“Implementing Cutting-Edge Technologies in Clinical Practice: A Practical Approach for Researchers”

March 21\textsuperscript{st}, 2024 – Aachen Germany

Joe Lennerz MD PhD
Chief Scientific Officer, BostonGene
Don’t Ban ChatGPT in Schools. Teach With It.

OpenAI’s new chatbot is raising fears of cheating on homework, but its potential as an educational tool outweighs its risks.
1997: Deep Blue defeats Garry Kasparov
2000: A Neural Probabilistic Language Model
2009: Large-Scale Deep Unsupervised Learning Using Graphics Processors
2011: Watson defeats humans on Jeopardy!
2011: Apple releases Siri
2012: Breakthrough in image recognition – Google’s deep neural network project
2014: China’s Tianhe-2 – fastest system
2014: Facebook introduces DeepFace
2016: AlphaGo defeats the world champion in the Chinese board game Go
2017: Sophia, the first robot to be granted citizenship
2017: Google introduces the Transformer
2018: Cimon, GPT, Lovot
2019: Turing Natural Language Generation model
2020: Curial GPT-3 LLM
2021: Dall-E
2022: ChatGPT
2023: GPT-4
Concerns about AI implications & Regulatory trends

AI Timeline – “Four Seasons”

- **Boom 1**: "GOFAI" with Technology
- **Boom 2**: "Expert Systems" with Data
- **Boom 3**: "Machine Learning" with Data
- **Winter 1**: with Technology
- **Winter 2**: with Technology
- **2010s**: "AI for Social Good"
Figure 1: Knight Capital’s shares are down more than 75% following its $440 million trading glitch.

Saltapidas & Maghsood
The Daunting Path to Patients

Idea Analyte Publish Device Trial Utilization Outcome

Technology Discovery Analytical Validation Clinical Validation Clinical Integration Clinical Utility
The Daunting Path to Patients
Identify key elements for integration into clinical practice

- How much? => Why? => strategy => **alignment** of initiative & funding source
- What? => and in what order? => what’s first => **operations**
- Who => cross-functionality => interdisciplinary teams
What do you need to realize innovation?

Great Team (int. & ext.)
Understand the framework
Healthcare system

How to integrate (Concept + Process)
Approaches to Financial Sustainability
Approach to apply and challenge regulation
Collaborating with the Enemy
How to Work with People You Don’t Agree with or Like or Trust
Adam Kahane
Bestselling author of Solving Tough Problems and Power and Love
Rationale

Socialized

Instinctive

Group combined
Agile Manifesto

“We are uncovering better ways of developing software by doing it and helping others do it. Through this work we have come to value:

Individuals and interactions over processes and tools
Working software over comprehensive documentation
Customer collaboration over contract negotiation
Responding to change over following a plan

That is, while there is value in the items on the right, we value the items on the left more.”
Project management is the organizational framework to organize people and align their skills. Here, we selected 10 core competencies in managing a project. One of these competencies is selection of a development methodology, which specifies the way to organize the work. By specifying the way to organize the work (e.g., agile vs. waterfall), the development methodology may influence project management (e.g., communication style).
What do you need to realize innovation?

Great Team (int. & ext.)
Understand the framework
Healthcare system
How to integrate (Concept + Process)
Approaches to Financial Sustainability
Approach to apply and challenge regulation
Synthetize the healthcare infrastructure for financially-sustainable genomics

Lennerz et al., 2016 JMD
What do you need to realize innovation?

Great Team (int. & ext.)
Understand the framework
Healthcare system

How to integrate (Concept + Process)
Approaches to Financial Sustainability
Approach to apply and challenge regulation
Patient journey vs. care pathway

Clinical
- Oncologist
- Diagnostic Radiology
- Intervventional Radiology
- Surgical Pathology
- Molecular Pathology
- Specialty Pharmacy

RCM
- Radiology Benefit Mgmt.
- Prior Auth.
- ICD CPT

Payor
- Benefit Mgmt.
- Prior Auth.
- Claim

Payor
- Benefit Mgmt.
- Prior Auth.
- MTM CPT
- Claim

Payor
- Benefit Mgmt.
- Prior Auth.
- Pharmacy

Routine care
Integrated care pathway
Rapid testing

Time from Diagnosis to molecularly-informed treatment start

Routine: 48 days
Integrated: 4 days
Lung, heme, neuro
What’s next

Pre-presentation time....
What do you need to realize innovation?

- Great Team (int. & ext.)
- Understand the framework
- Healthcare system
- How to integrate (Concept RWE Precomp)
- Approaches to Financial Sustainability
- Approach to apply and challenge regulation
Spidermap (Mindmap)
Designated framework

New assay launch

- TAT (for STAT, routine)
- Gene targets
- Predicted volume
- Launch date
- Intended use & requirements
- Assay priority
- Clinician education/ notification
- Requisition/EPIC update
- Proficiency testing
- Personnel training
- CPT code selection
- Billing/CoPath
- Addition of assay in CoPath
- SOPs
  - Pre-analytic
  - Analytic
  - Post-analytic
  - Write up
  - Review and approval
  - Troubleshooting steps
  - Contingency plans
- Samples
  - Collection instructions
  - Sample storage
- Validation
  - Obtain samples for validation
  - Analytical validation
  - Write-up
  - Review and approval
- Equipment
  - Space
  - Installation
  - Performance verification
  - Backup availability
- Chemistry
  - Establish QC metrics (NTC coverage, etc.)
- Informatics
  - Reagent storage

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Quality Management

Research

Translation

Clinical Practice

Idea

Analyte

Publish

IVD

Trial

Utilization

Outcome

Technology Discovery

Analytical Validation

Clinical Validation

Clinical Integration

Clinical Utility
Innovation = Integration

- Utilization
- Utilization Management
- Utilization Management Strategy

How to implement?
- Concept: U, UM, UMS

*Helen Hou et al., 2023 J Appl Lab Med*
Relevant Considerations Relevant Outcome Measures
RWD to RWE to transformation

Days to Treatment

- Real-world evidence
  - Evidence of clinical utility
- Real-world data
  - Data quality and sources
- Quality improvement
  - Care specific initiative
- Payor Matrix
  - Health system specific
  - Organizational knowledge
  - Policy database
  - Contact information

Practice transformation
- "Financially sustainability through functional synergy"

Policy Co-Creation
- Long term strategies

Engagement with Payor operations
- Health plan specific
- Financial structures
- Service requirement
- Audit specification
- Data sharing
- (Dis-)Incentive programs
- Prior auth exemption

Reimbursement

- 100±15.9
- 104±9.8
the pre-competitive space
We are all black swans...

I’m not
What was before USB?

How did USB take over?

IO
The pre-competitive space
+ is abstract
+ requires intricate structure(s)
+ e.g., anti-trust monitoring

a proven approach
underutilized in medicine
Federated models necessitate **human** governance structures
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“Developing and putting forth your own vision and then making it reality is no simple task”
## Paradigm for Financial Sustainability

<table>
<thead>
<tr>
<th>New Programs or Initiative</th>
<th>Deliverables</th>
<th>Value Proposition</th>
<th>Aims &amp; Goals</th>
<th>Funding Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic Science</td>
<td>Discover</td>
<td>Publication</td>
<td>Solve a Problem</td>
<td>Agencies</td>
</tr>
<tr>
<td>Pre-Clinical Studies</td>
<td>Applied Knowledge</td>
<td>Training</td>
<td>Focus area</td>
<td>Foundations</td>
</tr>
<tr>
<td>Translational Research</td>
<td>Competence</td>
<td>Outcome Change</td>
<td>Product success</td>
<td>Patients</td>
</tr>
<tr>
<td>Clinical Trials</td>
<td>Actionable Results</td>
<td>Optimize Care</td>
<td>Cost effectiveness</td>
<td>Industry</td>
</tr>
<tr>
<td>Clinical Practice</td>
<td>Reliability &amp; validity</td>
<td>Improved Health</td>
<td>Innovation</td>
<td>Payors</td>
</tr>
<tr>
<td>Clinical Application</td>
<td></td>
<td></td>
<td>Taxation</td>
<td>Society</td>
</tr>
</tbody>
</table>

Thierauf et al., 2019 The Oncologist
Realizing Precision Oncology is a Multi-Layered Challenge
The Art of Contracting

- Type and level of risk
- Return on investment
- Provider network requirements
- Service requirements
- Financial structures
- Data sharing
- Patient population
- Quality metrics and performance evaluation
- Consumer engagement
- Confidentiality requirements
Rapid testing reimbursement analysis

- **Coding strategy**
  - Payor tailored
  - Prior authorization
  - Pilot program(s)

- **Reimbursement analysis**
  - Dependent on Focus
  - Quality

*Reimbursement analysis*

- Overall (N = 214)
  - Reimbursed (n = 134)
  - Not reimbursed (n = 80)

63% reimbursed

*Dagogo-Jack et al., 2018 JCO PO*
Levels of Approaching Financial Sustainability

“a robust local program can be an effective strategy to ensure progress”
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Regulatory Science
Fig. 2  Selected regulatory science concepts.

https://doi.org/10.1038/s41746-022-00721-7
Regulatory Science

established
“...is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products”

new
“...is applying the scientific method to challenge current concepts and drive meaningful regulations”
Can Science be Trusted Without Government Regulation?

What is Discovery Bias? Do such biases limit our ability to see alternatives? Does publishing the full methods/results section of a SARS-CoV-2 paper increase our ability to protect public health from a future pandemic?
29th June: FDA approves 100th device containing AI / ML

2nd April: FDA publish Proposed Regulatory Framework for Modifications to Artificial Intelligence / Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback

12th May: FDA approves 250th device containing AI / ML

27th October: Guidance on Good Machine Learning Practice for Medical Device Development: Guiding Principles

6th April: MHRA publishes guidance on Software and Artificial Intelligence (AI) as a Medical Device

5th December: Public consultation closes on BS 30440 (Validation framework for the use of AI in healthcare)
What's next in Technology and Innovation

Diagnosis  Technologies  Data Science  Regulatory Sciences

Rules  Standards  Policies  Requirements  Regulations  Transparency  Law

Basic Science  Translational Science  Clinical Relevance
Let’s start where other initiatives end … pre-competitive space (=collaborate) Unique Format and output Benefit to the entire community

Next steps
How Health Data Integrity Can Earn Trust and Advance Health

Efforts to share health data across borders snag on legal and regulatory barriers. Before detangling the fine print, let’s agree on overarching principles.
Summary
What do you need to realize innovation?

- Great Team (int. & ext.)
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Start of presentation
Diagnostic Quality Model (DQM):
An Integrated Framework for the Assessment of Diagnostic Quality when Using AI/ML
What holds us back is a multidimensional problem
Diagnostic Quality Model (DQM)
Conceptual distinction
Diagnostic Quality Model (DQM)
Relationship of DQM components and AI

Quality Impact of the AI Model = \text{abs.} \left[ \text{Diagnostic Quality Without AI Model} - \text{Diagnostic Quality With AI Model} \right]

Quality of the Diagnostic Test + Quality of the Diagnostic Procedure + Quality of the Diagnostic Service
Figure 3

Integrated Diagnostic Service

Diagnostic Procedure (Modality 1)

Request
Patient Physician

Scheduling
CT-scan review

Diagnostic Test

Pre-analytics Analytics Post-analytics

Diagnosis Interpretation

Diagnostic Procedure (Modality 2)

Test start Accessioning Extract

PCR Analysis

Diagnosis Interpretation

Intake

Patient access

1. Assume the patient will be diagnosed with NSCLC, stage IV

Diagnostic Model $D_0$

Deployed model using fixed training and validation data (initial performance)

Data store Model

"initial model"

e.g., AUC: 0.82

Prior authorization workflow e.g., for precision oncology

Prior authorization workflows exist for each component (radiology, diagnostic test, molecular test, targeted therapy etc.)

Assumption is that real-world data can be used to further improve model performance (after vetting)

Diagnostic Model $D_1$

Deployed model using new, local real-world data (evolving performance)

Data store Model

"evolved model"

e.g., AUC: 0.83

Recurrent model optimization (e.g., ‘monthly’)

Clinical genetic test results are used as new input data to evolve the model assuming acceptance criteria are met (e.g., AUC > 10)

Prior authorization for diagnostic test coupled to specialty pharmacy workflow

Note: treatment decisions rely on the integration of a variety of factors

The quality of the workflow with or without the AI model can be assessed in many ways (e.g., time to intake of first dose)

Depicted workflow: Specialty Pharmacy

Policy review Prior authorization Test claim Signed order

Approval and cost-coverage

Electronic Medical Record

Therapeutic decision Prescription, outcome

Genetic data store

PCR

Analysis

Diagnosis Interpretation

Intake

Patient access

Abbreviated workflow e.g., biopsy not shown