</td>
</tr>
<tr>
<td>Regulatory Approval</td>
<td>None</td>
<td>Health Canada, US FDA</td>
</tr>
<tr>
<td>Leverage Opportunities</td>
<td>None</td>
<td>Multiple potential Applications</td>
</tr>
<tr>
<td>Technology</td>
<td>qRT-PCR (amplification, prone to bias)</td>
<td>Linear</td>
</tr>
<tr>
<td>Clinical Evidence-base</td>
<td>Some predictive</td>
<td>Superior Prognostic</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>TransATAC, Sestak. SABCS Dec 2016</em></td>
</tr>
<tr>
<td>Cost</td>
<td>~ $990,000/yr</td>
<td>~$700,000/yr + $350K start-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Incl. labour, maintenance and amortization</em></td>
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Replacing an Existing Test with a New Improved Test

Idea
Identify:
• Clinical Need
• Best test

Acquire test
• Feasibility
• Funding

Build the case
• Guidelines
• Local Analyses
• Trials/Comparisons

Get Consensus

Roll it out
• Testing Centres
• Specimen transport
• Reporting into LIS

• Lab (Technical support, Accreditation)
• End Users (Pathologists, Oncologists)
• Governing bodies (Networks, AHS, AH)
Challenges:
Moving from Oncotype Dx™ to Prosigna™

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

2011IDEA
2012-2014ACQUIRETEST
2015-2016BUILDTHECASE
2016-2017GETCONSENSUS
2017ROLLITOUT

Guidelines
Local Analyses
Trials/Comparisons
"And the Guidelines said....."

Feb. 2016

For chemotherapy decisions in ER/PR-positive, HER2 negative, Node negative breast cancer:

<table>
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<tr>
<th></th>
<th>Oncotype Dx</th>
<th>Endo-Predict</th>
<th>Mamma-Print</th>
<th>Prosigna</th>
<th>Breast Cancer Index</th>
<th>Mammastrat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved for use</td>
<td>may</td>
<td>may</td>
<td>not</td>
<td>may</td>
<td>may</td>
<td>not</td>
</tr>
<tr>
<td>Evidence Quality</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
</tr>
<tr>
<td>Strength of Evidence</td>
<td>strong</td>
<td>moderate</td>
<td>moderate</td>
<td>strong</td>
<td>moderate</td>
<td>moderate</td>
</tr>
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“And the Guidelines said…..”

Should this patient receive Chemotherapy?

?OK for “No” ChemoRx

Good evidence that ODx, & Prosinga, can support the withholding of ChemoRx

?OK for “Yes” ChemoRx

Only ODx has proven ability to predict benefit from ChemoRx
“And the Local Analysis said.....”

How the two tests differed in their calls

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<td>15</td>
</tr>
<tr>
<td>Intermed (9)</td>
<td>4</td>
</tr>
<tr>
<td>High (10)</td>
<td>1</td>
</tr>
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How the tests compared with Oncologists decisions around patient treatment...

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IDEA

2012-2014
ACQUIRE
TEST

2015-2016
BUILD
THE
CASE

2016-2017
GET
CONSENSUS

Guidelines
Local Analyses
Trials /
Comparisons

2017
ROLL
IT
OUT
Each of us follows the change curve.

William Bridges Theory on Change

Courtesy of Mr. Alan Day, Senior Advisor, Transformational Change, Organizational Health and Effectiveness, University of Alberta
Lab Engaging the Oncologists

“Obviously the Academics don’t have enough to do..”
Oncologist, March 2015

Lab Proposal:
Transition period of dual testing
April 2016

“Not acceptable at the present time:
• Double testing delays/confuses treatment
• Agree only to a prospective multi-institutional trial”
Oncologist September 2016

Comparison data
Prosigna is superior to Oncotype Dx
SABCS Dec 2016

Verbal provincial consensus to adopt Prosigna
March 2017
What is the Best way to Replace an Existing Test?

1. **Idea**
   - Identify:
     - Clinical Need
     - Best test

2. **Acquire test**
   - Feasibility
   - Funding

3. **Build the case**
   - Guidelines
   - Local Analyses
   - Trials/Comparisons

4. **Get Consensus**
   - Lab (Technical support, Accreditation)
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   - Governing bodies (Networks, AHS, AH)

5. **Roll it out**
   - Testing Centres
   - Specimen transport
   - Reporting into LIS
What is the Best way to Replace an Existing Test?

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“If we get consensus before moving forward, we’re just playing catch-up”
Acknowledgements

**People:**

1. **Co-applicant on the Canadian Foundation for Innovation Grant.**
   **Dr. Michael Mengel**, Chair of the Department of Laboratory Medicine and Pathology, U of A.

2. **The Provincial multi-disciplinary team that validated Prosigna in Alberta:**
   **Dr. Gilbert Bigras** (Director of Edmonton zone IHC Lab),
   **Dr. Hua Yang** (Medical Lead for Breast Cancer, Calgary Lab Services),
   **Dr. Iyare Izevbaye** (Medical Lead, Molecular Pathology, U of A),
   **Dr. Anil Joy** (Chair, Provincial Breast Tumour Group, till 2015)

3. **The ALMDx Team:**
   **Dr. Don Juzwishin** (Director Health Technology Assessment and Innovation),
   **Dr. Christopher McCabe** (Professor School of Public Health and Department of Economics, U of A),
   **Dr. Tania Bubela** (Professor, School of Public Health, U of A) and
   **Dr. Michael Mengel** (Professor and Chair, Department of Lab Med and Pathology, U of A).

4. **Medical Oncology Champions:**
   **Dr. Karen King** (Medical Lead, Northern Alberta Breast Cancer Program),
   **Dr. Sasha Lupichuk** (Chair, Provincial Breast Tumour Group),
   **Dr. Matthew Parliament** (Chair, Cancer Care Alberta)

5. **Alberta Health Services, Laboratory Leaders:**
   **Dr. Carolyn O’Hara** (Interim Provincial Medical Director),
   **Shelley Rawlake** (Senior Operating Officer, Lab Services, Edmonton Zone).

**Funding:**

Canadian Foundation for Innovation, ALMDx, Cancer SCN

*Lilian McCullough Chair in Breast Cancer Research, University of Alberta*
Opportunities

- Innovation can serve AHS purpose:
  - increase efficiency, improve quality, i.e. aligned with patient’s need

- Rapid evidence-based adoption of innovations is supported through leadership and represents a strategic priority

- AHS is a large provider which is on its way to becoming fully integrated
  - excellent beta-site

- Has depth and breadth to be competitive globally
Business models – Regulatory Pathways

• A business model is how a firm creates, captures, and shares value. It is how a firm contributes to a value chain or network

• Business models can be drivers or barriers to innovation

• Service: Laboratory Developed Test
  • Offer service and bill from Genetic Laboratory Services, AHS

• Market In Vitro diagnostic as a medical device
  • Regulatory approval based on clinical evidence
  • High cost of development

• Software Licensing: Develop and market analytical software
  • Bioinformatics and programming capacity needed to develop a commercial product
ALMDX/PACEOMICS
DEMONSTRATION PROJECT TWO

Support Alberta Dx Developers
Mitochondrial Disease NGS Panel
Dr. Stacey Hume
Mitochondrial diseases

- Multi-systemic and lead to variable clinical presentation
- Estimated to affect 1/5000 individuals
- Caused by mutations in mitochondrial DNA (mtDNA) or nuclear genes (nuDNA) that encode mitochondrial components
- Inherited or acquired

Testing

• Definitive diagnosis remains difficult
  • Primarily biochemical testing
  • 28% of U.S. physicians surveyed order genetic tests

• Next-Generation Sequencing test has advantages
  • Cost
  • Accuracy
  • Patient empowerment
  • Healthcare resource savings?

• Main competitor
  • Baylor College of Medicine, Texas
  • 667 genes (cost approx. $8,000 USD)
Alberta Development Status

• Nuclear gene panel finalized (189 genes)
  • Validation tests demonstrate good clinic utility
  • Base costs (to cover labor and reagents) much less than competitor
• In process of optimizing in-house Mitochondrial Genome Database and variant information
  • Developing bioinformatics pipeline and software
  • ~1 year of bioinformatician attention to complete
• Cost-effectiveness analysis in progress
  • Significant delays (over one year) in data access due to need to aggregate patient-level healthcare utilization, cost AND diagnostics data.
Complex Legislative Framework

- **Health Information**
  - *Personal Information Protection and Electronic Documents Act* R.S. 2000 c. 5 [PIPEDA]

- **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**

- **Personal Information Held by the Alberta Government**
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:

- flow of health information without consent restricted to:
  - A person providing continuing treatment and care to the individual
  - The individual, the individual’s authorized representative or others with the individual’s consent
  - A professional body, auditor and quality assurance committee
  - A researcher under certain conditions
  - Under other acts
  - The court or a quasi-judicial body
Outside the Controlled Arena

- The custodian must act as the trusted gatekeeper of the information
- Informed consent and expressed wishes of the individual must still be considered
- The custodian must only disclose the least amount of information at the highest degree of anonymity
- The custodian must protect the information while it is in transit
- The custodian must make a notation of disclosure without consent of a record containing individually identifying diagnostic, treatment and care information unless otherwise noted.
- The custodian must ensure that a researcher submits the research project for review by an approved research ethics board and to comply with the requirements of the board.
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
Identified commercialization 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
CONCLUSIONS ON PRECISION MEDICINE FOR ALBERTA

ALMDx/PACEOMICS Team
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