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

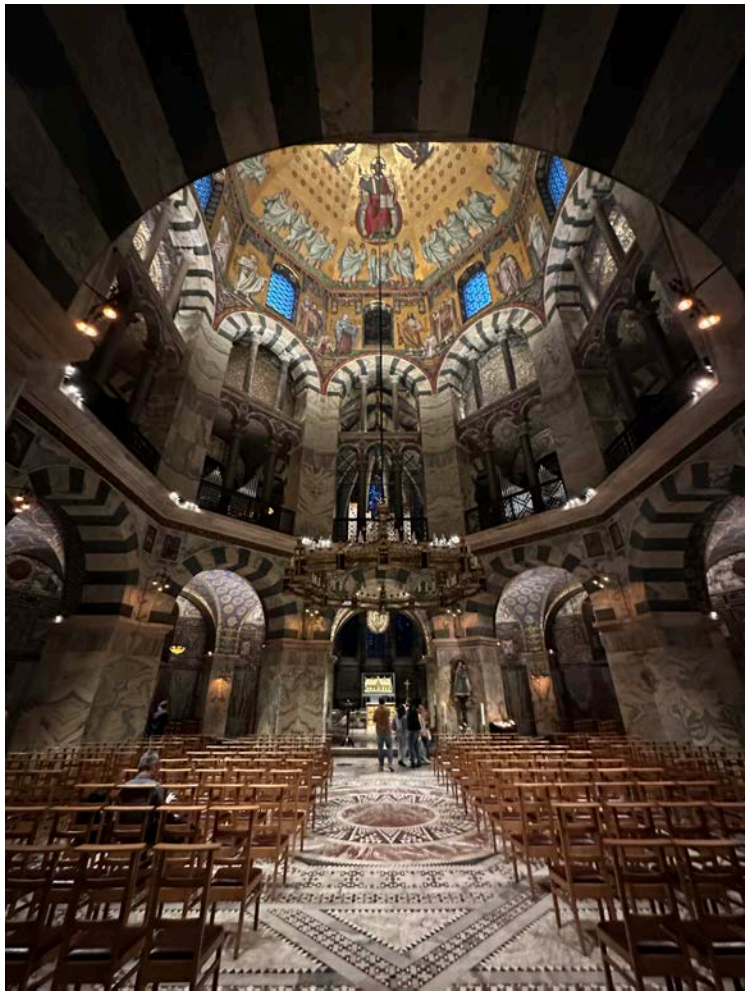
March 21st, 2024 – Aachen Germany

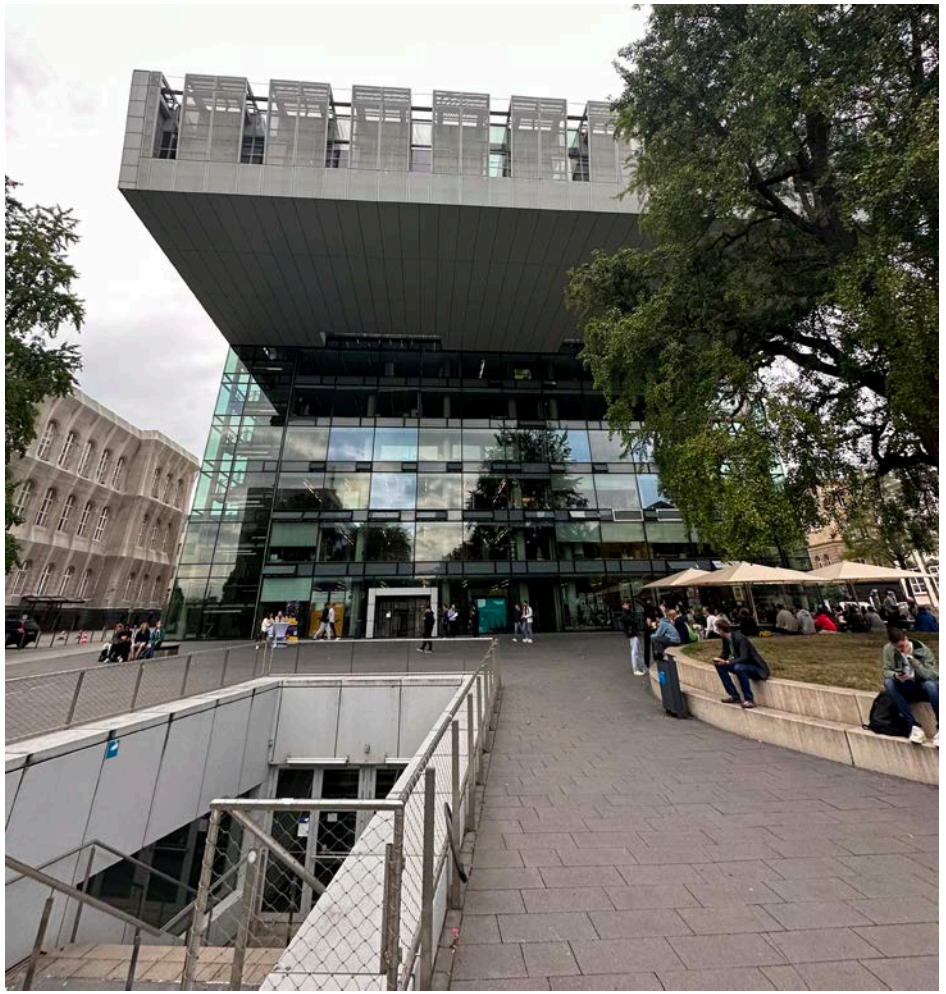
Joe Lennerz MD PhD

Chief Scientific Officer, BostonGene

15th TMF-Conference
21. – 22. March, Aachen, Germany
2024

Medical Innovation • First in Patient • First in Human



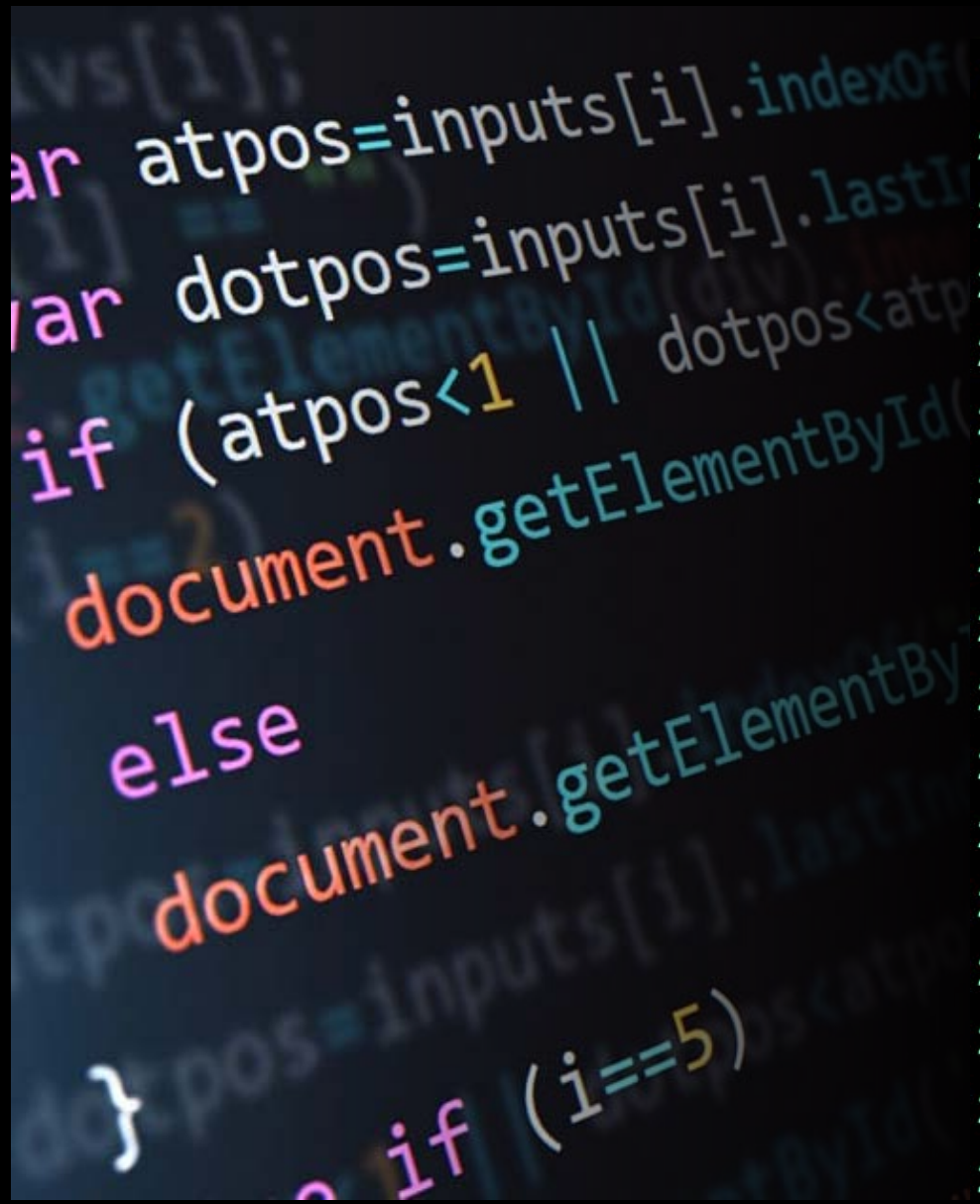


The New York Times by Kevin Roose. Jan. 12, 2023

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.

Nata Metlukh



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

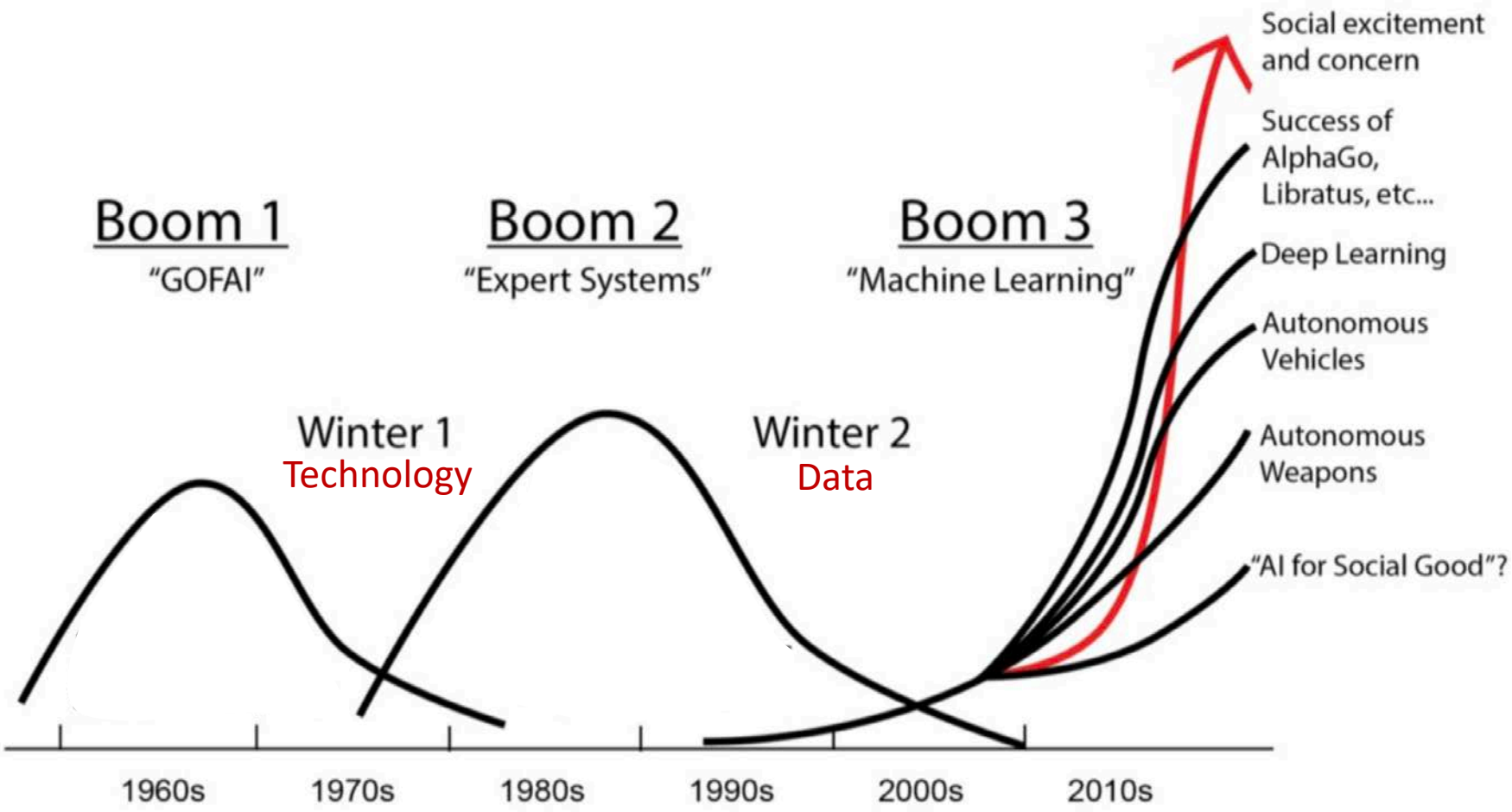
2020: Curial GPT-3 LLM

2021: Dall-E

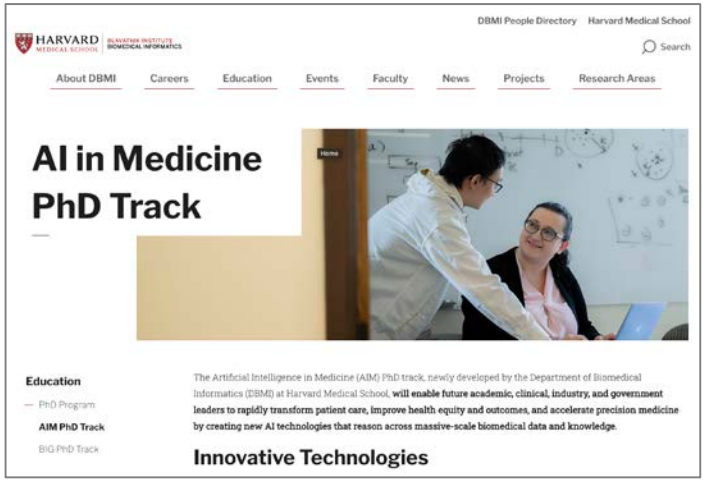
2022: ChatGPT

2023: GPT-4

AI Timeline – “Four Seasons”



Concerns about AI implications & Regulatory trends



Technology Breakdown August 2012

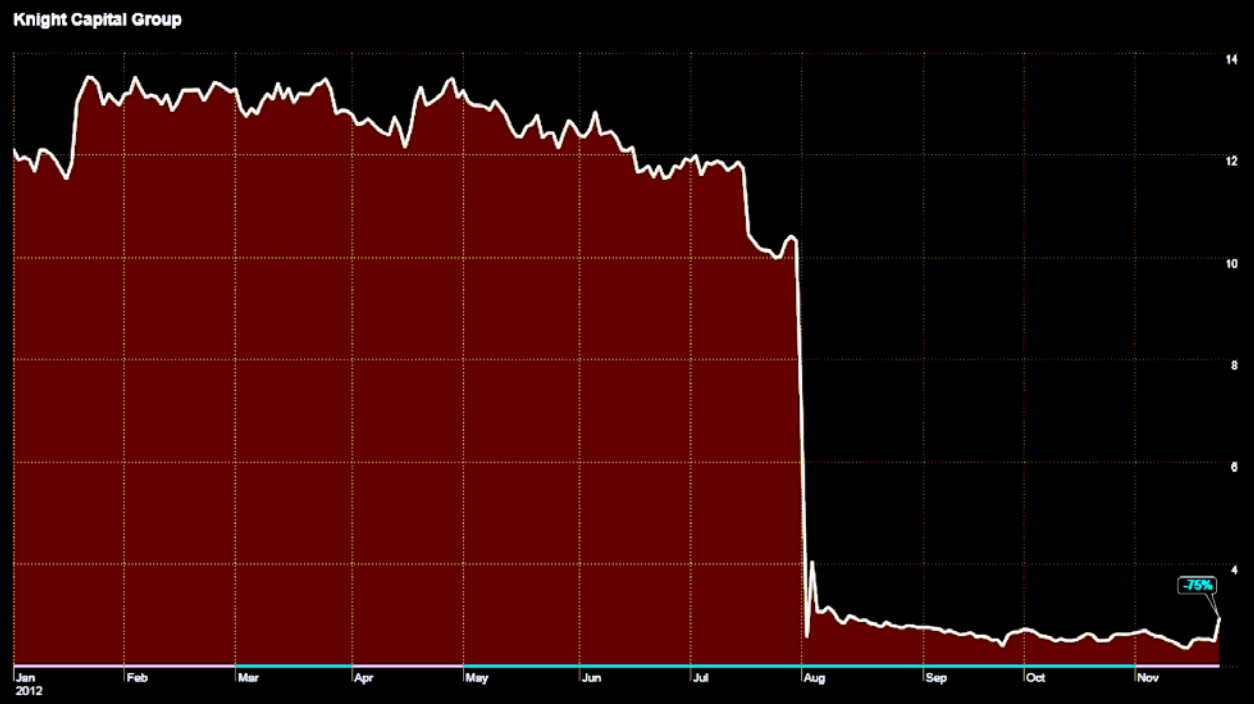


Figure 1: Knight Capital's shares are down more than 75% following its $440 million trading glitch.

Saltapidas & Maghsood

The Daunting Path to Patients

The Daunting Path to Patients

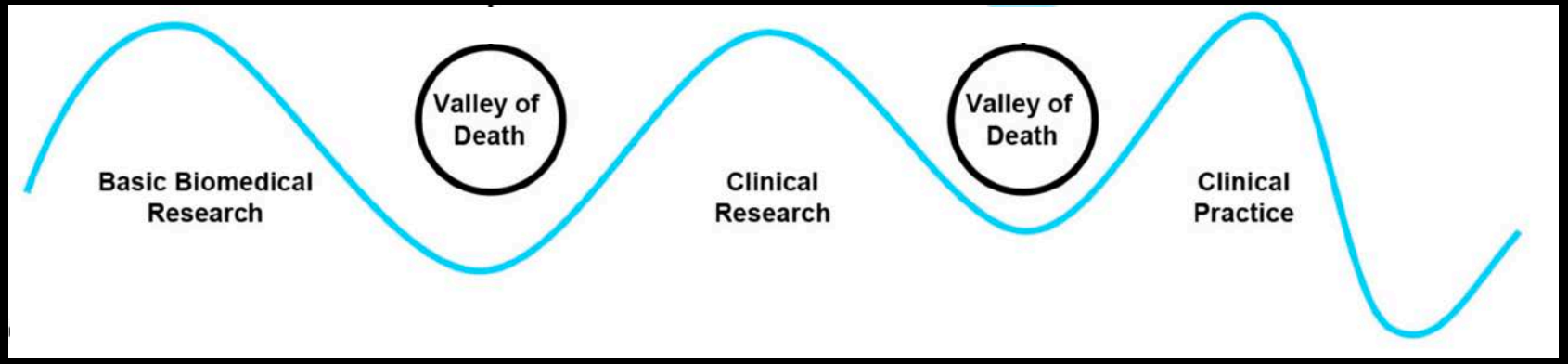
Technology Discovery

Analytical Validation

Clinical Validation

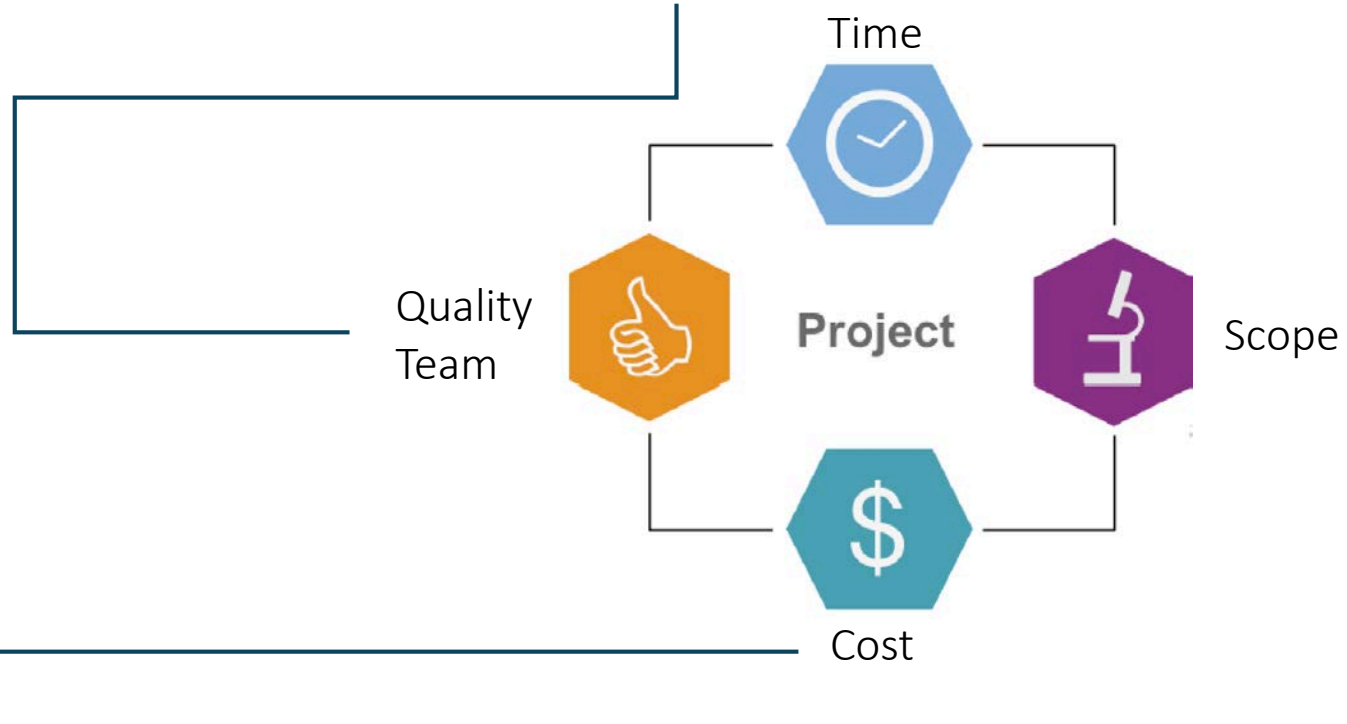
Clinical Integration

Clinical Utility



Draft of Joe's talk Feb 16th 2024

Identify key elements for integration into clinical practice



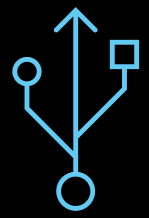
- How much? => Why? => strategy => **alignment** of initiative & funding source
- What ? => and in what order ? => what's first => operations
- Who => cross-functionality => interdisciplinary teams

What do you need to realize innovation?

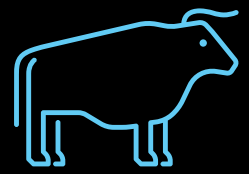
Great Team
(int. & ext.)

Understand
the framework

Healthcare
system



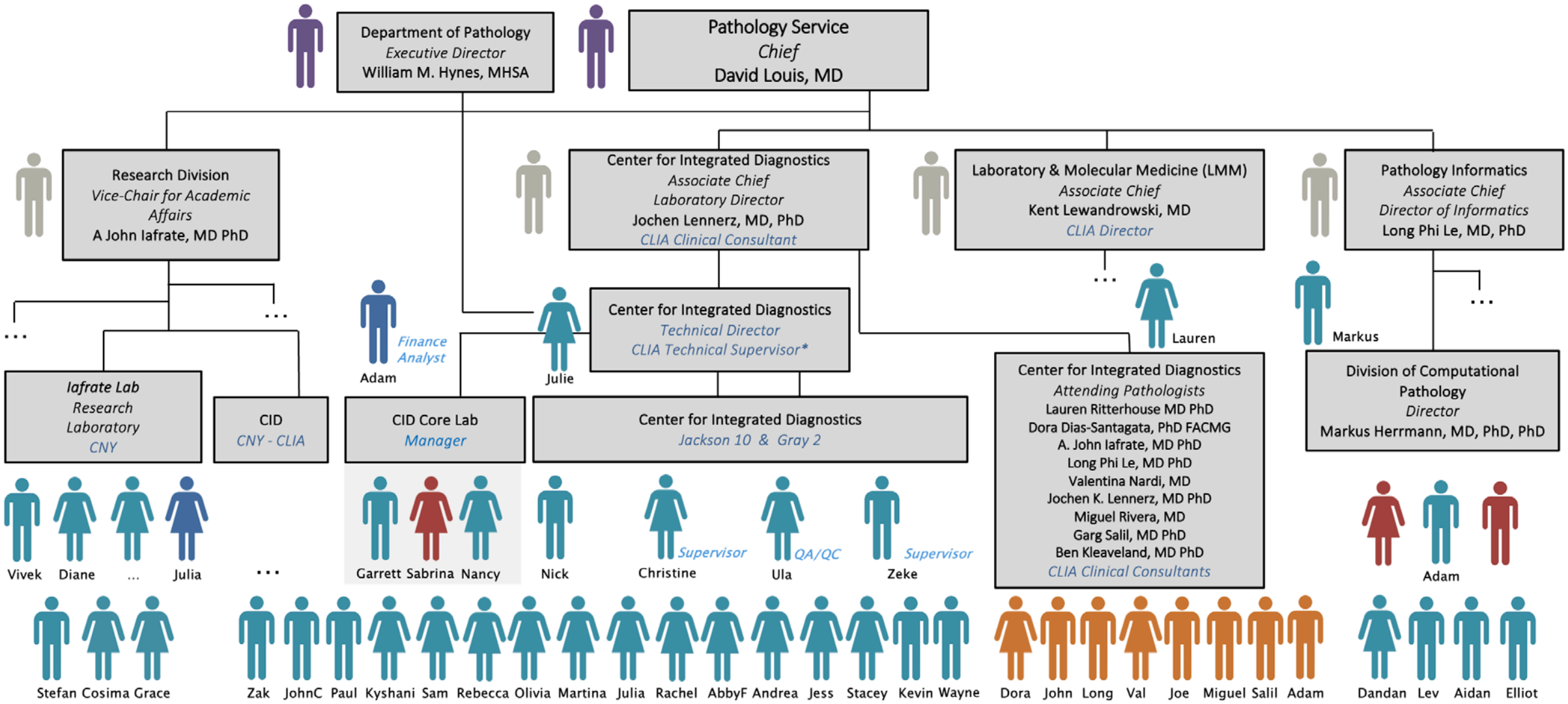
How to integrate
(Concept +Process)

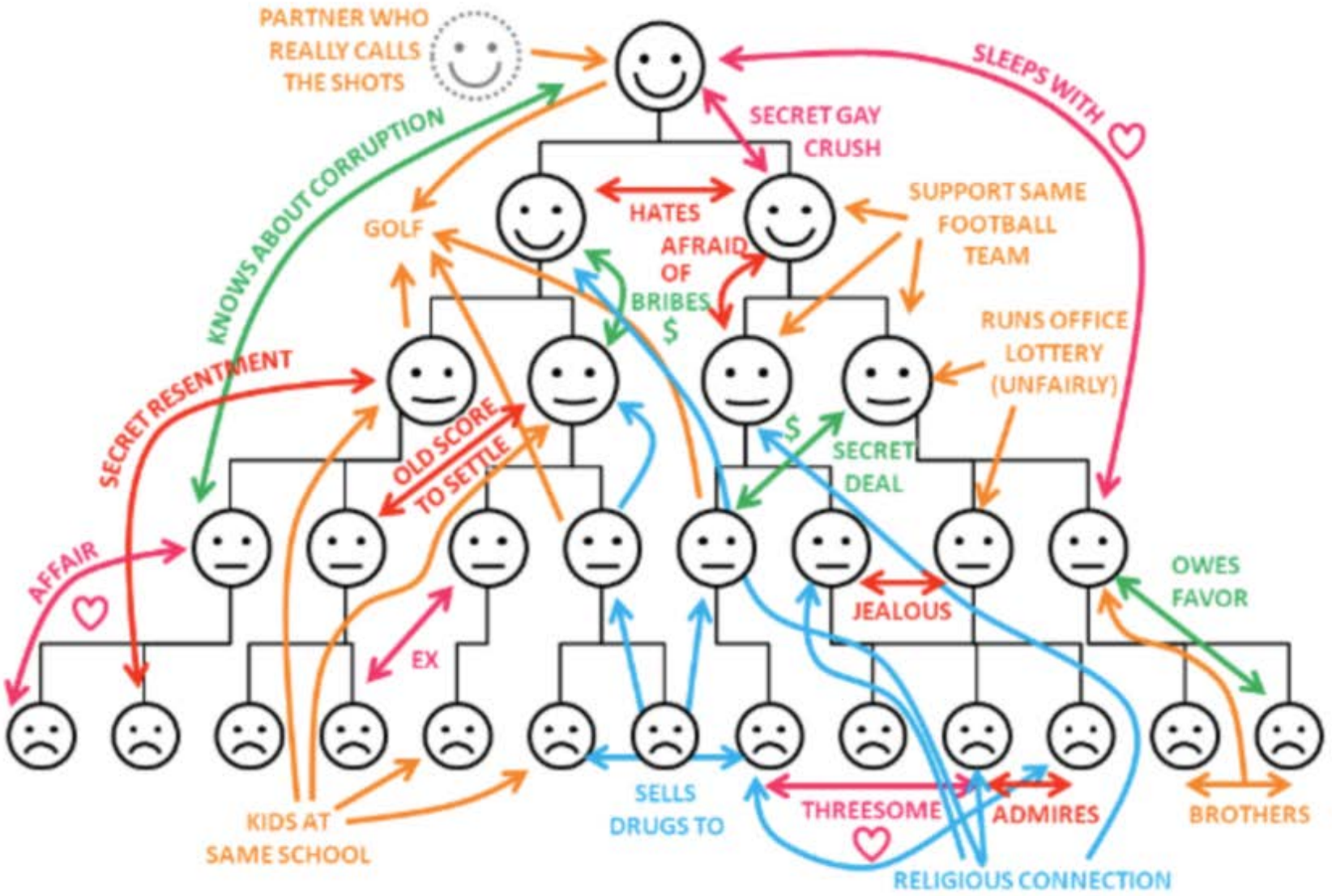


Approaches to
Financial Sustainability

Approach to apply
and challenge regulation

CID Organization




PARTNER WHO REALLY CALLS THE SHOTS
SLEEPS WITH
SECRET GAY CRUSH
KNOWS ABOUT CORRUPTION
HATES
SUPPORT SAME FOOTBALL TEAM
GOLF
AFRAID OF BRIBES $
RUNS OFFICE LOTTERY (UNFAIRLY)
SECRET RESENTMENT
OLD SCORE TO SETTLE
$
SECRET DEAL
AFFAIR
JEALOUS
OWES FAVOR
EX
KIDS AT SAME SCHOOL
SELLS DRUGS TO
THREESOME
ADMIRES
BROTHERS
RELIGIOUS CONNECTION

Foreword by Peter Block

Bestselling Author of *Community* and *Stewardship*

Collaborating *with the* Enemy

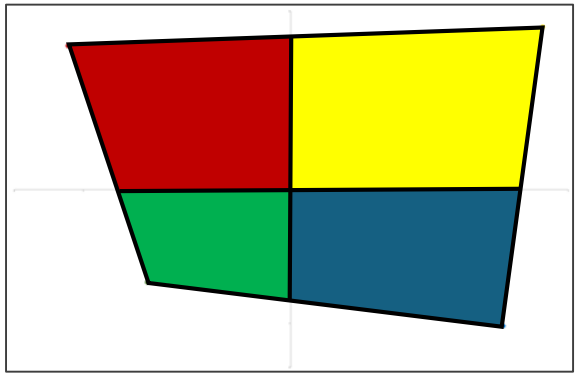
How to Work with People You Don't Agree with or Like or Trust

Adam Kahane

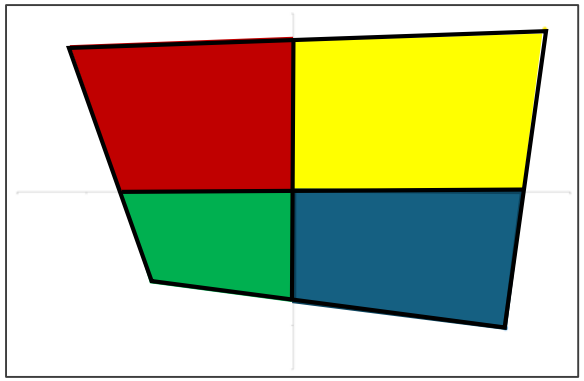
Bestselling author of *Solving Tough Problems* and *Power and Love*

Group combined

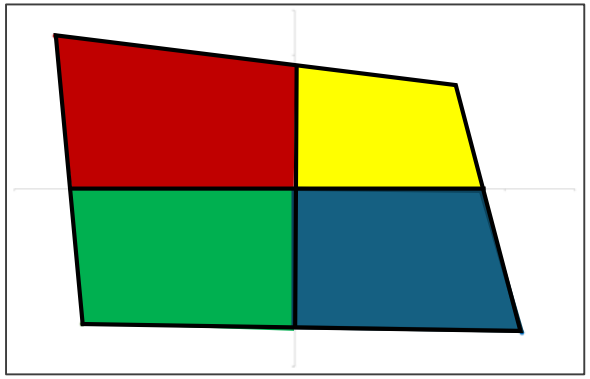
Rationale



Socialized



Instinctive



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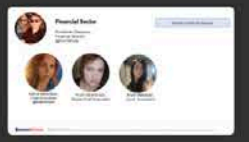
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Agile Manifesto

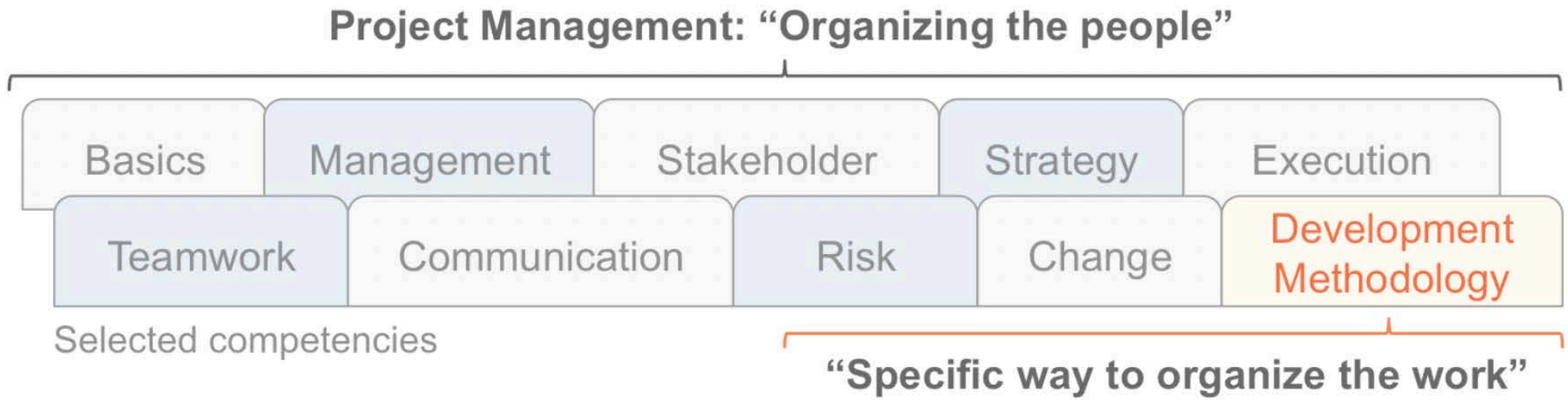
"We are uncovering better ways of developing
software by doing it and helping others do it.
Through this work we have come to value:

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."

Process

Supplemental Figure 2. Difference between project management and development methodology.



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).

Lennerz et al., 2016 JMD

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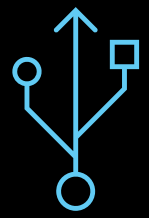

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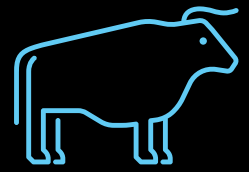
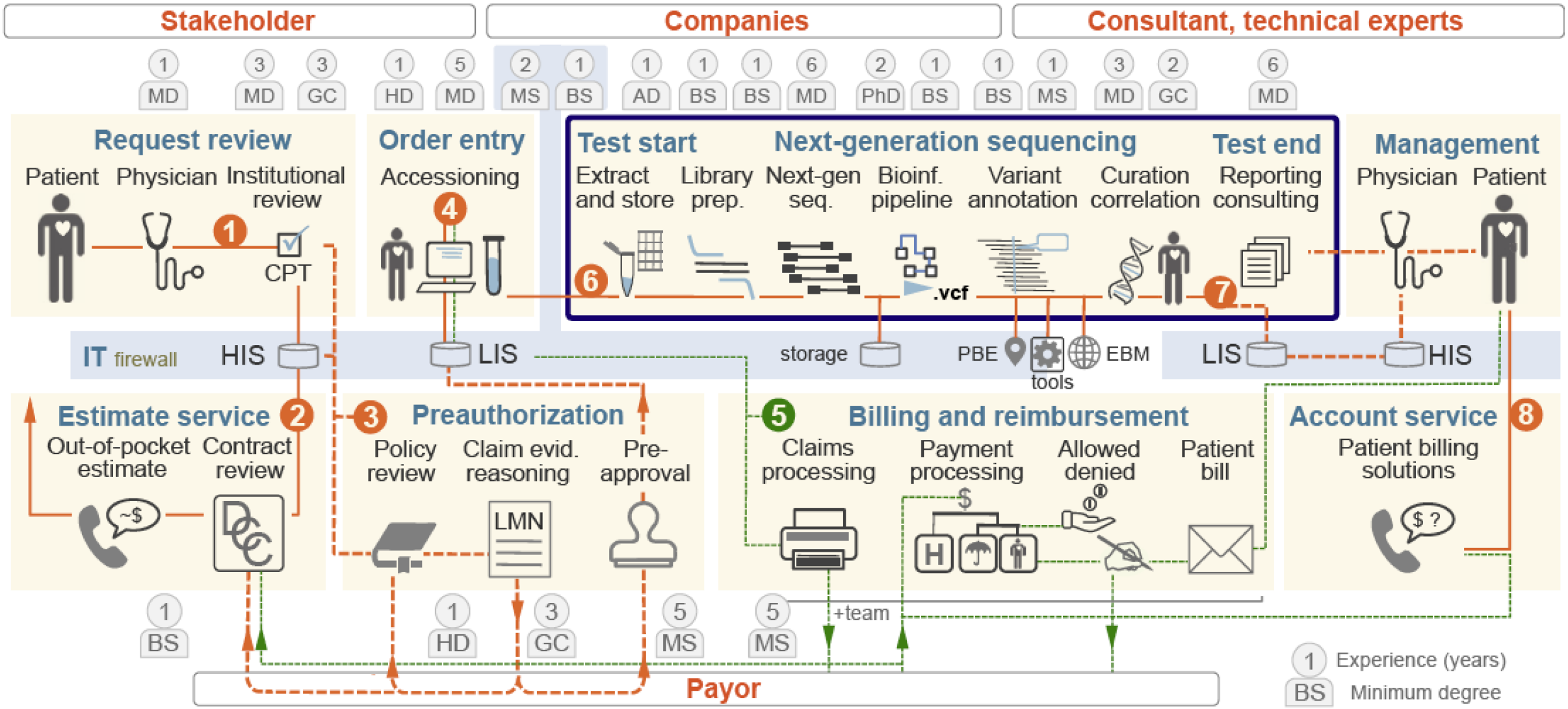
(Concept +Process)



Approaches to
Financial Sustainability

Approach to apply
and challenge regulation

Synthetize the healthcare infrastructure for financially-sustainable genomics



Lennerz et al., 2016 JMD

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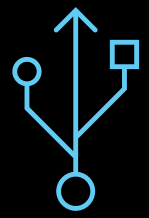

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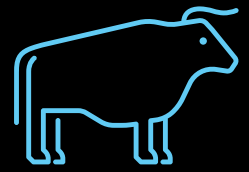

Approaches to
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Approach to apply
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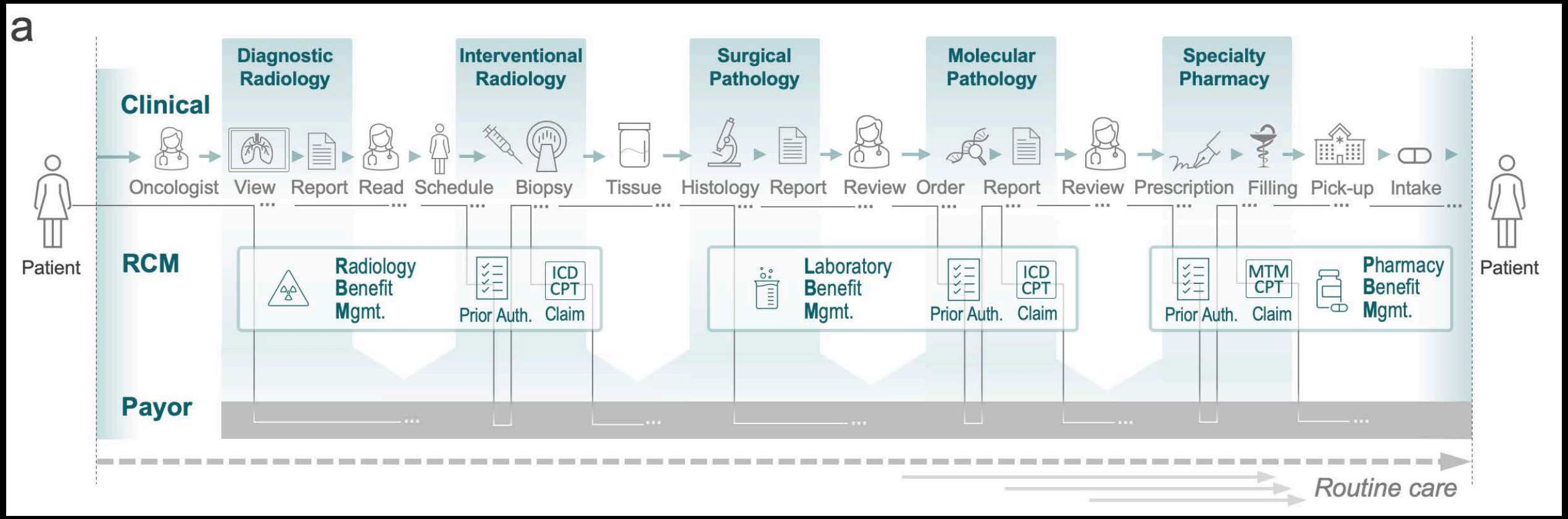
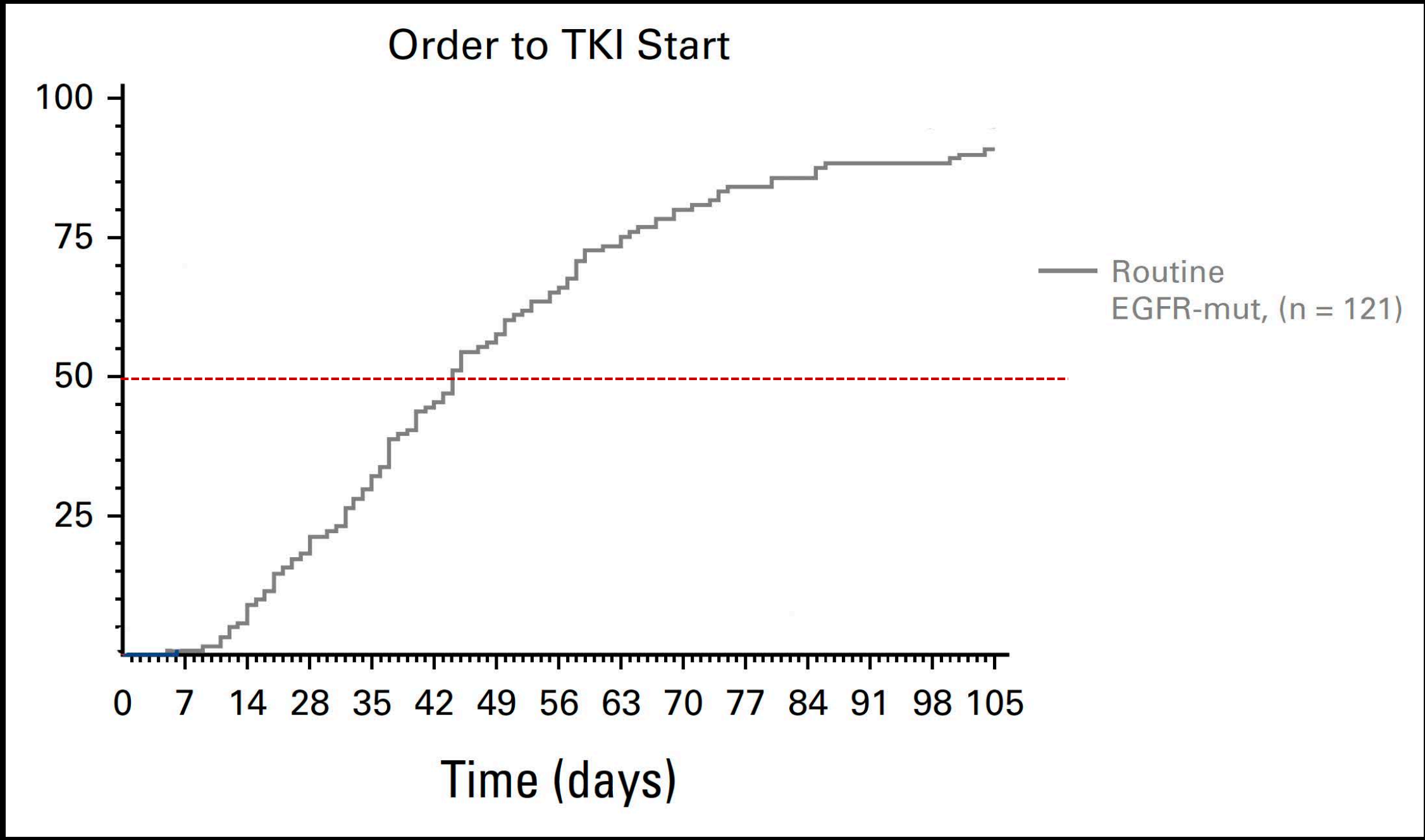
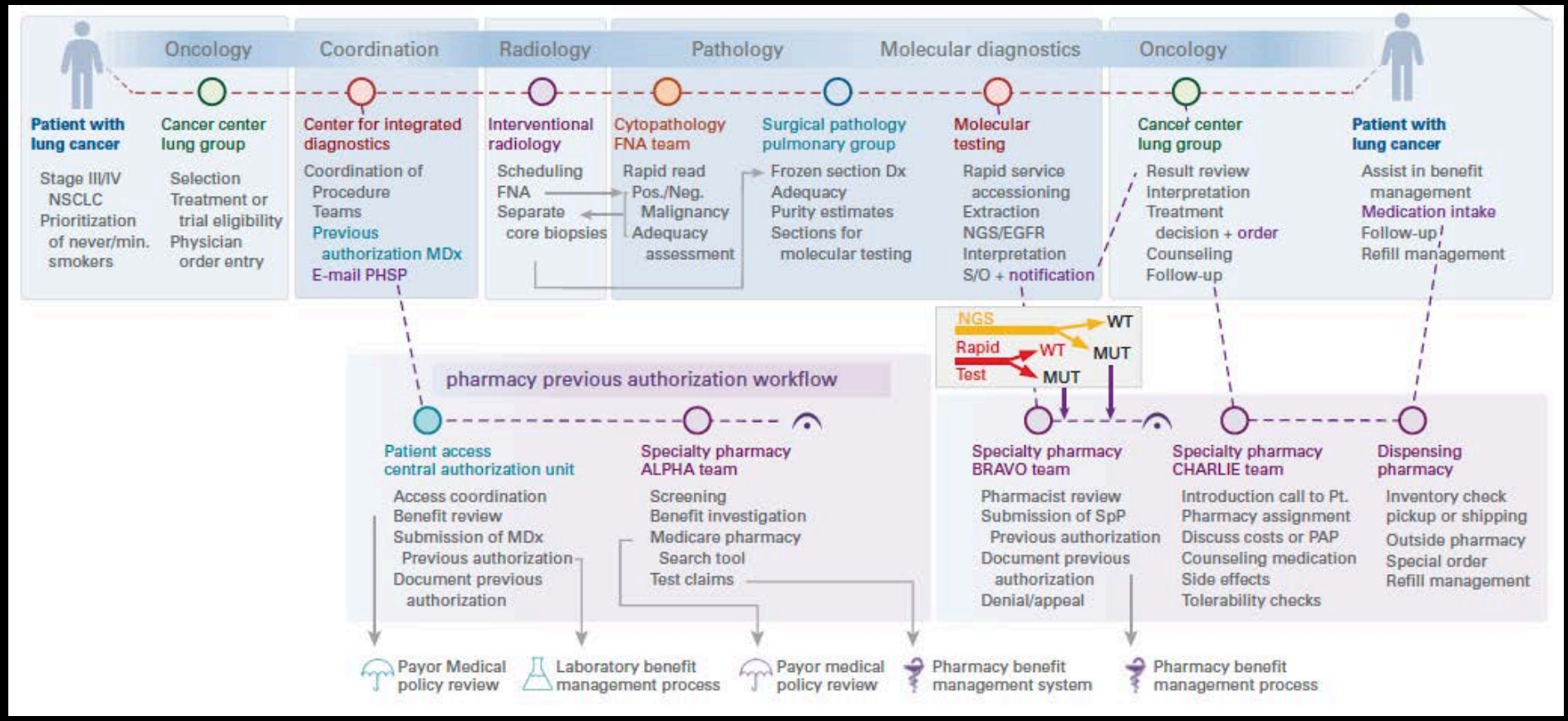
Patient ~~journey~~ vs. care pathway




Order to TKI Start
100
75
50
25
0
7
14
28
35
42
49
56
63
70
77
84
91
98
105
Time (days)
Routine
EGFR-mut, (n = 121)

Integrated care pathway

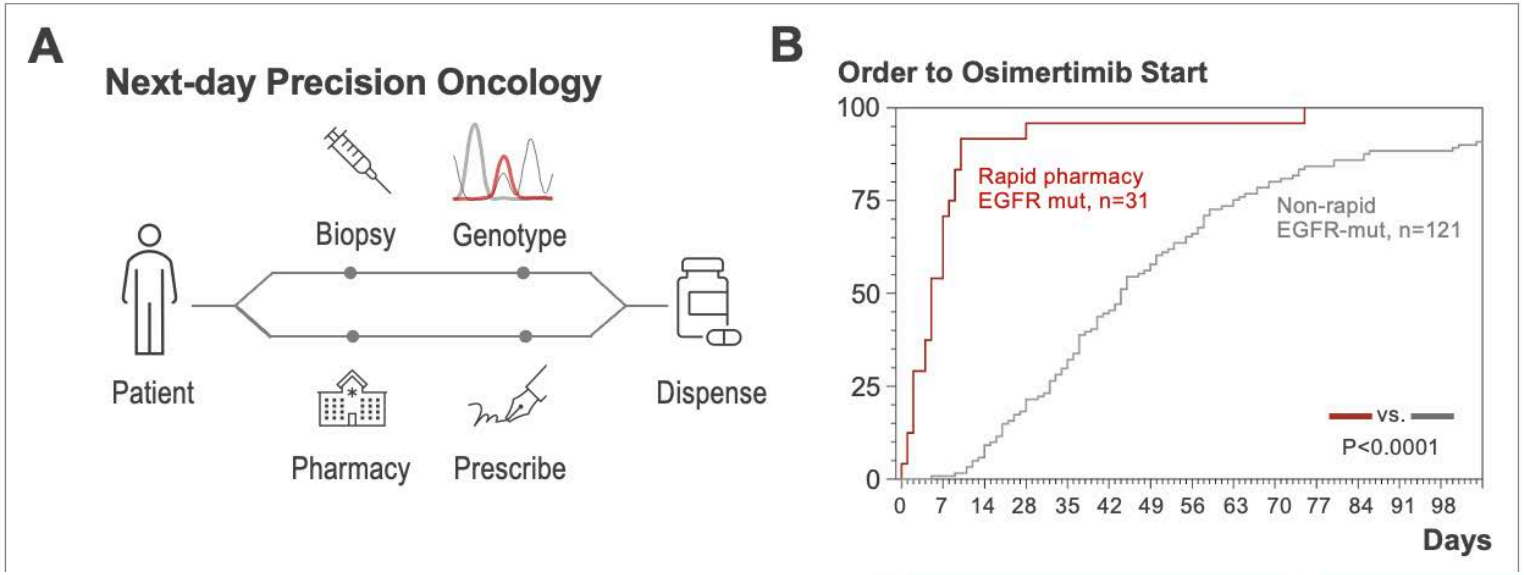


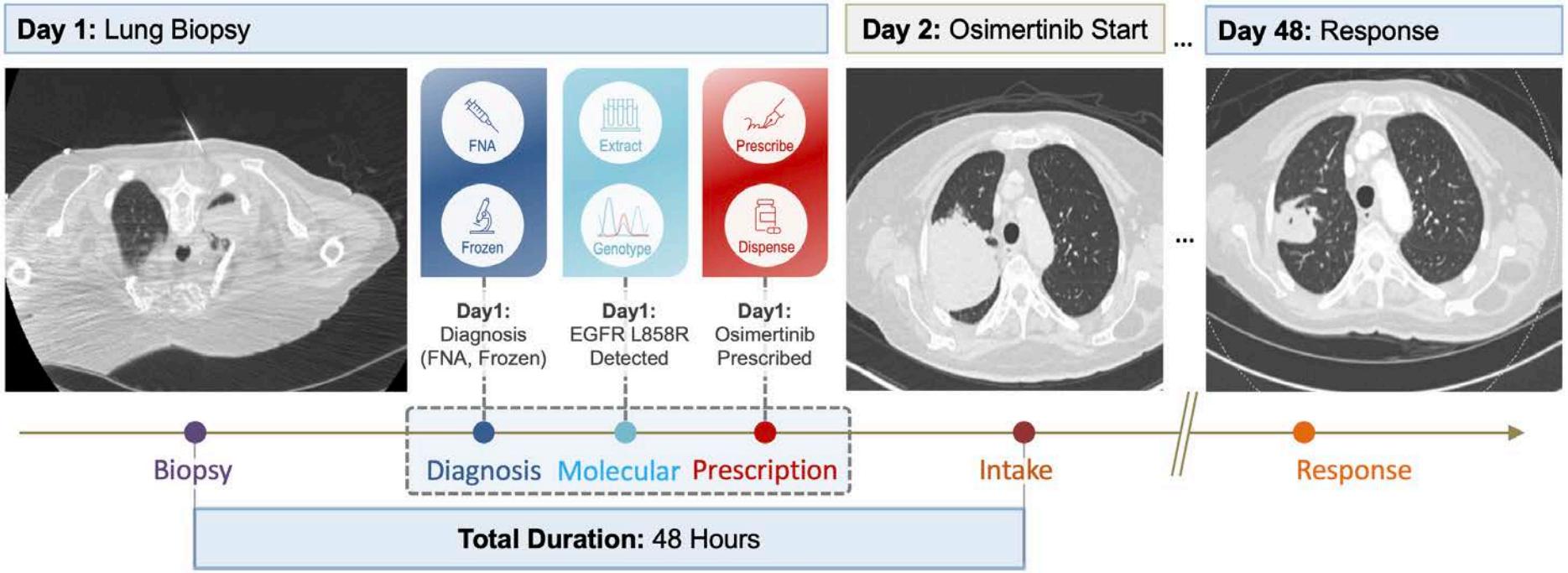
Rapid testing

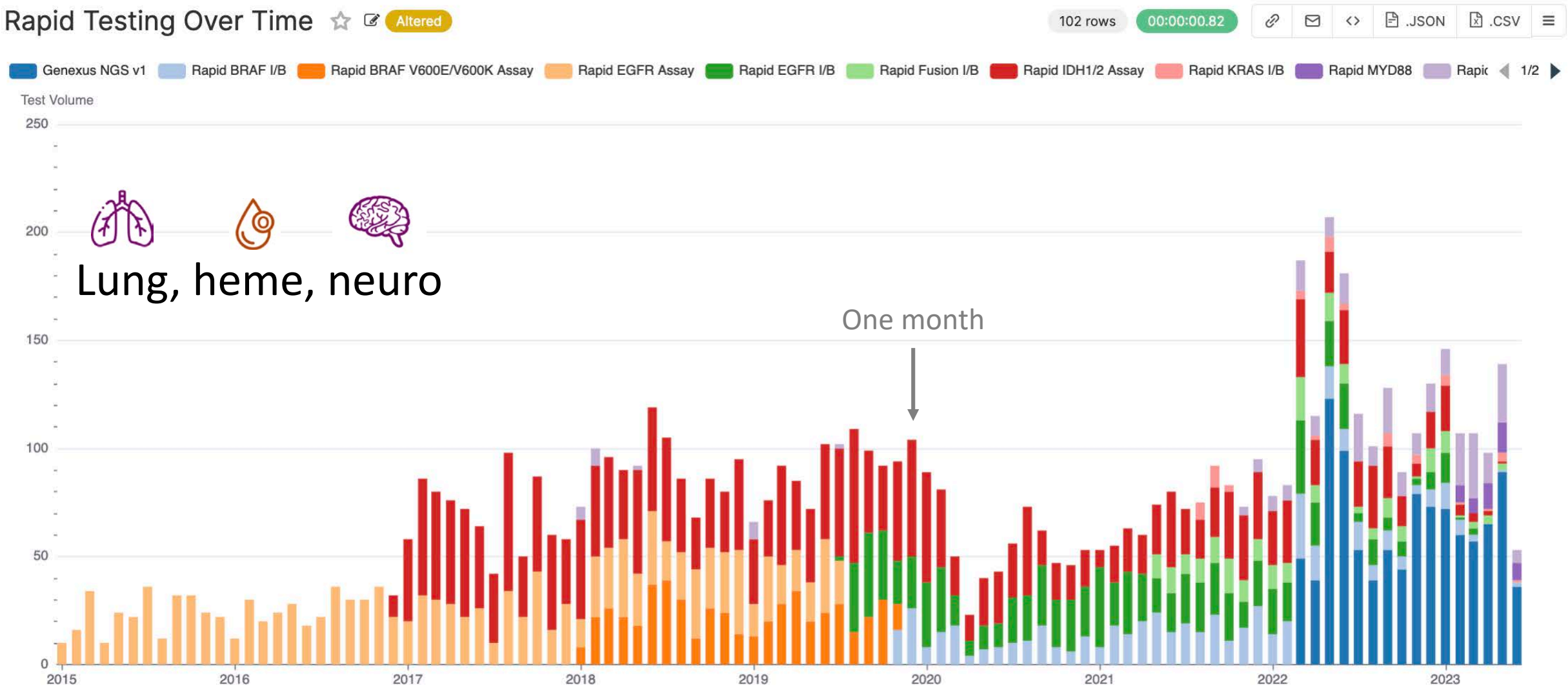
Time from Diagnosis to molecularly-informed treatment start

Routine: 48 days

Integrated: 4 days

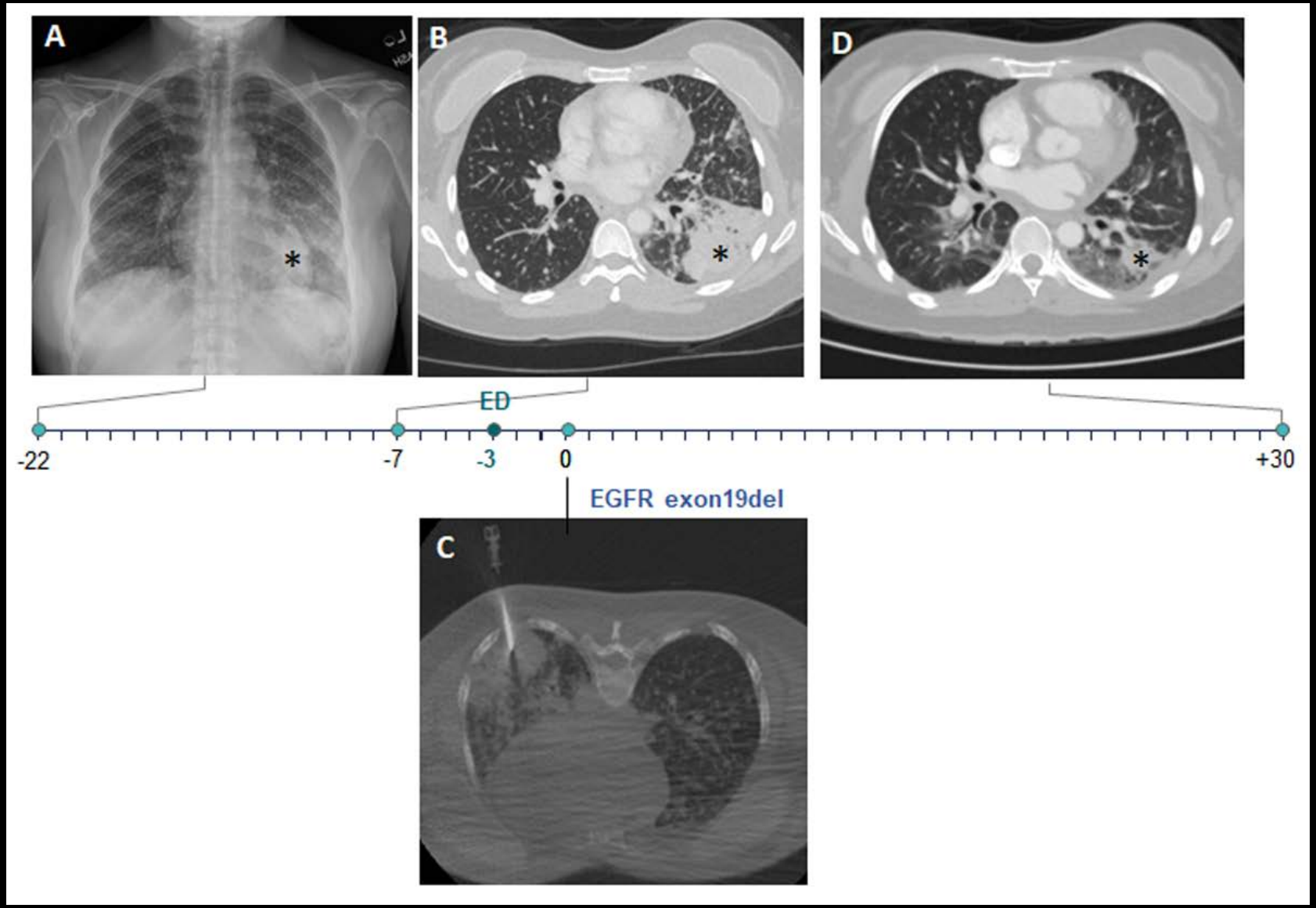





Rapid Testing Over Time
Altered
102 rows
00:00:00.82
.JSON
.CSV
Genexus NGS v1
Rapid BRAF I/B
Rapid BRAF V600E/V600K Assay
Rapid EGFR Assay
Rapid EGFR I/B
Rapid Fusion I/B
Rapid IDH1/2 Assay
Rapid KRAS I/B
Rapid MYD88
Rapic
1/2
Test Volume
250
200
150
100
50
0
Lung, heme, neuro
One month
2015
2016
2017
2018
2019
2020
2021
2022
2023

What’s next

Pre-presentation time….



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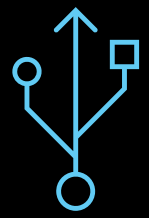
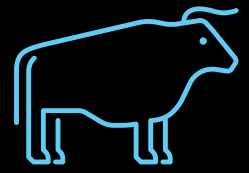


How to integrate
(Concept RWE Precomp)

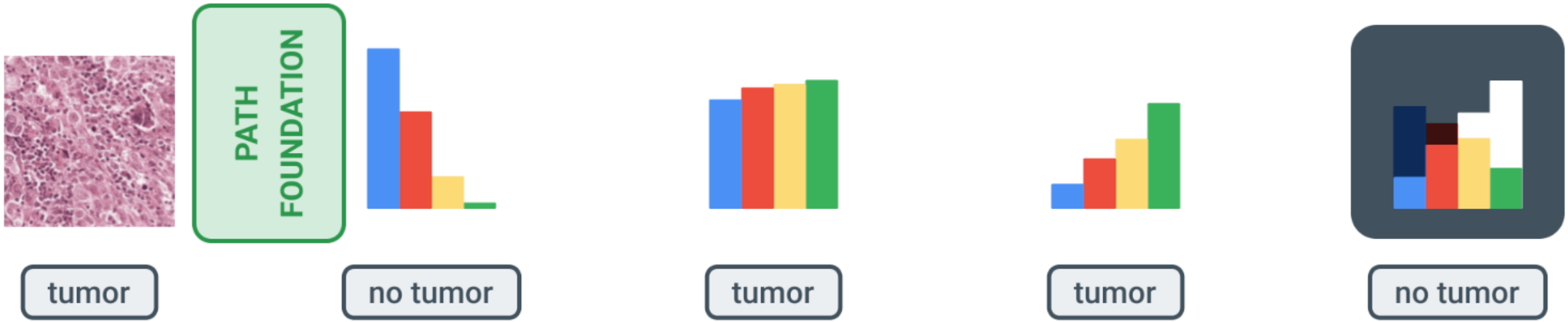


Approaches to
Financial Sustainability

Approach to apply
and challenge regulation

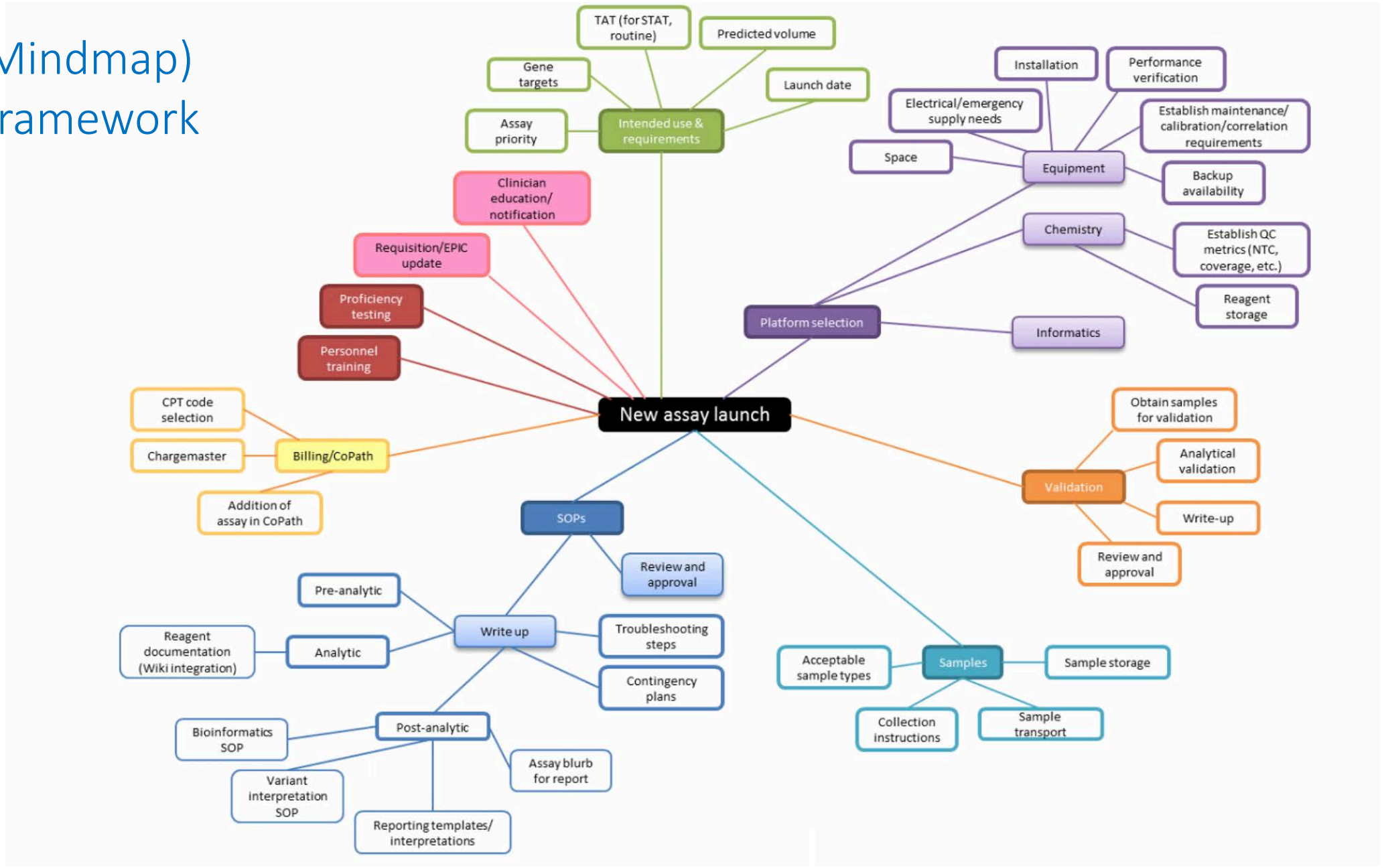
https://blog.research.google/2024/03/health-specific-embedding-tools-for.html?m=1

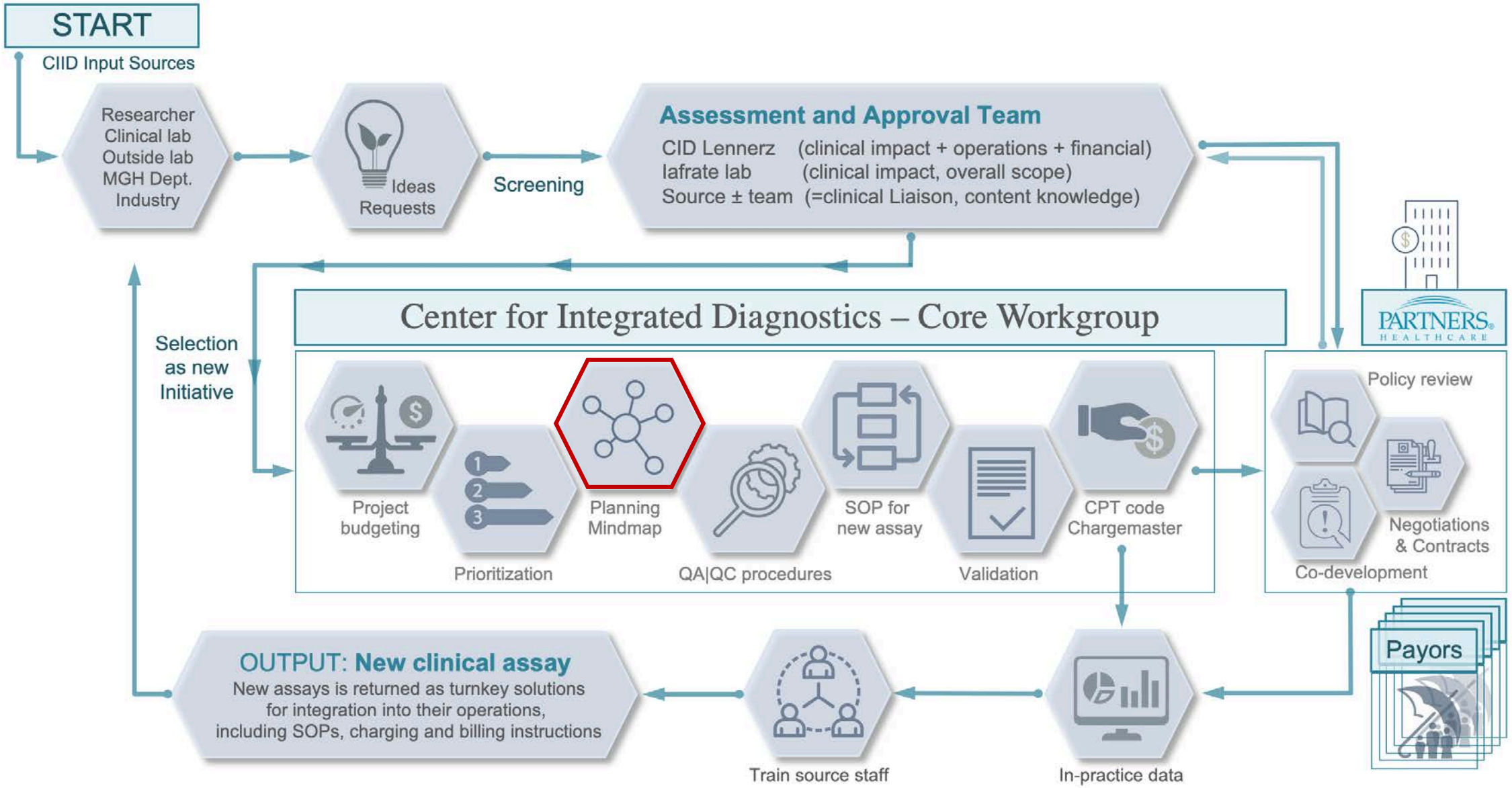
EVALUATE LINEAR PROBE



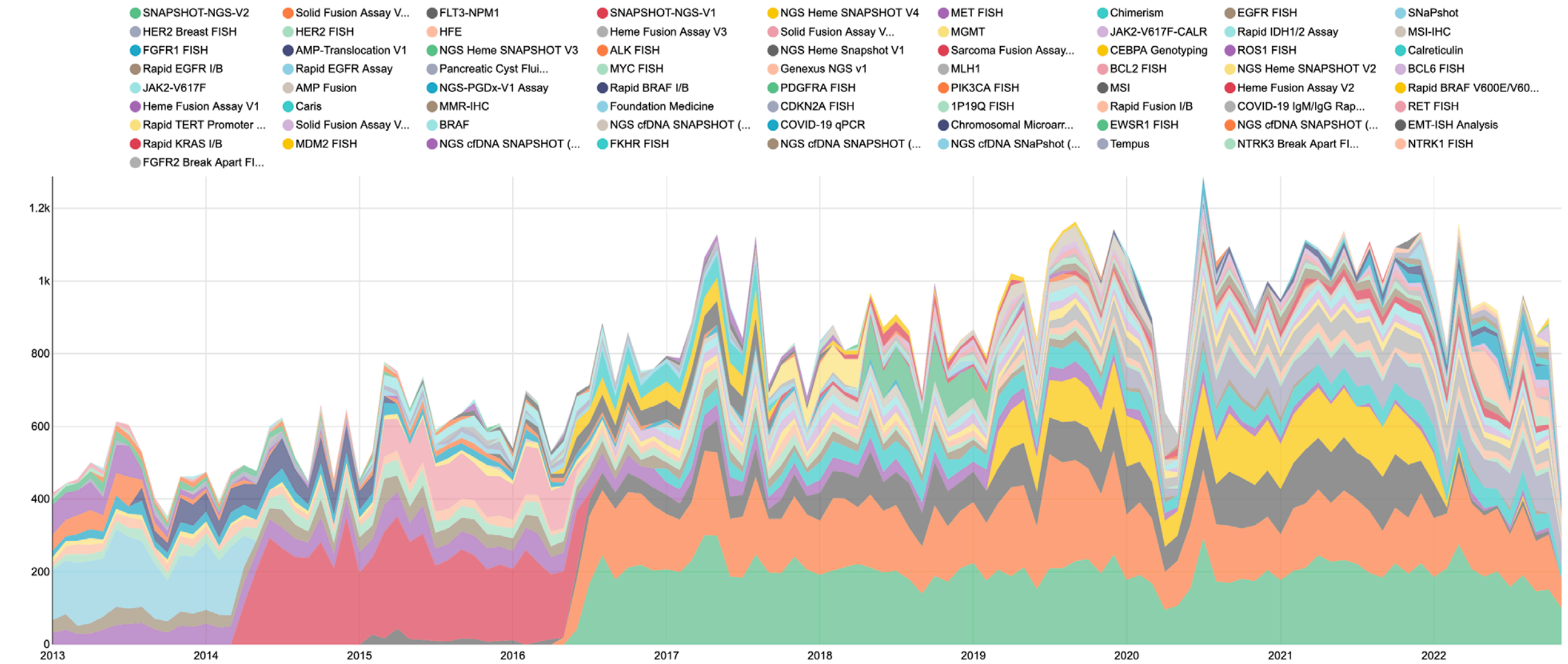
https://blog.research.google/2024/03/health-specific-embedding-tools-for.html?m=1

Spidermap (Mindmap)
Designated framework

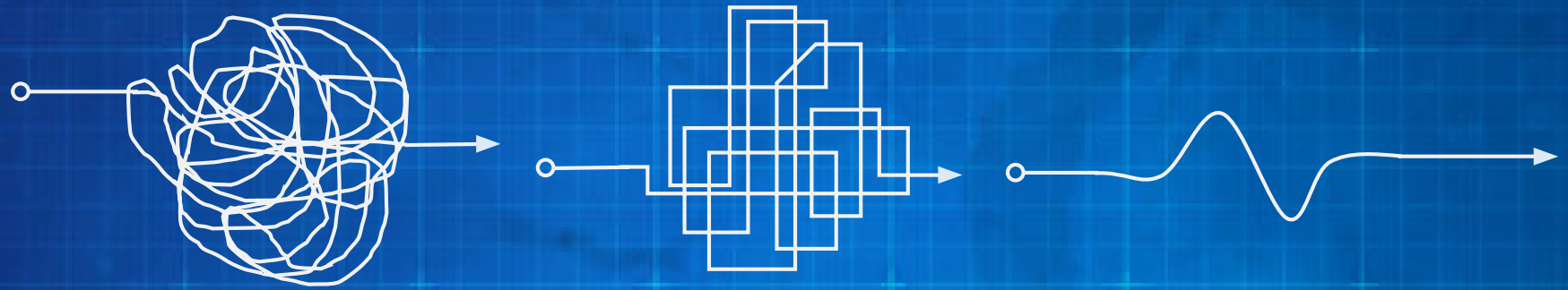



START
CIID Input Sources
Researcher
Clinical lab
Outside lab
MGH Dept.
Industry
Ideas
Requests
Screening
Assessment and Approval Team
CID Lennerz (clinical impact + operations + financial)
Iafrate lab (clinical impact, overall scope)
Source ± team (=clinical Liaison, content knowledge)
Selection as new Initiative
Center for Integrated Diagnostics – Core Workgroup
Project budgeting
Prioritization
Planning Mindmap
QA|QC procedures
SOP for new assay
Validation
CPT code Chargemaster
PARTNERS HEALTHCARE
Policy review
Negotiations & Contracts
Co-development
Payors
In-practice data
Train source staff
OUTPUT: New clinical assay
New assays is returned as turnkey solutions for integration into their operations, including SOPs, charging and billing instructions

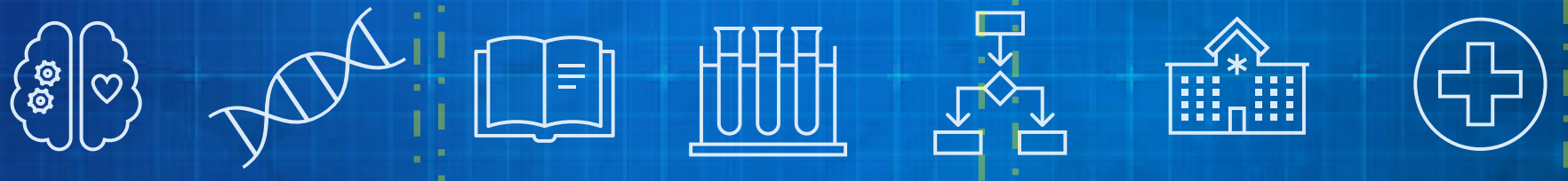
Earth Section



Quality Management



Research | Translation | Clinical Practice



Idea | Analyte | Publish | IVD | Trial | Utilization | Outcome

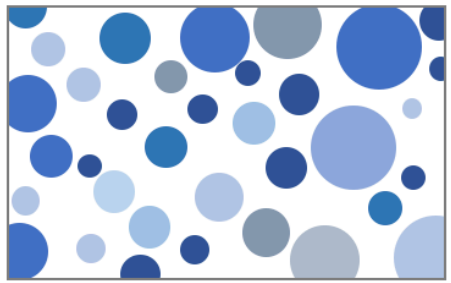
Technology Discovery

Analytical Validation

Clinical Validation

Clinical Integration

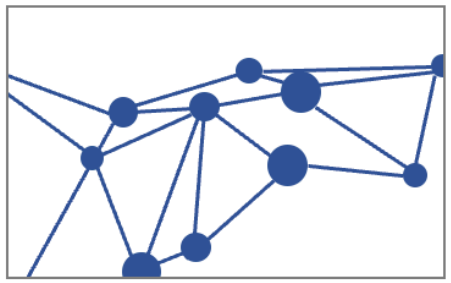
Clinical Utility



Real-world data (RWD)

Data Processing

Anonymization	Auditability
Data Standards	Data cleansing
Analytical plan	Study Design
Patient engagement	Regulatory compliance

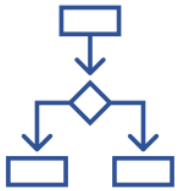


Real-world evidence (RWE)

Selected Principles

Patient-level (instead of literature /summary) data

Availability of exposure, outcome, covariates



Identical inclusion and exclusion criteria

Appropriate use of statistical methods

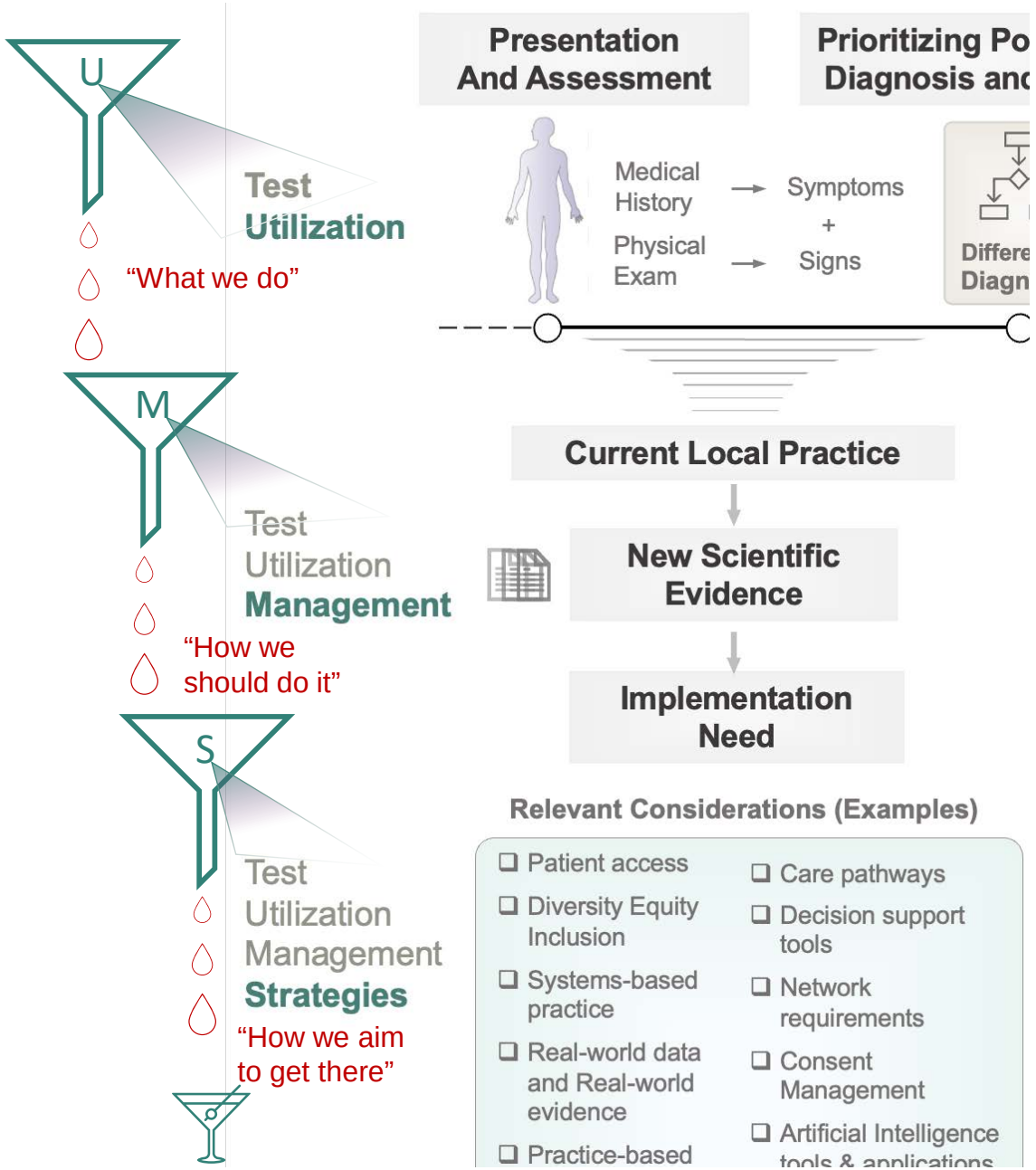
Innovation = Integration

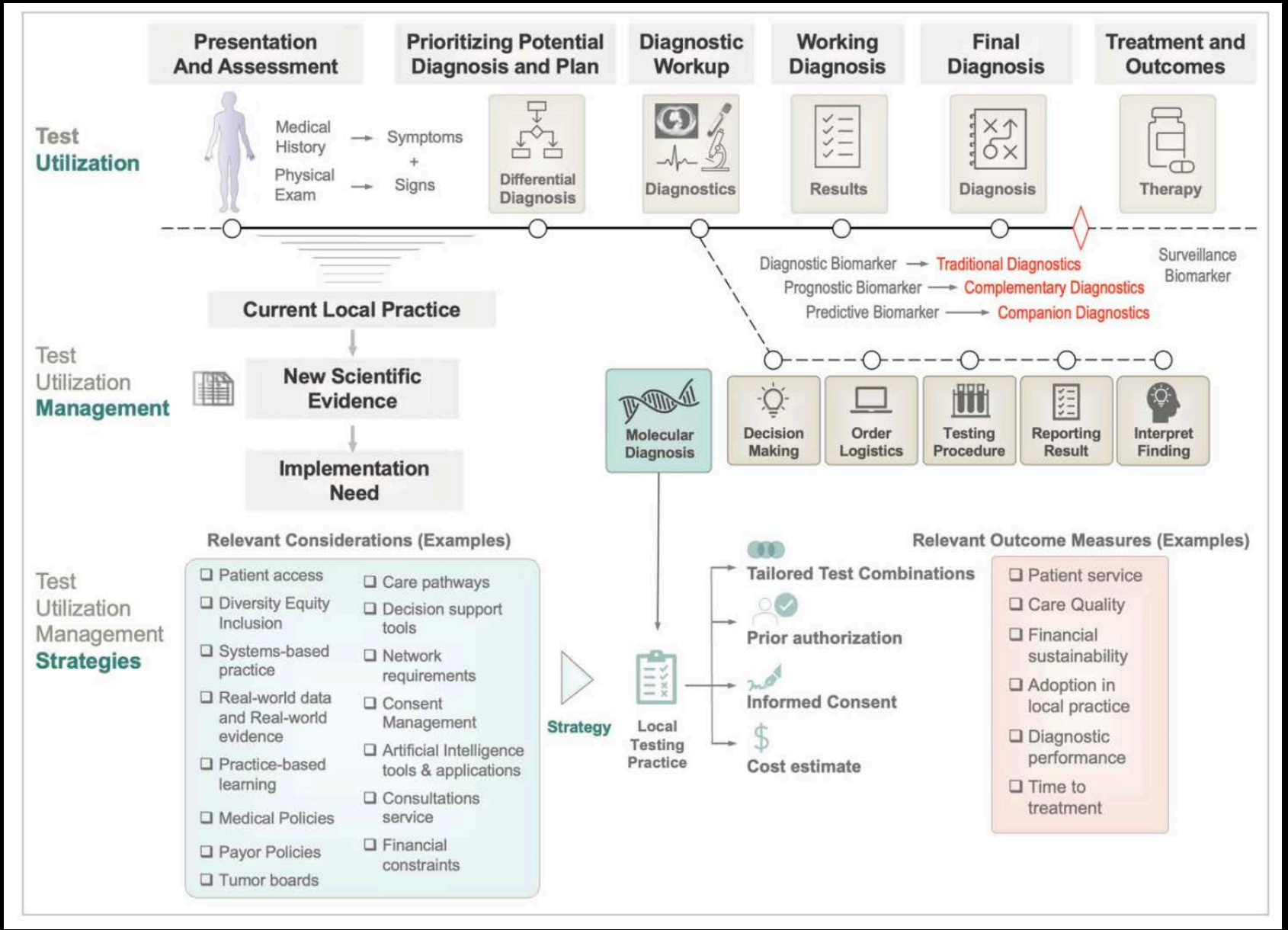
- Utilization
- Utilization Management
- Utilization Management Strategy

How to implement?

- **Concept: U, UM, UMS**

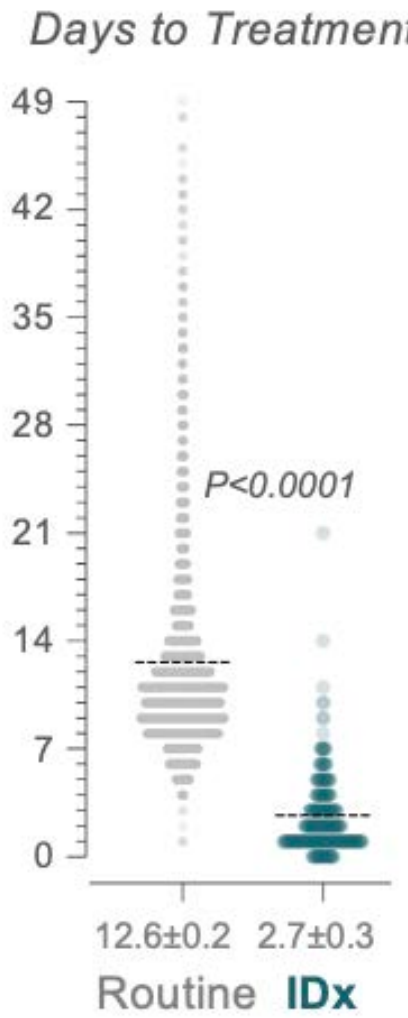
Helen Hou et al., 2023 J Appl Lab Med





Relevant Considerations → Relevant Outcome Measures

RWD to RWE to transformation



Real-world evidence
- Evidence of clinical utility

Real-world data
- Data quality and sources

Quality improvement
- Care specific initiative

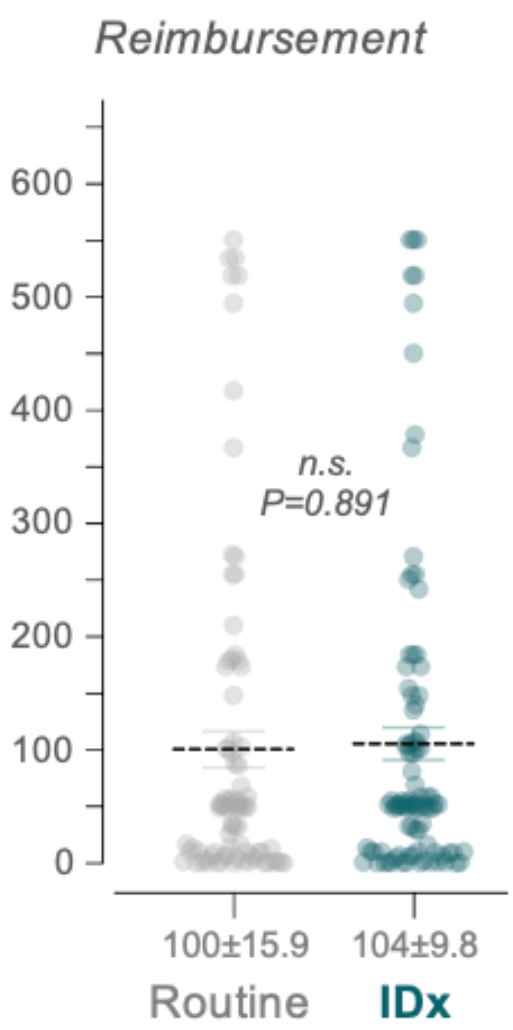
Payor Matrix
- Health system specific
- Organizational knowledge
- Policy database
- Contact information

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



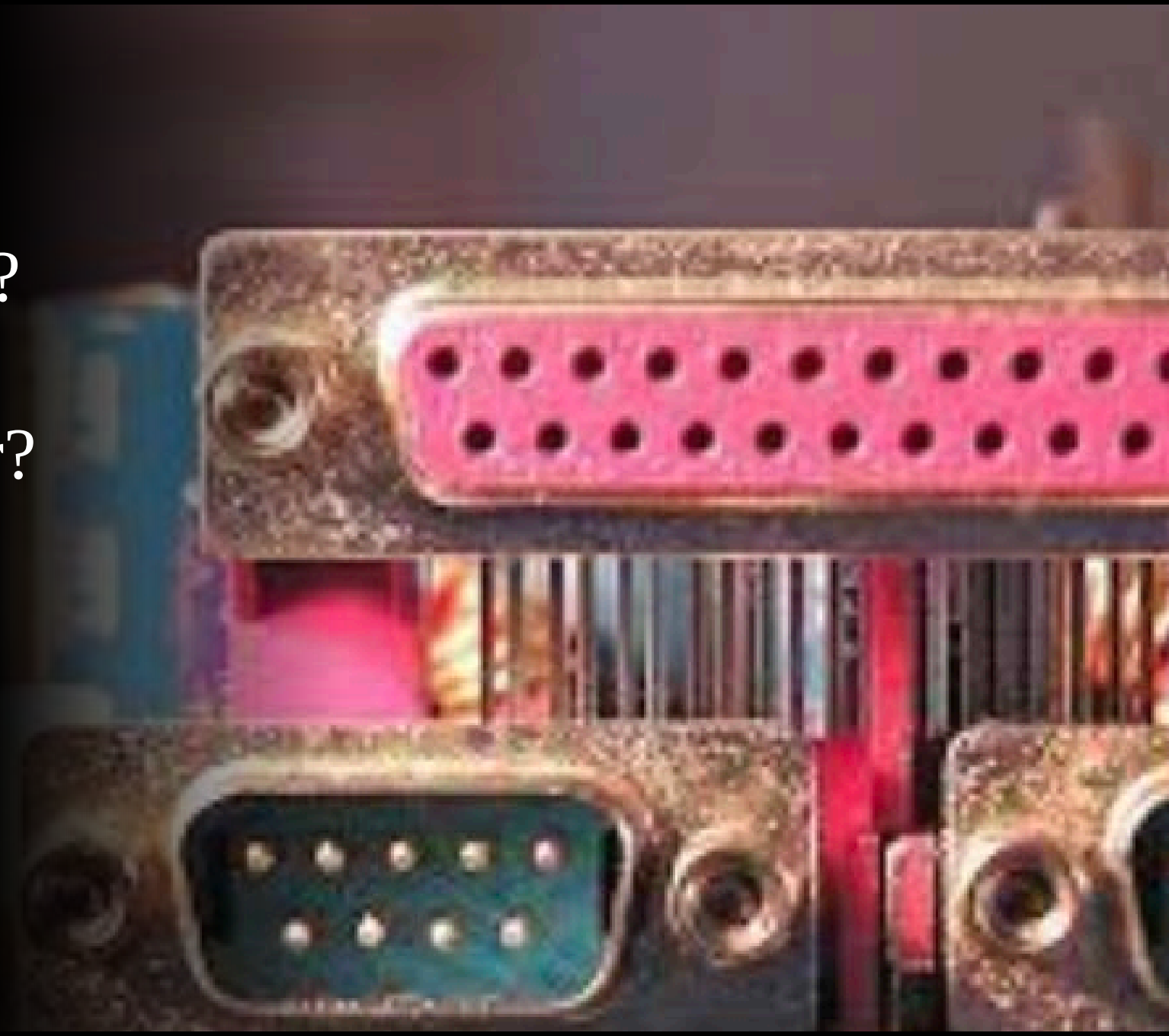

the pre-competitive space


We are all black swans…
I’m not

What was before USB ?

How did USB take over?

IO

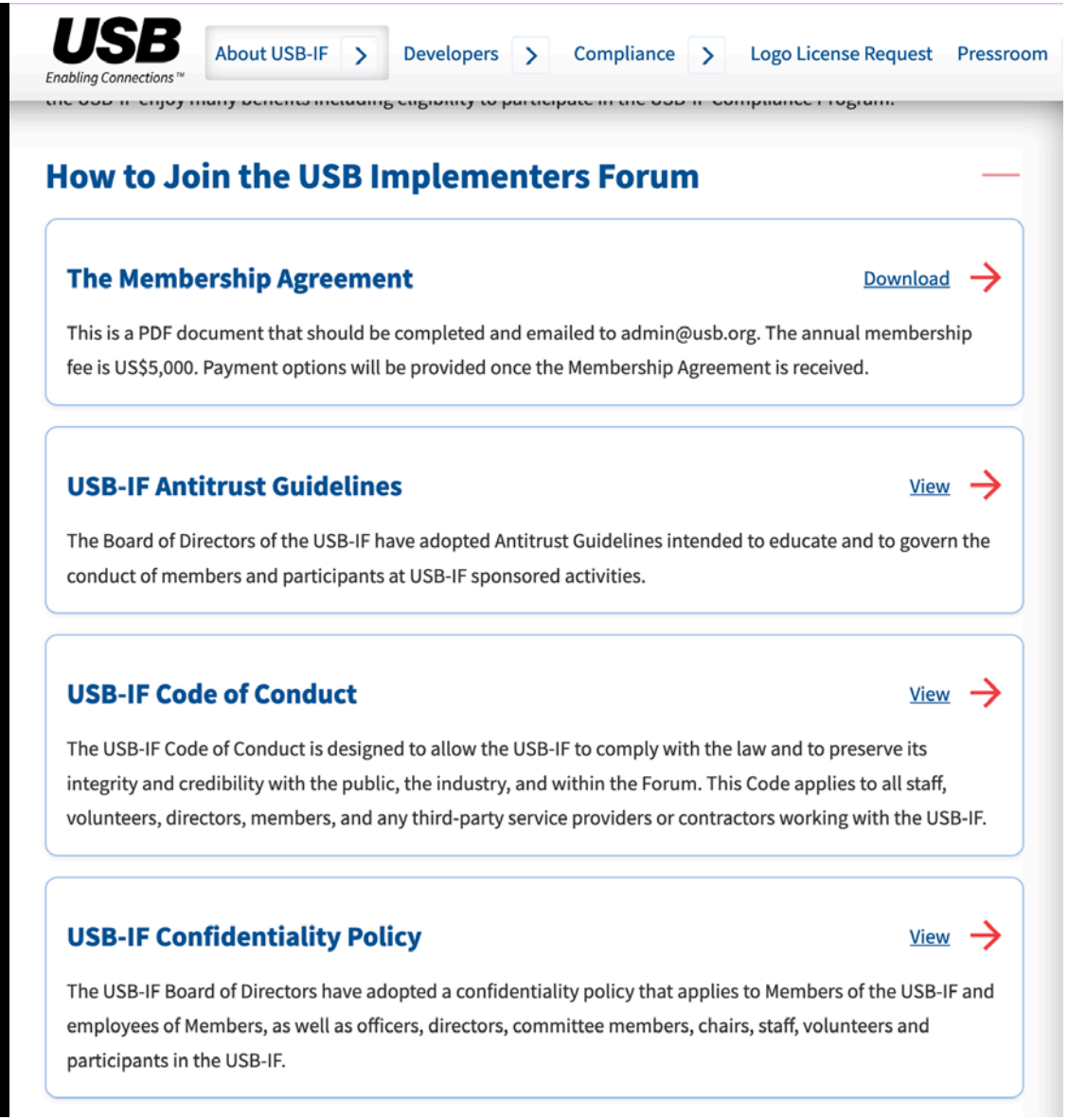


The pre-competitive space

+ is abstract
+ requires intricate structure(s)
+ e.g., anti-trust monitoring

a proven approach

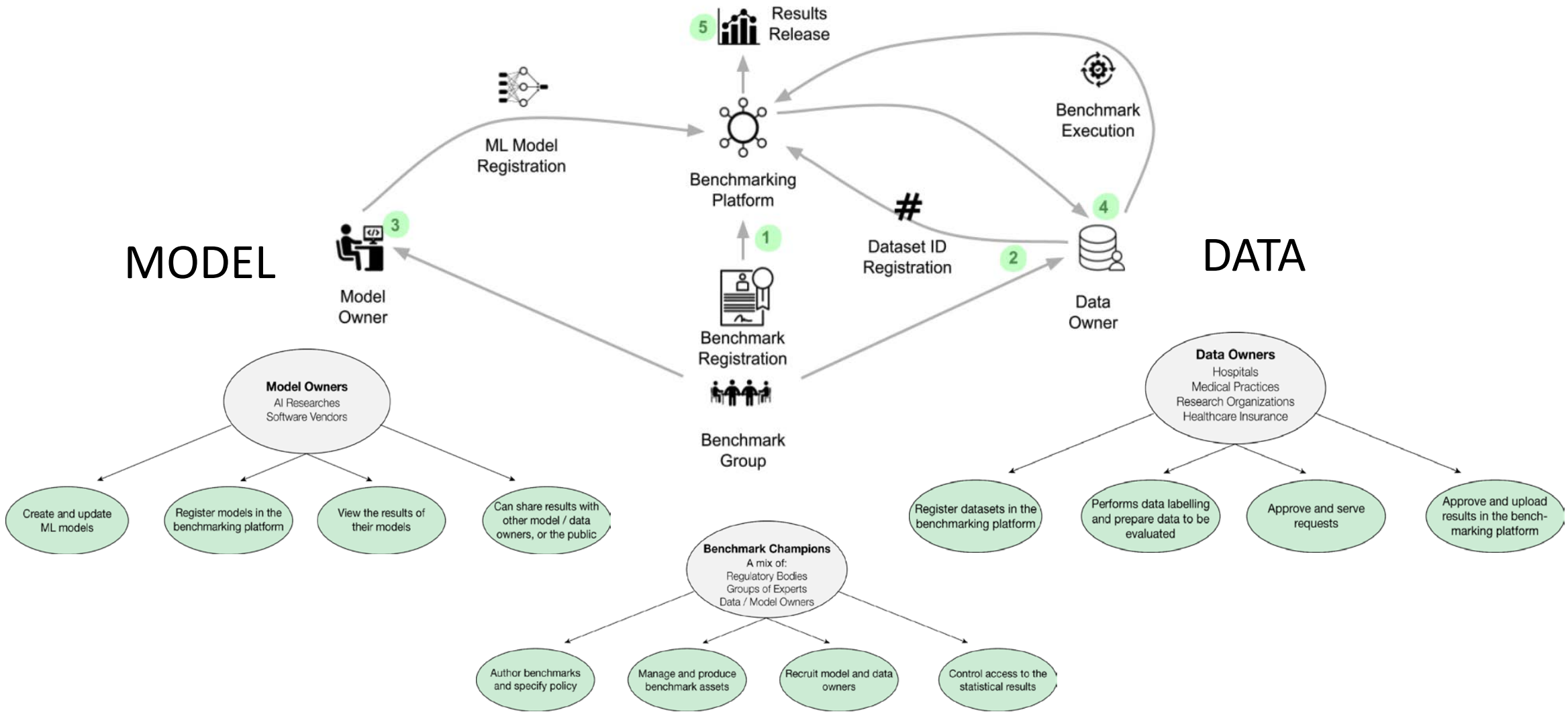
underutilized in medicine




IDEAS
COLLABORATE
INNOVATE
COLLABORATE
INNOVATE
COLLABORATE
INNOVATE
COLLABORATE
INNOVATE
SOLUTIONS
Members
Funding
Direction
Project Teams
Board
DELIVER
Implementation
Strategy
Steering Committees
Operations Team
Operation


Optimization
Automation
Visibility
Standardization

Federated models necessitate **human** governance structures

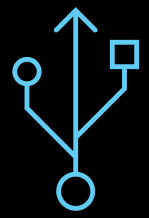


What do you need to realize innovation?

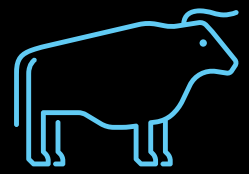
Great Team
(int. & ext.)

Understand
the framework

Healthcare
system



How to integrate
(Concept +Process)

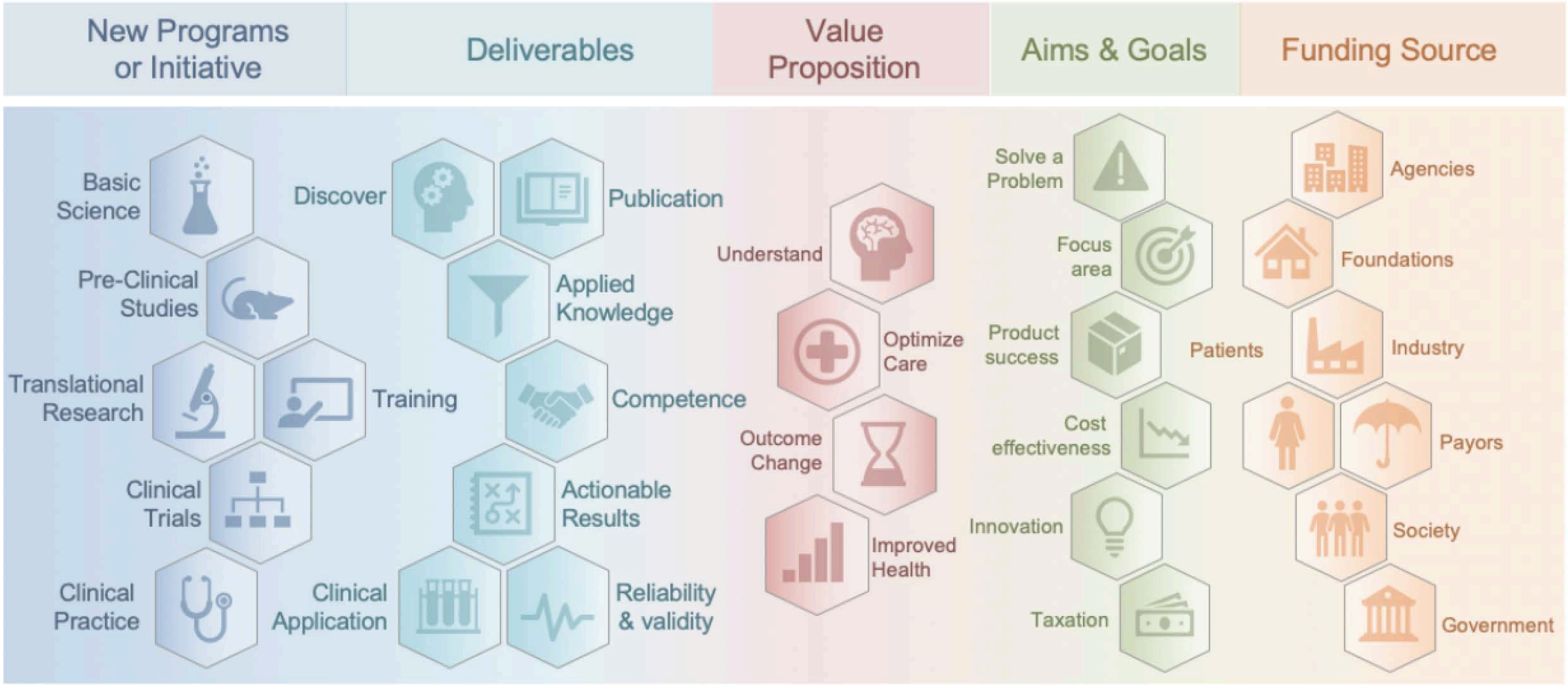


Approaches to
Financial Sustainability

Approach to apply
and challenge regulation

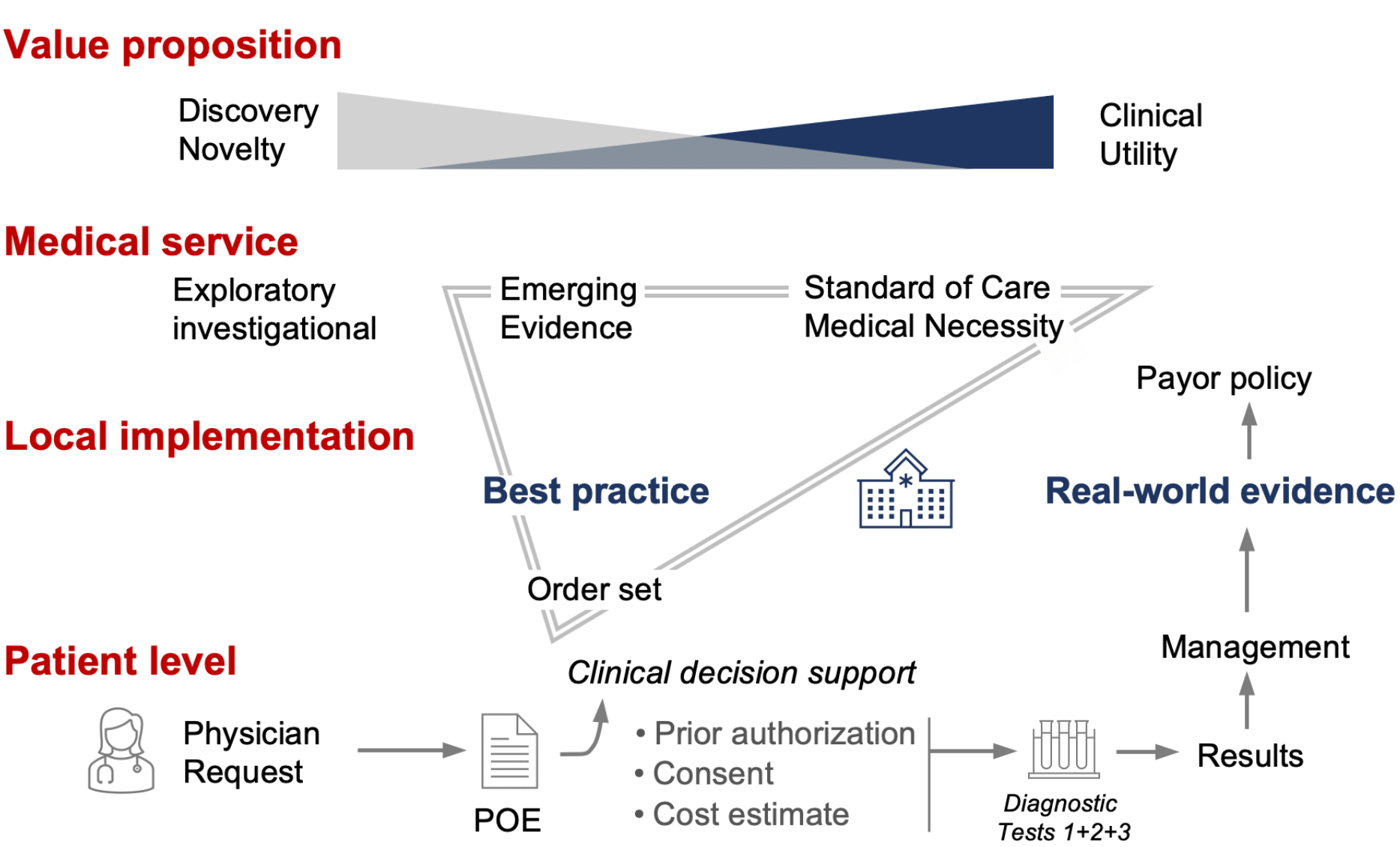
“Developing and putting forth your own vision and then making it reality is no simple task”

Paradigm for Financial Sustainability

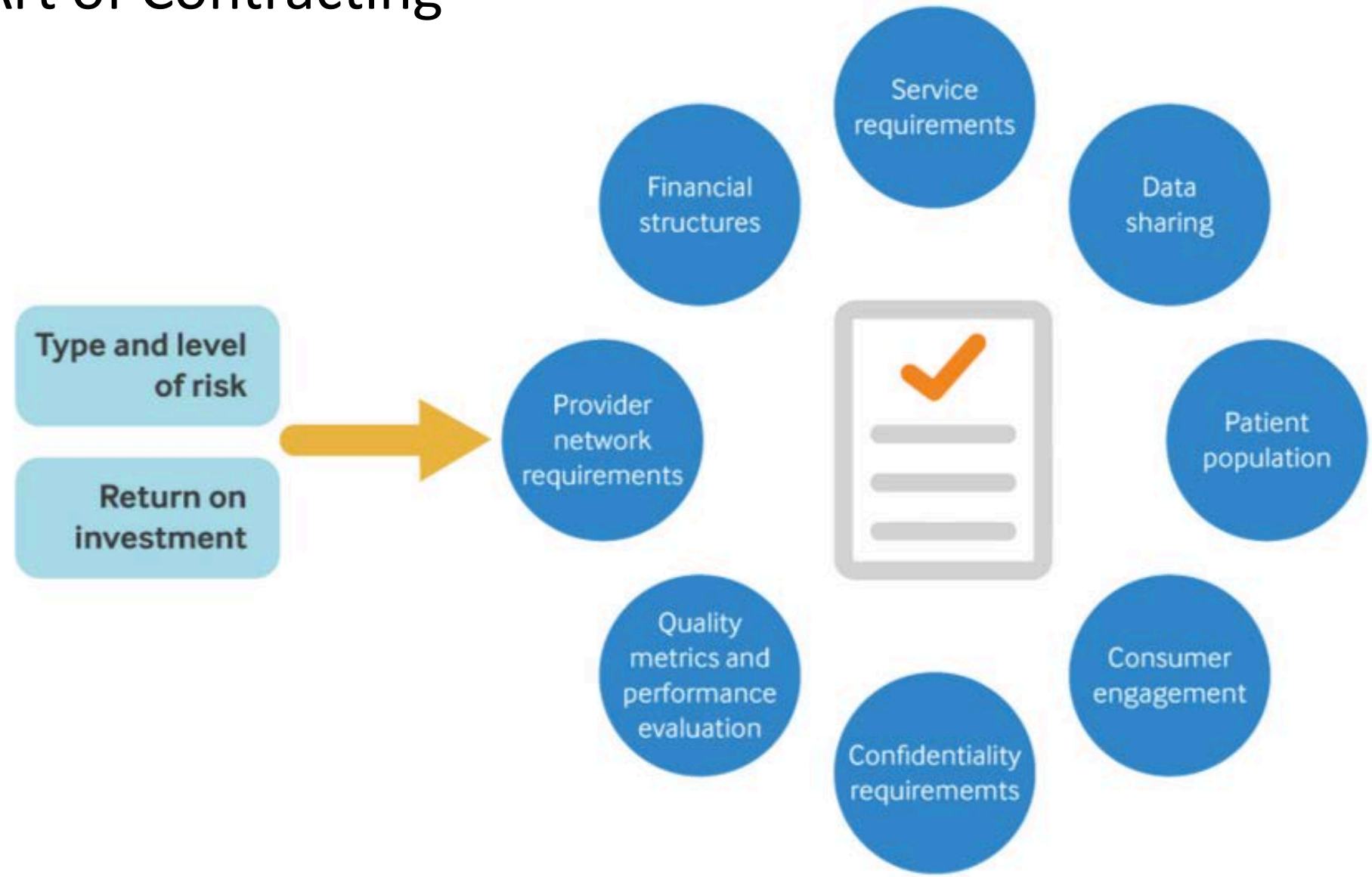


Thierauf et al., 2019 The Oncologist

Realizing Precision Oncology is a Multi-Layered Challenge

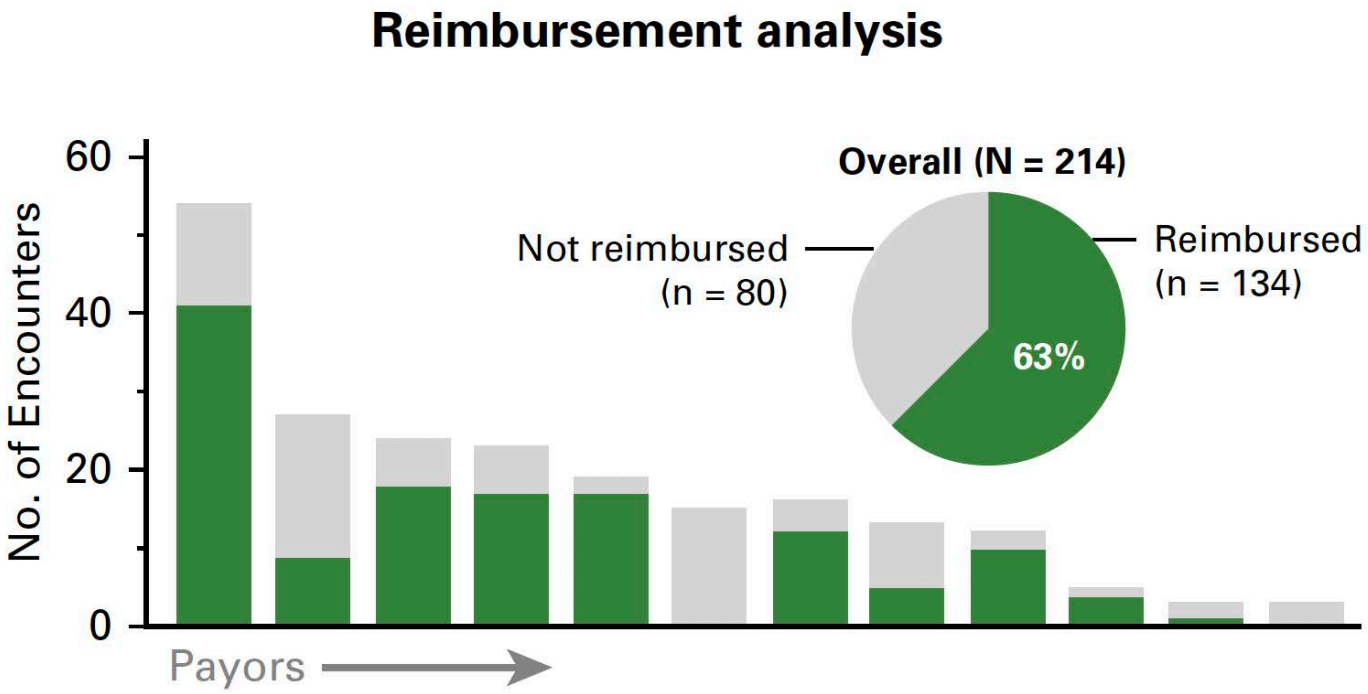


The Art of Contracting



Rapid testing reimbursement analysis

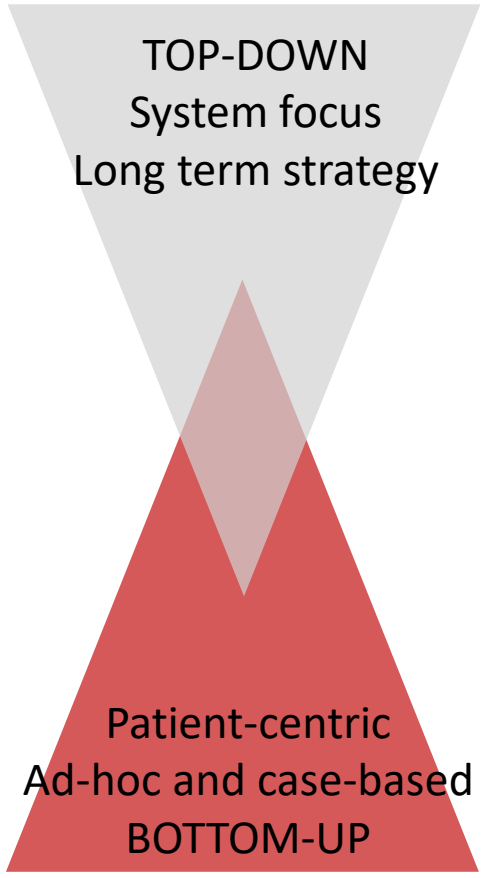
- **Coding strategy**
  - Payor tailored
  - Prior authorization
  - Pilot program(s)
- **Reimbursement analysis**
  - Dependent on Focus
  - Quality



Dagogo-Jack et al., 2018 JCO PO

Levels of Approaching Financial Sustainability

Global or International level
National or US-level
State level
Region
Local
System
Institutional
Departmental
Divisional
Patient Level
Procedure(s)
Test(s) ordering
Out of pocket estimate



"a robust local program can be an effective strategy to ensure progress"

What do you need to realize innovation?

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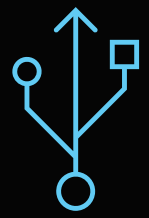
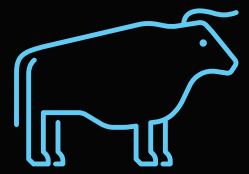
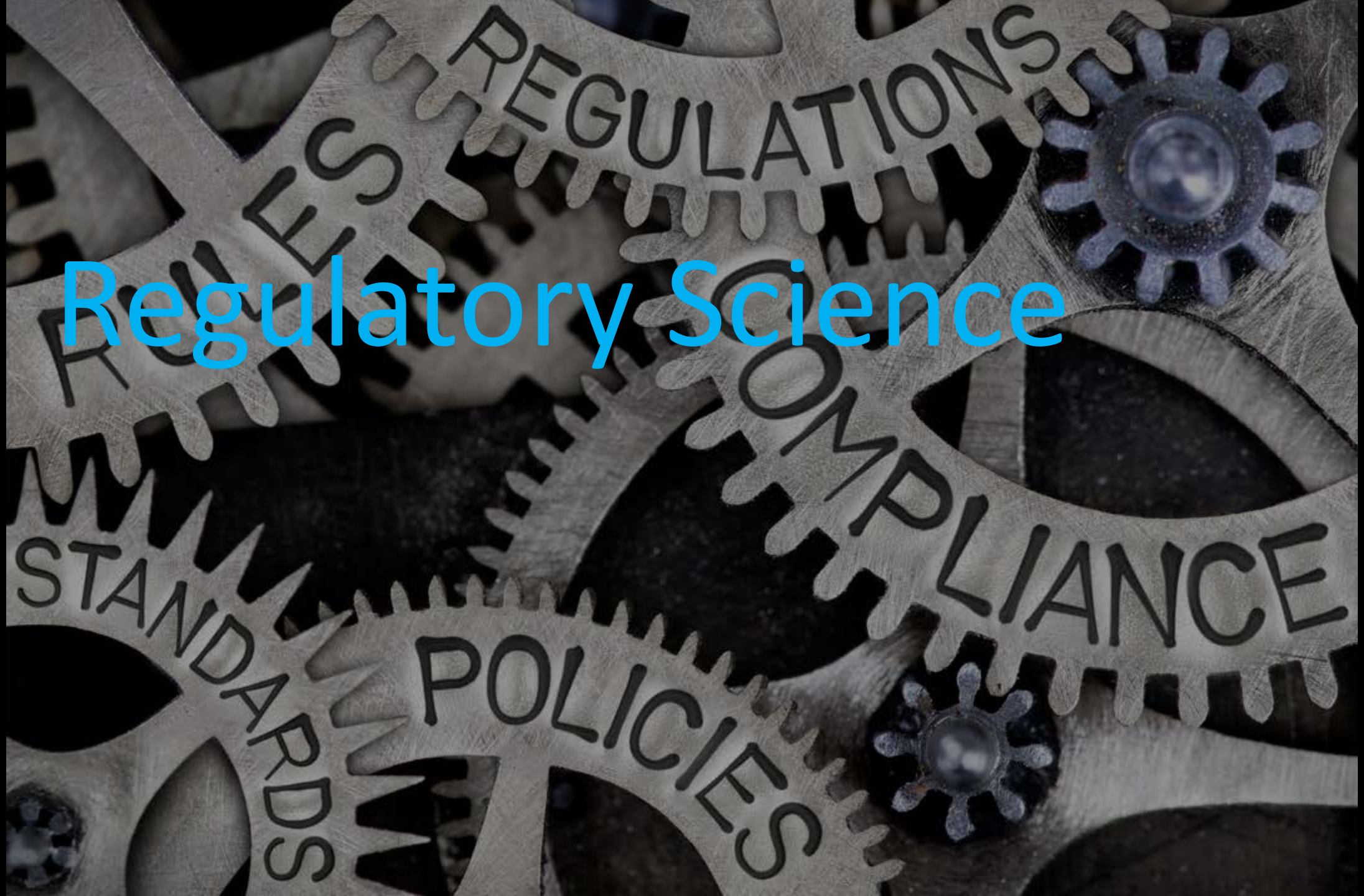


How to integrate
(Concept +Process)

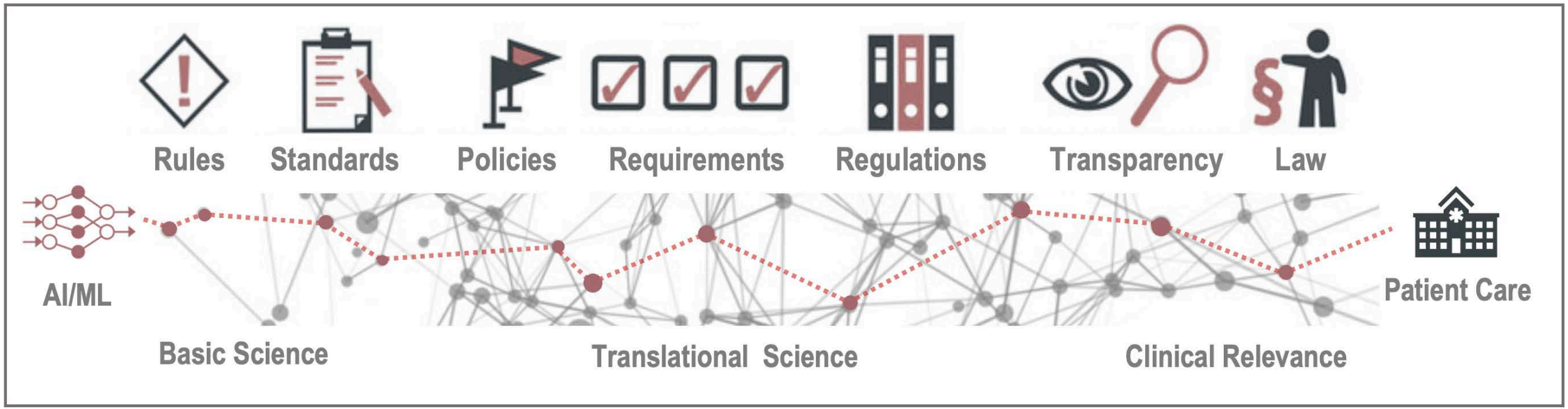


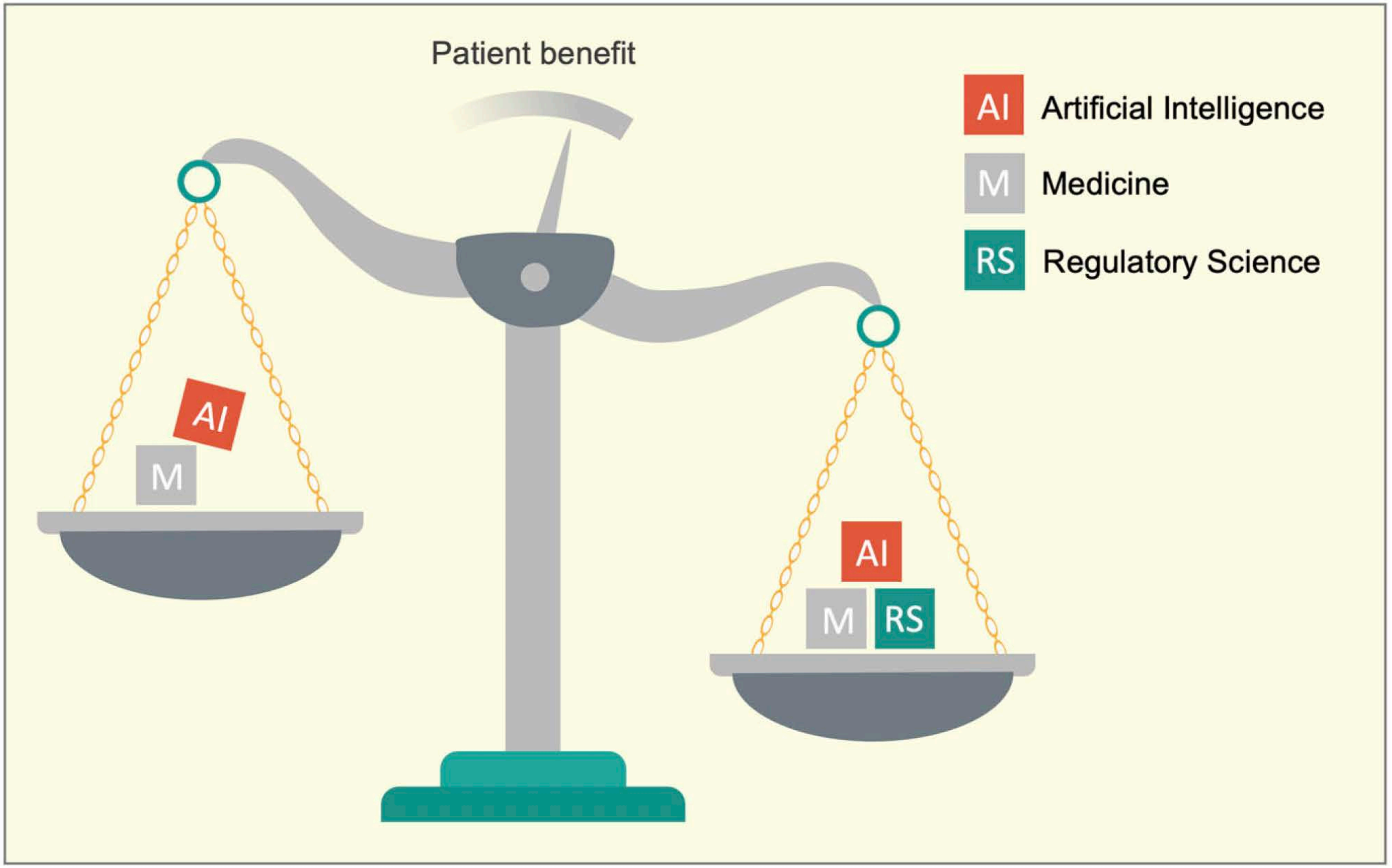
Approaches to
Financial Sustainability

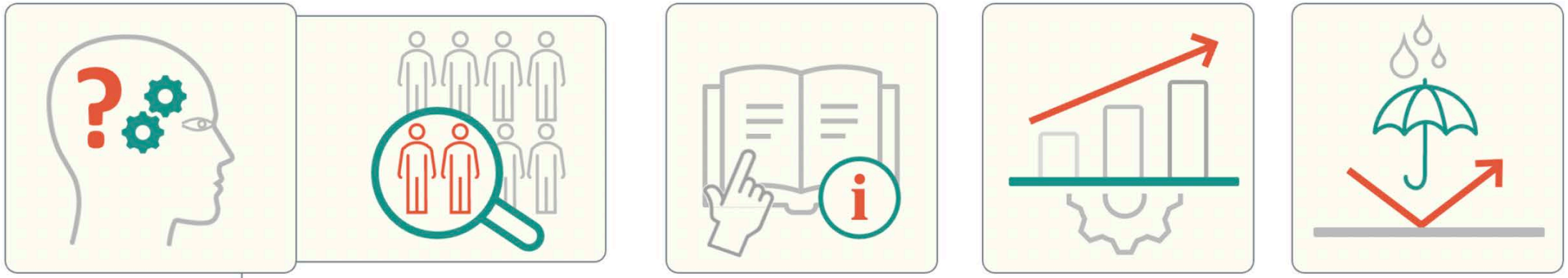
Approach to apply
and challenge regulation



Regulatory Science


Rules
Standards
Policies
Requirements
Regulations
Transparency
Law
AI/ML
Patient Care
Basic Science
Translational Science
Clinical Relevance


Patient benefit
AI
Artificial Intelligence
M
Medicine
RS
Regulatory Science
AI
M
AI
M
RS



Intended Use

"what"

Defined as the general purpose of the device or its function and encompass the indications for use; criticality of context, serious situation, significance of information (i.e., to treat, to diagnose, to drive management, to inform clinical management)

Indication of use

"who + why"

The intended patient population (target population) including the disease(s) or condition(s) the device is intended to address (i.e., diagnose, treat, prevent, cure or mitigate).

Instructions for use

"how"

Provide a detailed, action-oriented, step-by-step written and visual instruction for how to use the device

Performance measures

Establishing, based on a specified technical protocol, that the performance specifications correspond to the associated claims and uncertainty; concepts of analytical validation and verification; acceptance criteria/conformance to

Mitigation strategy

Actions taken to recover benefit or to limit harm. Mitigations address a variety of aspects and risk acceptability is assessed after any appropriate mitigation

Fig. 2 Selected regulatory science concepts.

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

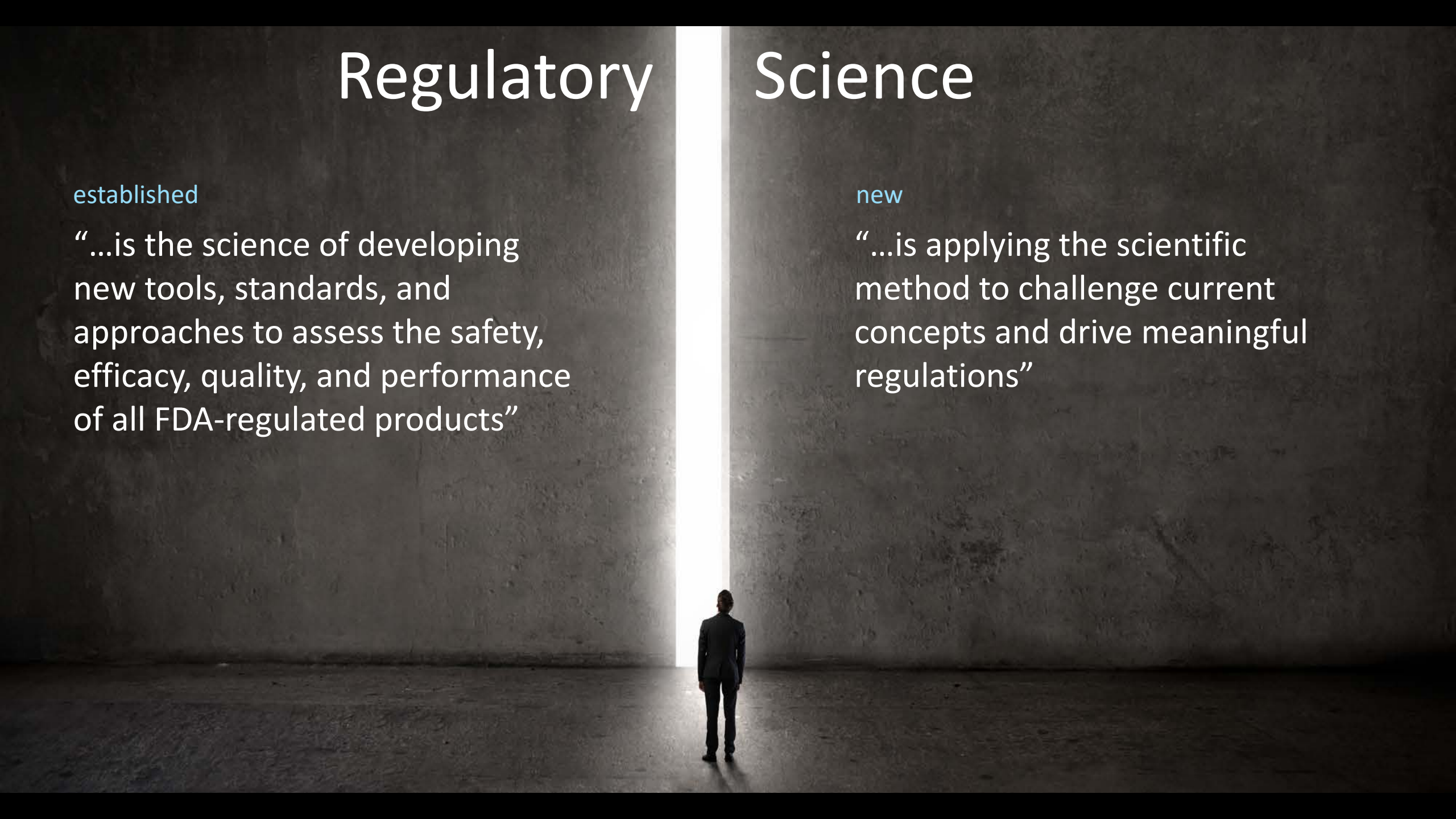
Regulatory Science

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 ?

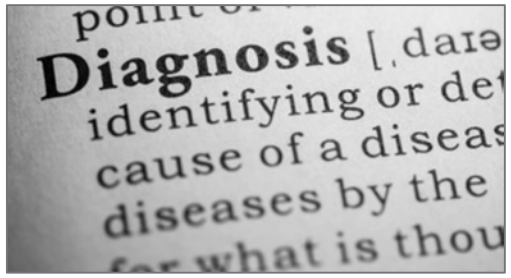
Do such biases limit our ability to see alternatives?

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
2018
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
2019
12th May
FDA approves 250th device containing AI / ML
2020
27th October
Guidance on Good Machine Learning Practice for Medical Device Development: Guiding Principles
2021
6th April
MHRA publishes guidance on Software and Artificial Intelligence (AI) as a Medical Device
2023
5th December
Public consultation closes on BS 30440 (Validation framework for the use of AI in healthcare)

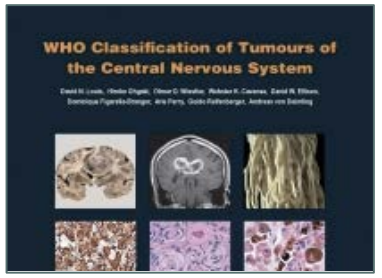
What's next in Technology and Innovation

Diagnosis

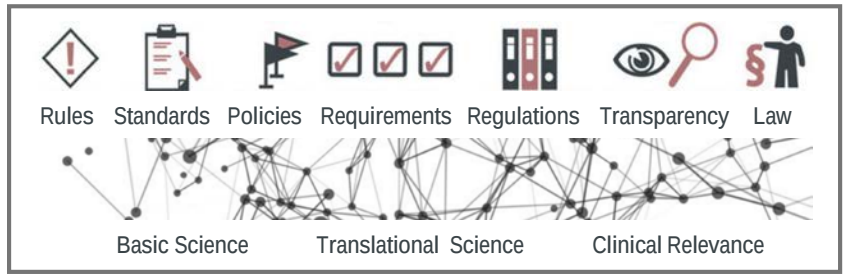


Technologies

Data Science



Regulatory Sciences



Data for Health

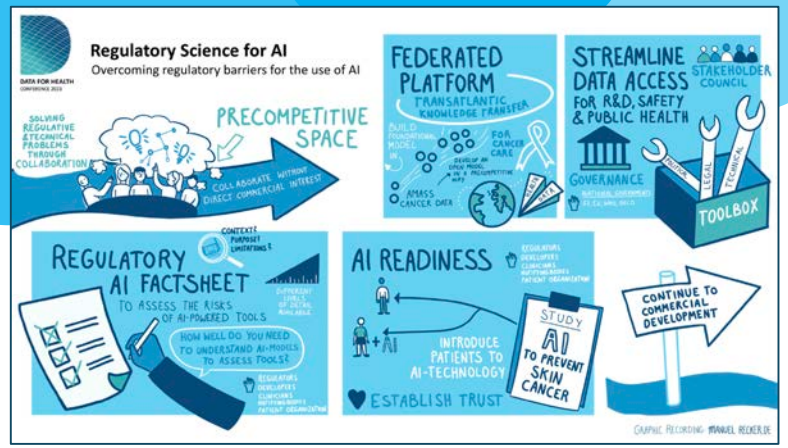
Let's start where other initiatives end …

pre-competitive space (=collaborate)

Unique Format and output

Benefit to the entire community

Next steps



JOCHEN LENNERZ, NICK SCHNEIDER, AND KARL LAUTERBACH

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.

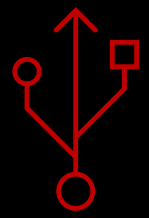
ummary

What do you need to realize innovation?

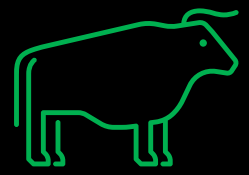
Great Team
(int. & ext.)

Understand
the framework

Healthcare
system



How to integrate
(Concept +Process)



Approaches to
Financial Sustainability

Approach to apply
and challenge regulation

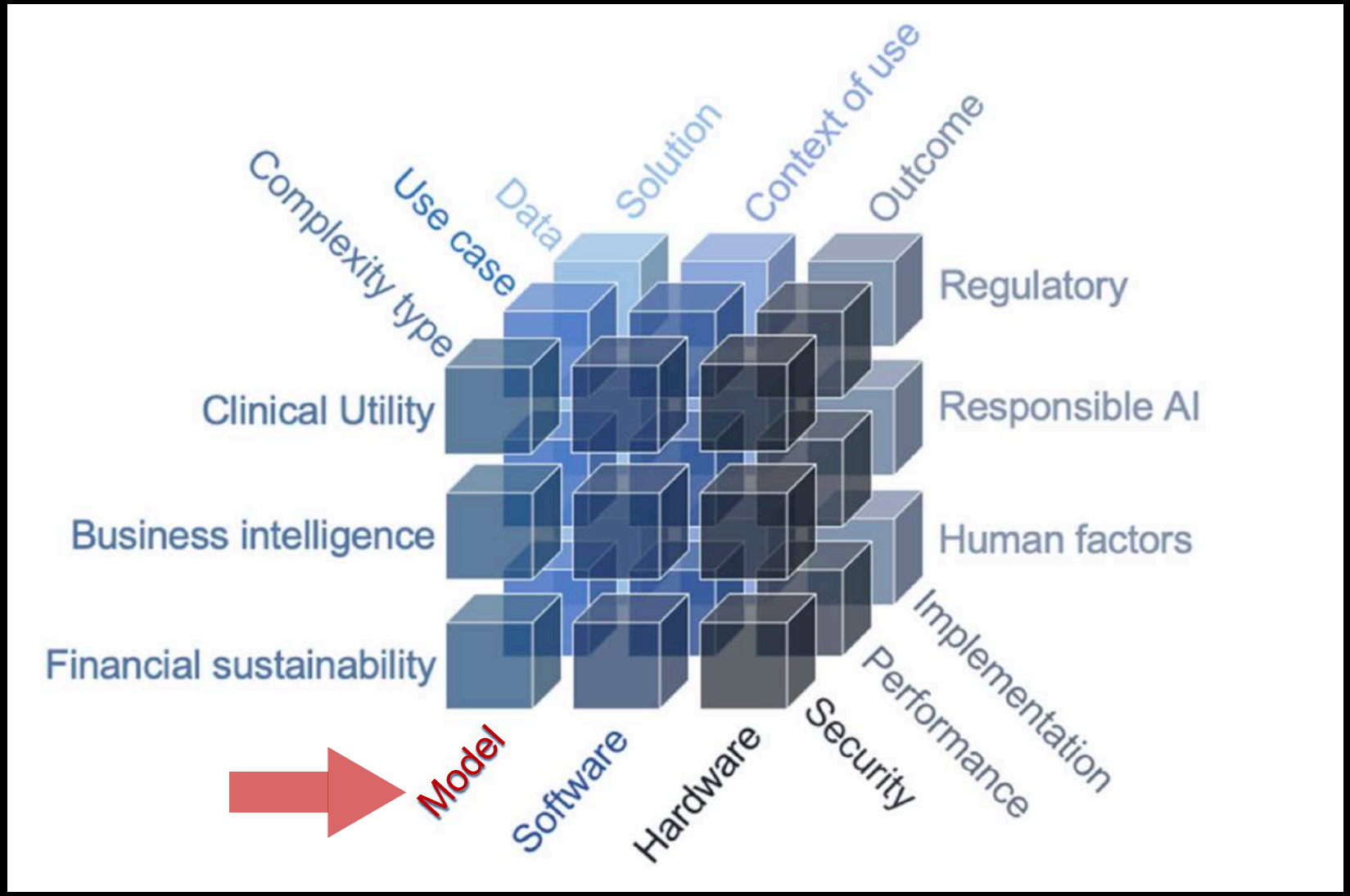
Joe.Lennerz@bostongene.com

Start of presentation

Diagnostic Quality Model (DQM):

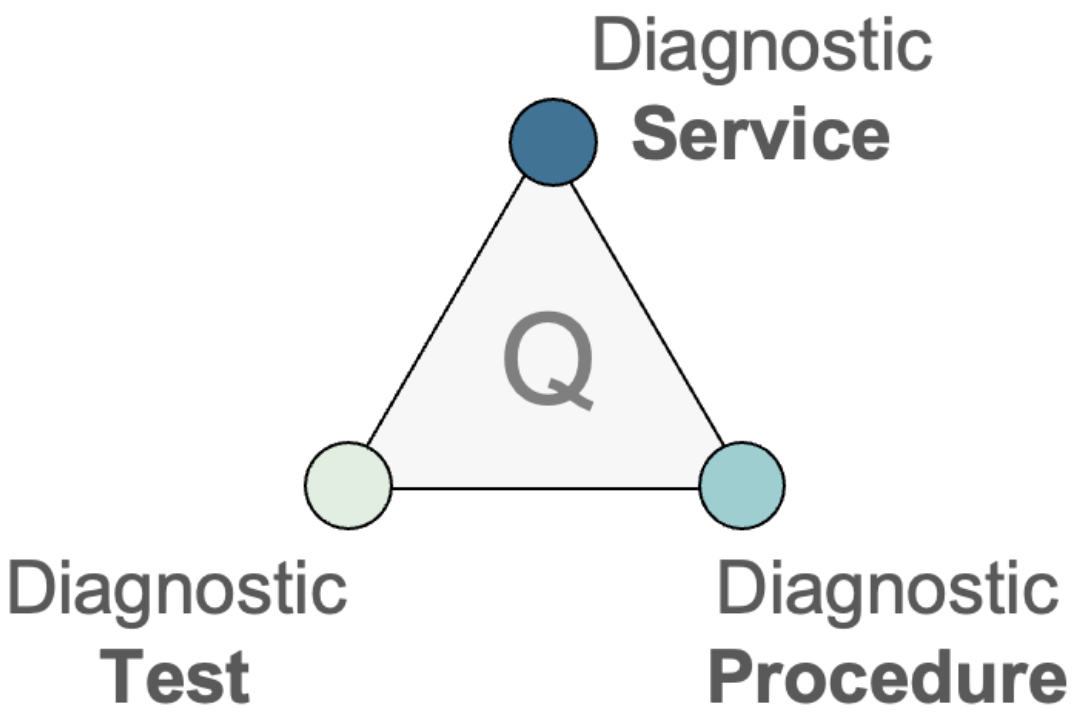
An Integrated Framework for the Assessment of Diagnostic Quality when Using AI/ML

What holds us back is a multidimensional problem



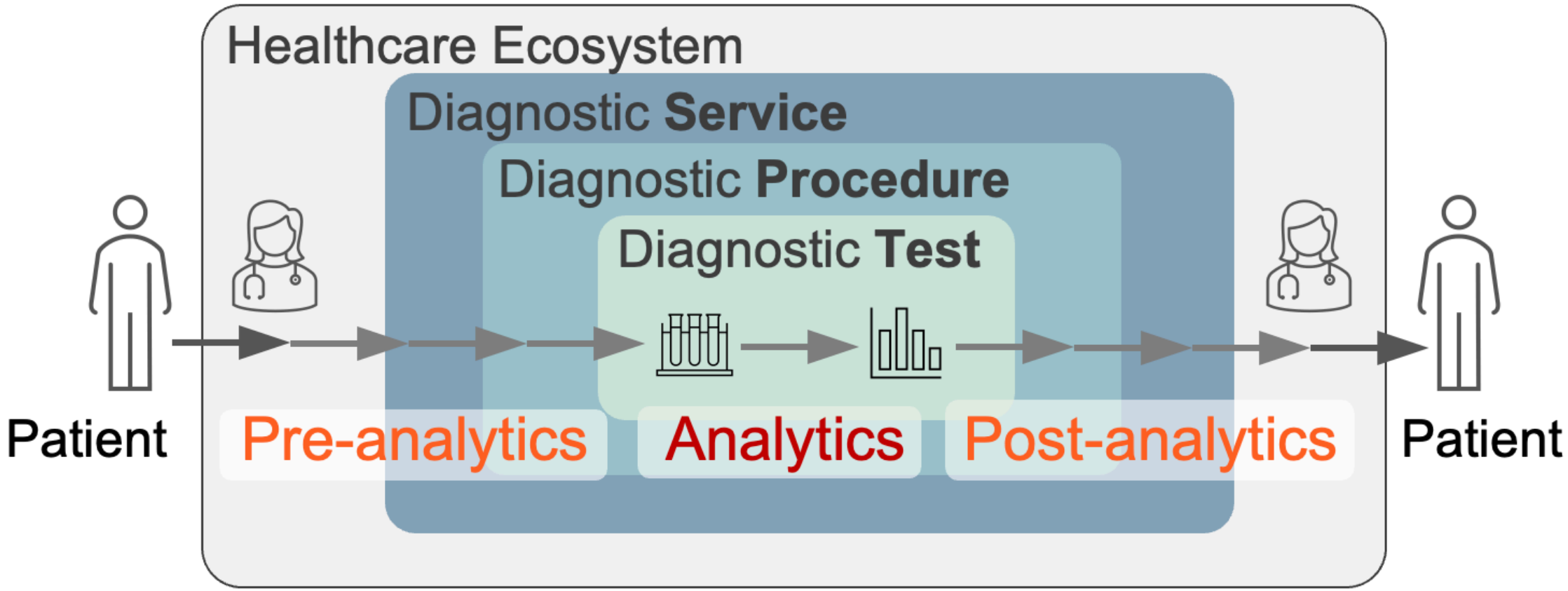
Diagnostic Quality Model (DQM)

Conceptual distinction



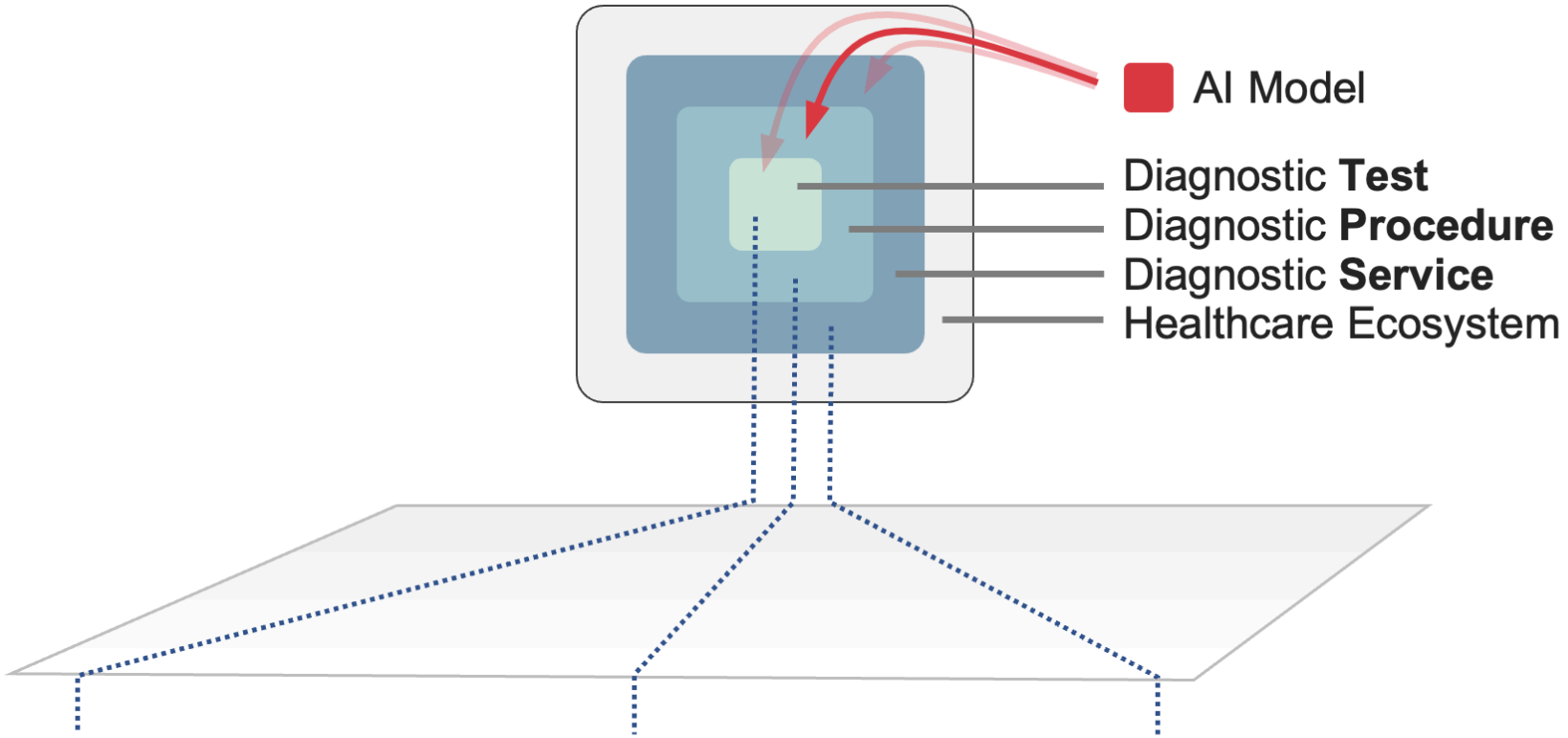
Diagnostic Quality Model (DQM)

Clinical Workflow



Diagnostic Quality Model (DQM)

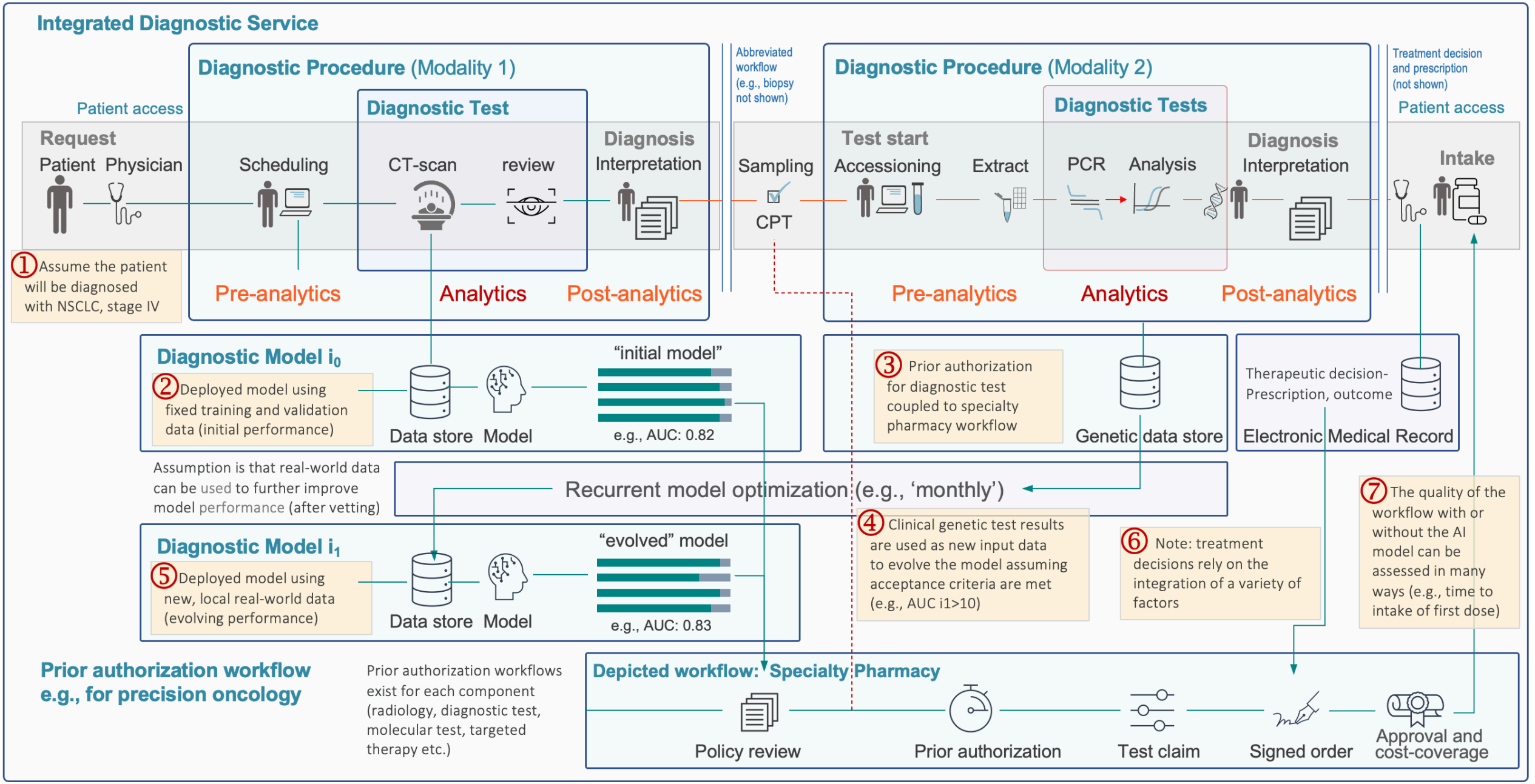
Relationship of DQM components and AI



Diagnostic **Quality** = Quality of the Diagnostic **Test** + Quality of the Diagnostic **Procedure** + Quality of the Diagnostic **Service**

Quality Impact of the **AI Model** = *abs.* [Diagnostic Quality **Without AI Model** − Diagnostic Quality **With AI Model**]

Figure 3


Integrated Diagnostic Service
Diagnostic Procedure (Modality 1)
Patient access
Diagnostic Test
Request
Patient
Physician
Scheduling
CT-scan
review
Diagnosis
Interpretation
Abbreviated workflow (e.g., biopsy not shown)
Sampling
CPT
Diagnostic Procedure (Modality 2)
Diagnostic Tests
Test start
Accessioning
Extract
PCR
Analysis
Diagnosis
Interpretation
Treatment decision and prescription (not shown)
Patient access
Intake
1 Assume the patient will be diagnosed with NSCLC, stage IV
Pre-analytics
Analytics
Post-analytics
Pre-analytics
Analytics
Post-analytics
Diagnostic Model i_0
2 Deployed model using fixed training and validation data (initial performance)
Data store
Model
"initial model"
e.g., AUC: 0.82
3 Prior authorization for diagnostic test coupled to specialty pharmacy workflow
Genetic data store
Therapeutic decision-Prescription, outcome
Electronic Medical Record
Assumption is that real-world data can be used to further improve model performance (after vetting)
Recurrent model optimization (e.g., 'monthly')
Diagnostic Model i_1
5 Deployed model using new, local real-world data (evolving performance)
Data store
Model
"evolved" model
e.g., AUC: 0.83
4 Clinical genetic test results are used as new input data to evolve the model assuming acceptance criteria are met (e.g., AUC i1>10)
6 Note: treatment decisions rely on the integration of a variety of factors
7 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)
Prior authorization workflow e.g., for precision oncology
Prior authorization workflows exist for each component (radiology, diagnostic test, molecular test, targeted therapy etc.)
Depicted workflow: Specialty Pharmacy
Policy review
Prior authorization
Test claim
Signed order
Approval and cost-coverage