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# NEWDIGS

## The VA as a Platform for Research and Learning

**Lou Fiore**
**Mary Brophy**

18 July 2018

# Magic Bus Stops

- Big Data in Healthcare – Observational Research
- Woes of Comparative Effectiveness Studies
- Point of Care Clinical Trials
- The Biomarker Story
- The VA Precision Oncology Program

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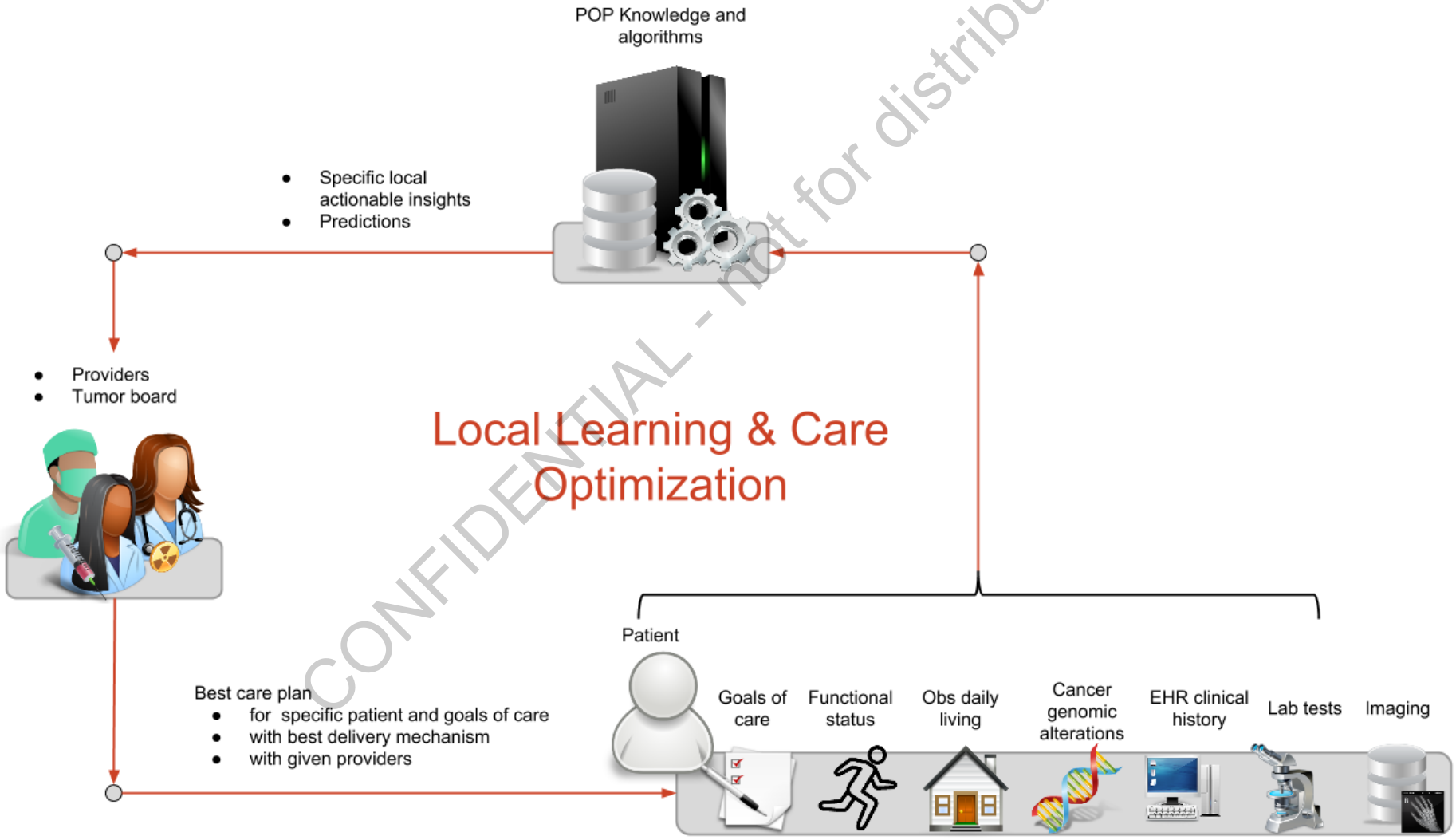
# Local Learning and Care Optimization

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# Chapter 1: Big Data in Healthcare

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# Knowledge Generation with EHR Data

- How much can be learned at the population level?
- How much can be learned at the patient level?
    - Are there “Patients like me?”
- How can we optimize learning healthcare system activities?

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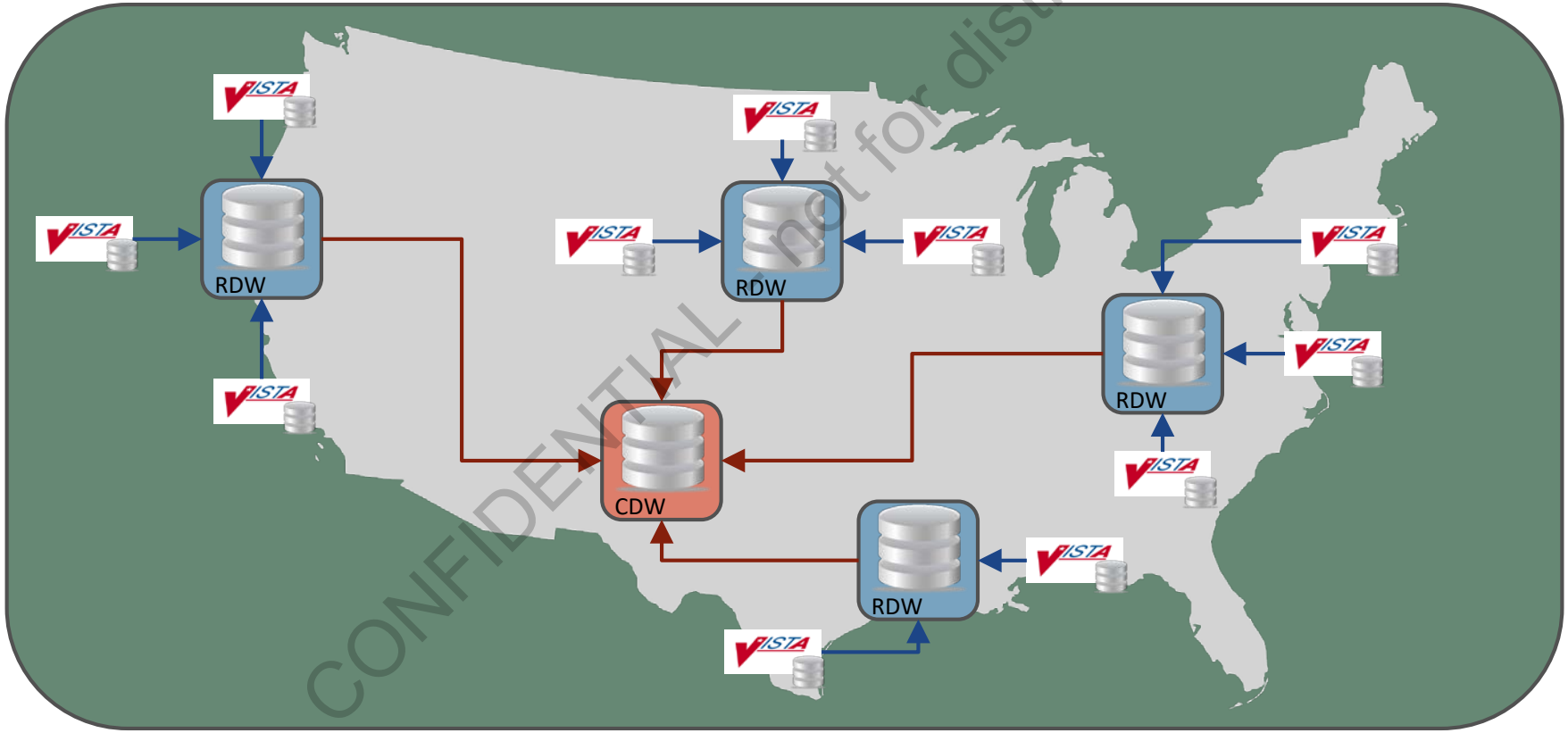
# The VA VistA/CPRS National EHR

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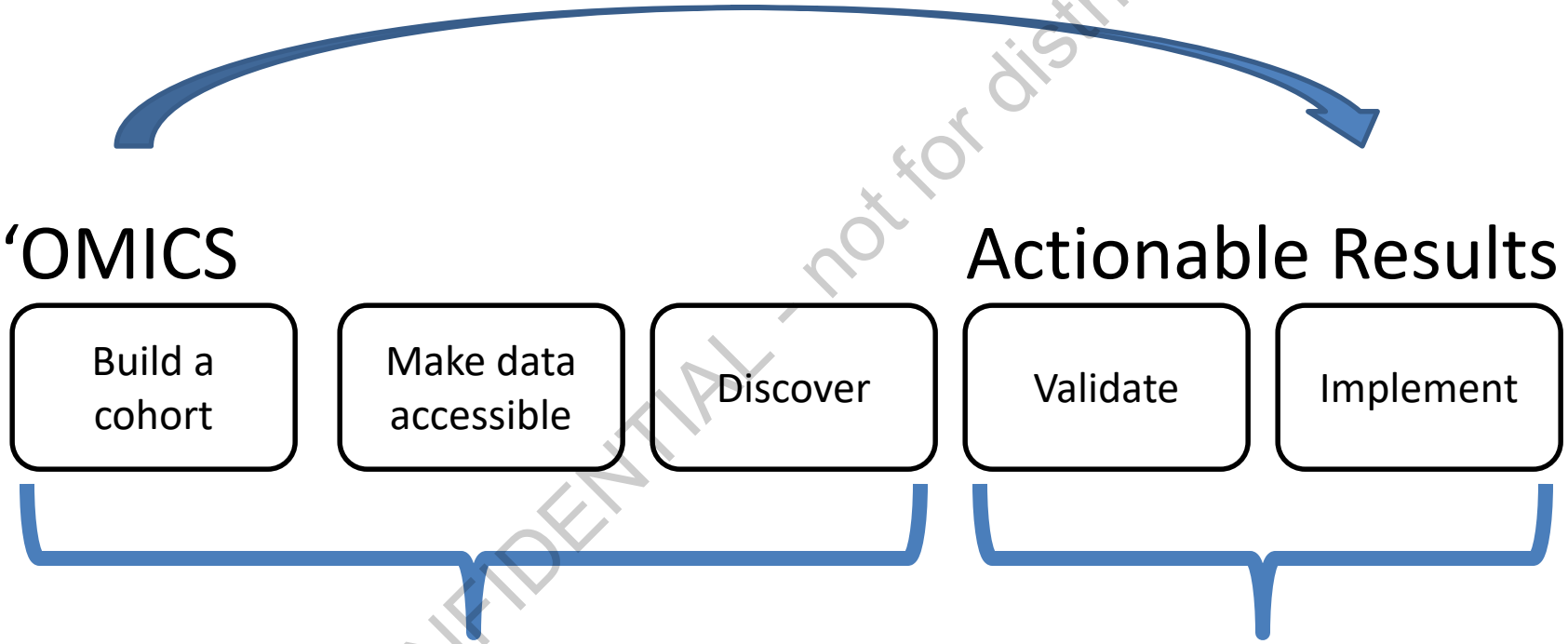
# The MAVERIC Response to the Challenge of Personalized Medicine

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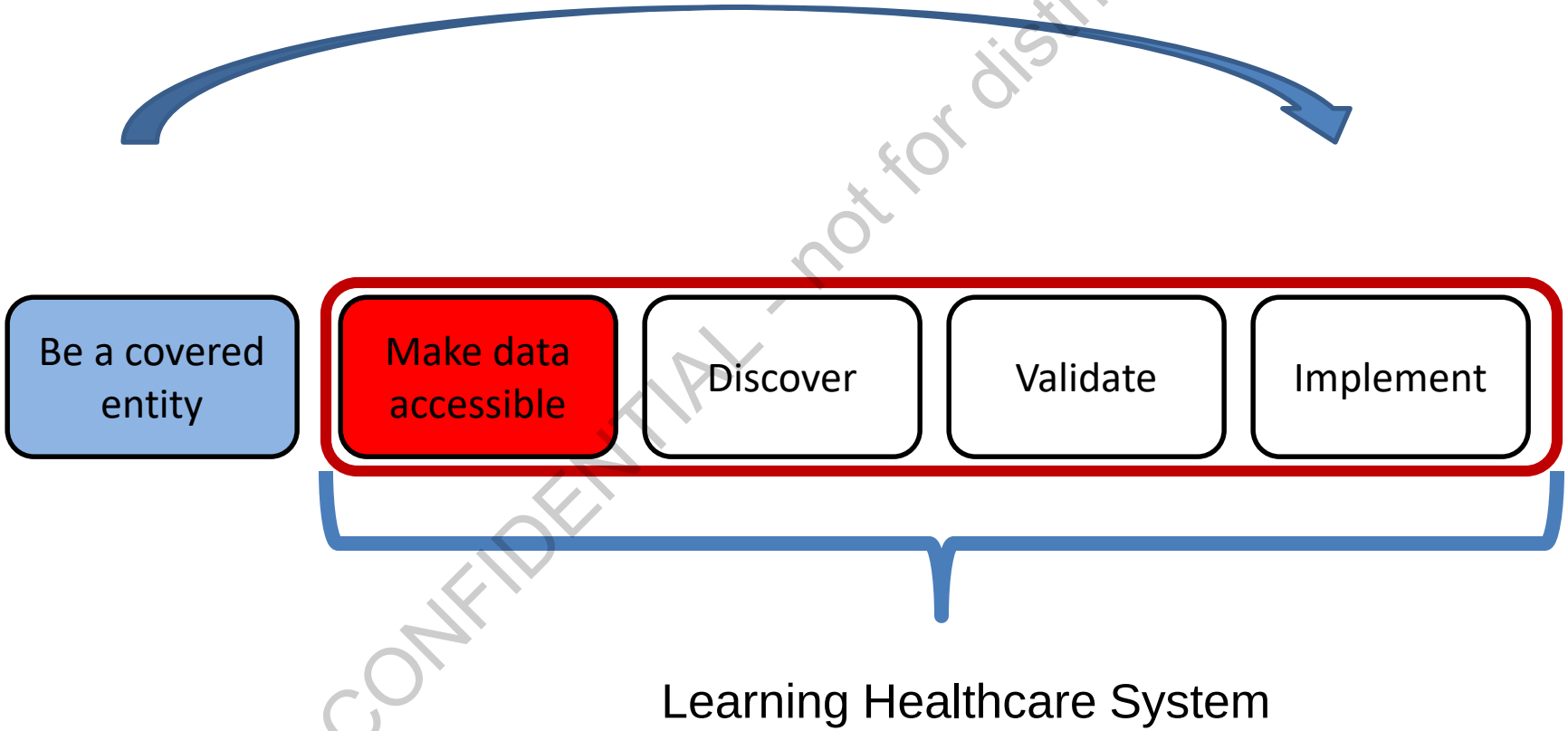
# The MAVERIC Response to the Improving Healthcare

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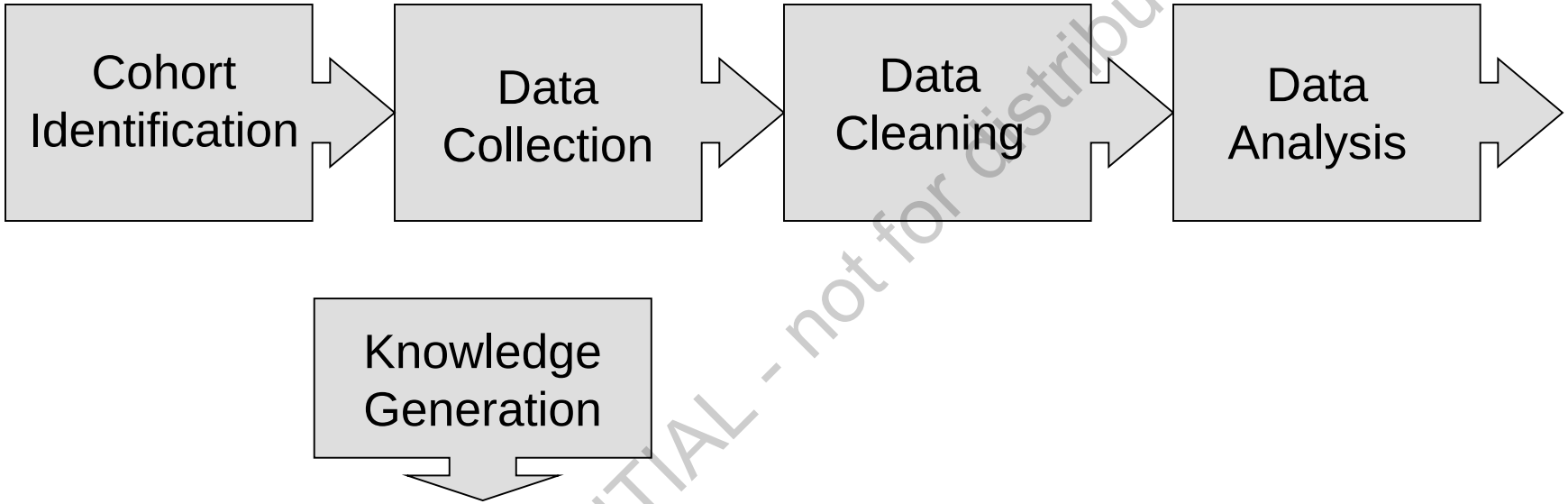
# Traditional Observational Health Research

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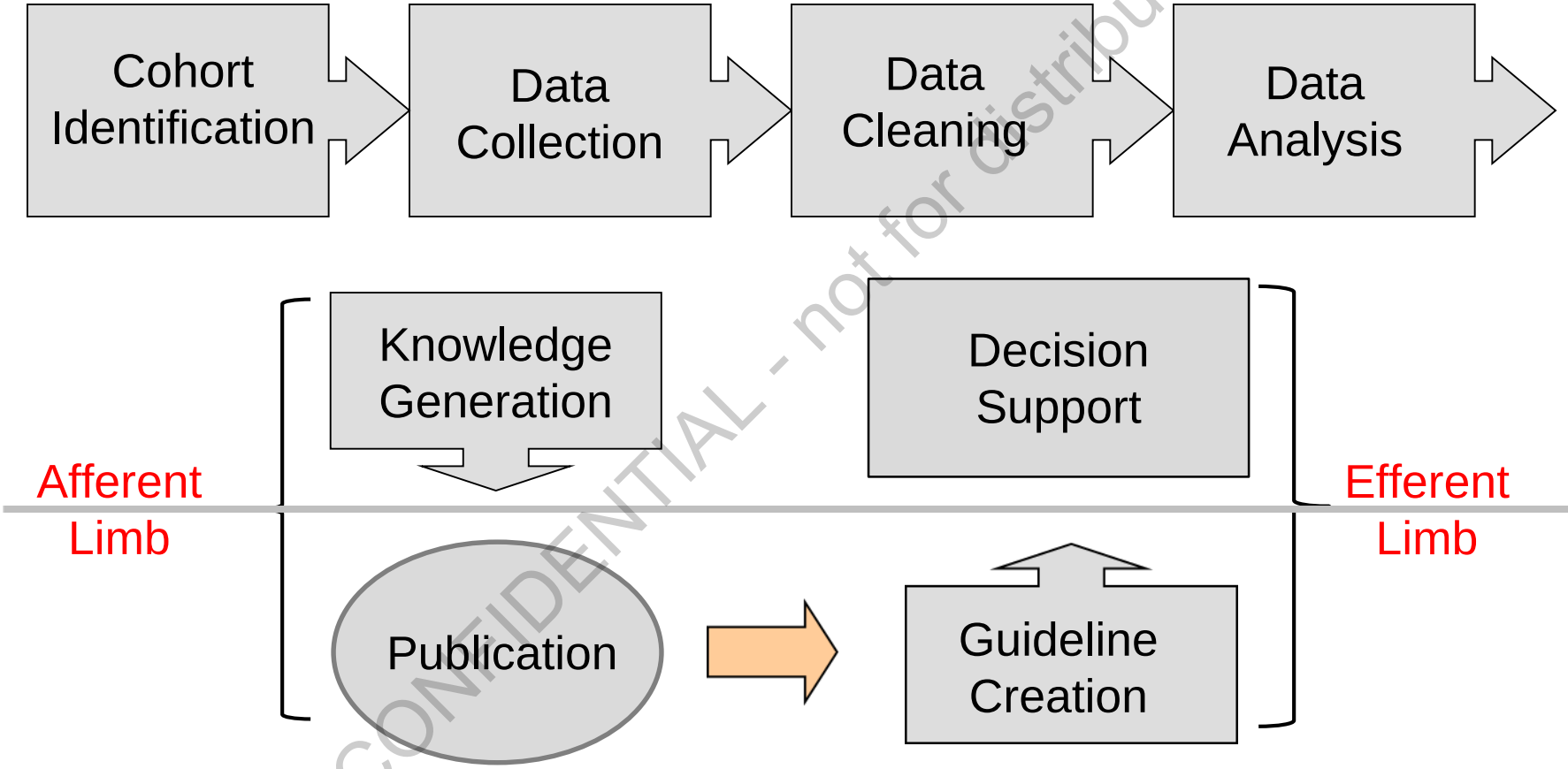
# Observational Research with Guideline Implementation

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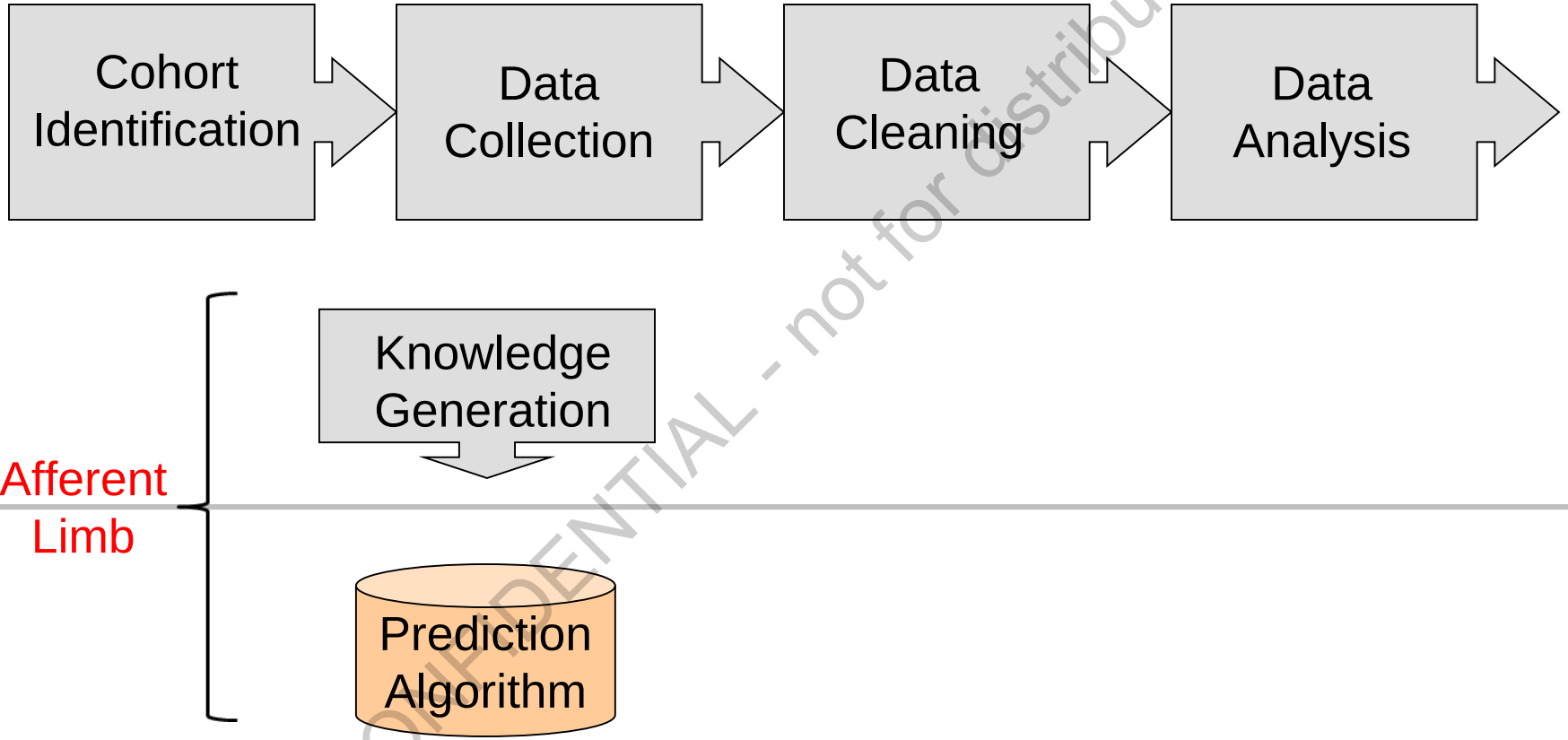
# Predicative Analytics Development

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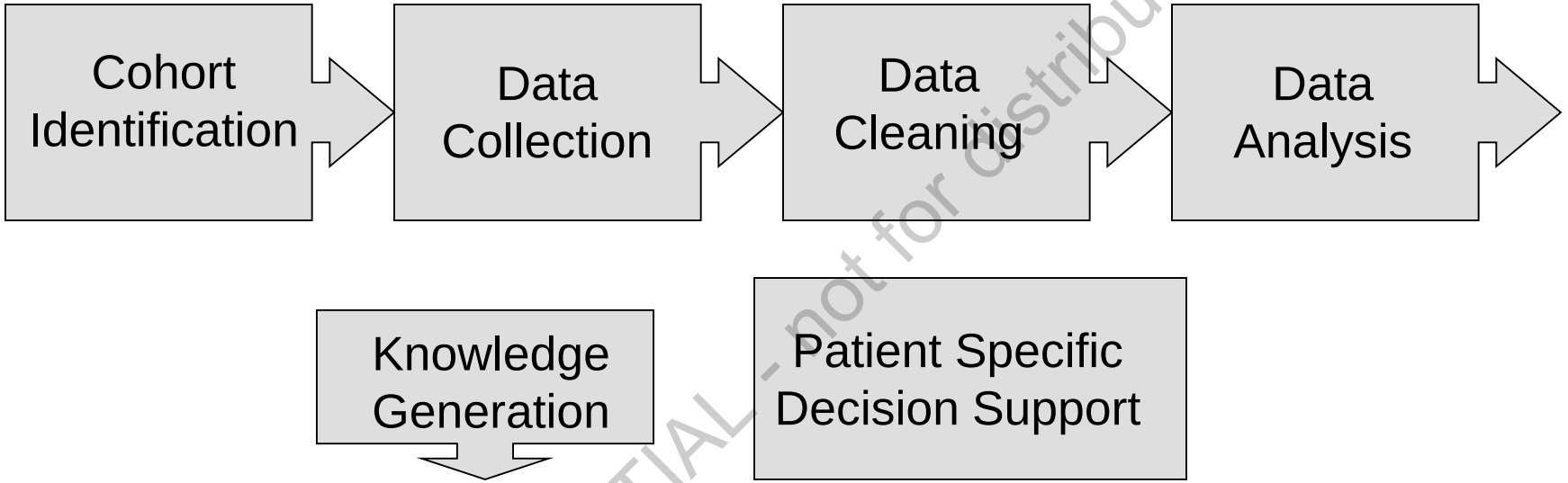
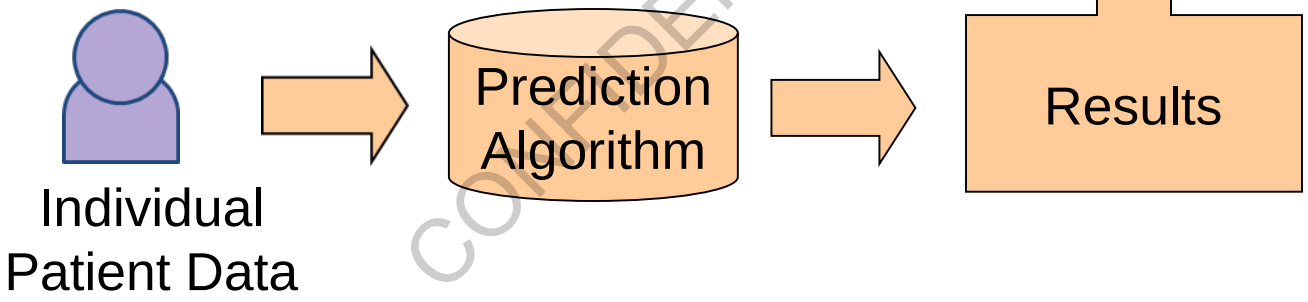
# Local Learning with Implementation

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# Chapter 2: The Woes of Comparative Effectiveness Studies

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# Implementation Problem - The T2 Gap

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Long-Acting Risperidone and Oral Antipsychotics in Unstable Schizophrenia

Robert A. Rosenheck, M.D., John H. Krystal, M.D., Robert Lew, Ph.D., Paul G. Barnett, Ph.D., Louis Fiore, M.D., M.P.H., Danielle Valley, M.P.H., Soe Soe Thwin, Ph.D., Julia E. Vertrees, Pharm.D., and Matthew H. Liang, M.D., M.P.H., for the CSP555 Research Group*

N Engl J Med. 2011 Mar 3;364(9):842-51. doi: 10.1056/NEJMoa1005987.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Therapies for Active Rheumatoid Arthritis after Methotrexate Failure

James R. O'Dell, M.D., Ted R. Mikuls, M.D., M.S.P.H., Thomas H. Taylor, M.D., Vandana Ahluwalia, M.D., Mary Brophy, M.D., M.P.H., Stuart R. Warren, J.D., Pharm.D., Robert A. Lew, Ph.D., Amy C. Cannella, M.D., Gary Kunkel, M.D., Ciaran S. Phibbs, Ph.D., Aslam H. Anis, Ph.D., Sarah Leatherman, M.A., and Edward Keystone, M.D., for the CSP 551 RACAT Investigators*

N Engl J Med. 2013 Jul 25;369(4):307-18. doi: 10.1056/NEJMoa1303006. Epub 2013 Jun 11.

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

**THE CHANGING FACE OF CLINICAL TRIALS**

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

# Integrating Randomized Comparative Effectiveness Research with Patient Care

Louis D. Fiore, M.D., M.P.H., and Philip W. Lavori, Ph.D.

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N Engl J Med. 2016 Jun 2;374(22):2152-8. doi: 10.1056/NEJMra1510057.

# Chapter 3: Point of Care (Integrated) Clinical Trials

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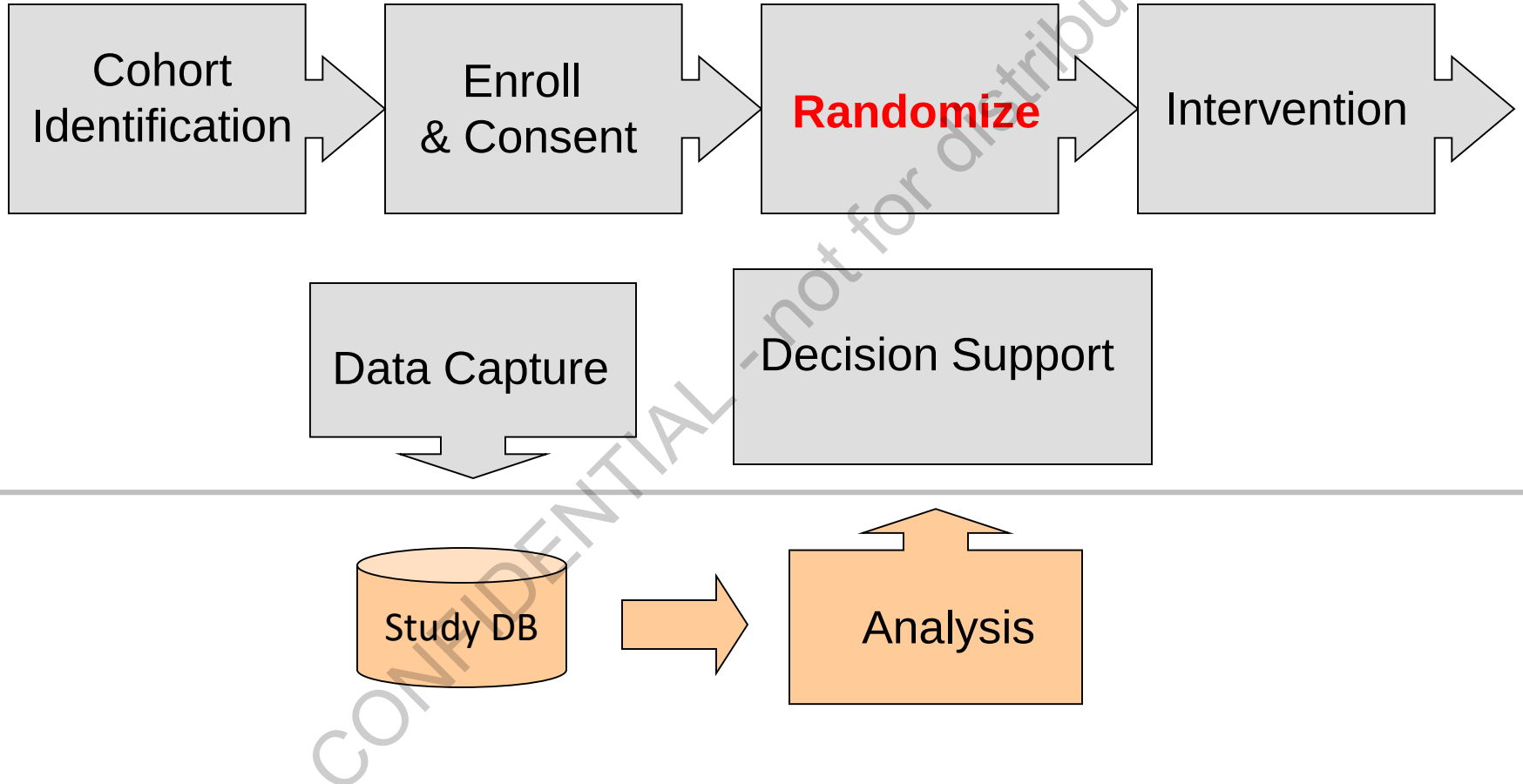
# Point of Care (Embedded) Clinical Trials

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CLINICAL TRIALS DESIGN

Clinical Trials 2011; 8: 183–195

# A point-of-care clinical trial comparing insulin administered using a sliding scale *versus* a weight-based regimen

*Louis D Fiore[a,b,c], Mary Brophy[a,c], Ryan E Ferguson[a,b], Leonard D'Avolio[a,d], John A Hermos[a,c,e], Robert A Lew[a,f], Gheorghe Doros[a,f], Chester H Conrad[a,c], Joseph A ("Gus") O'Neil Jr[a], Thomas P Sabin[a], James Kaufman[a,c], Stephen L Swartz[a], Elizabeth Lawler[a,g,h], Matthew H Liang[a,i], J Michael Gaziano[a,g,h] and Philip W Lavori[j,k]*

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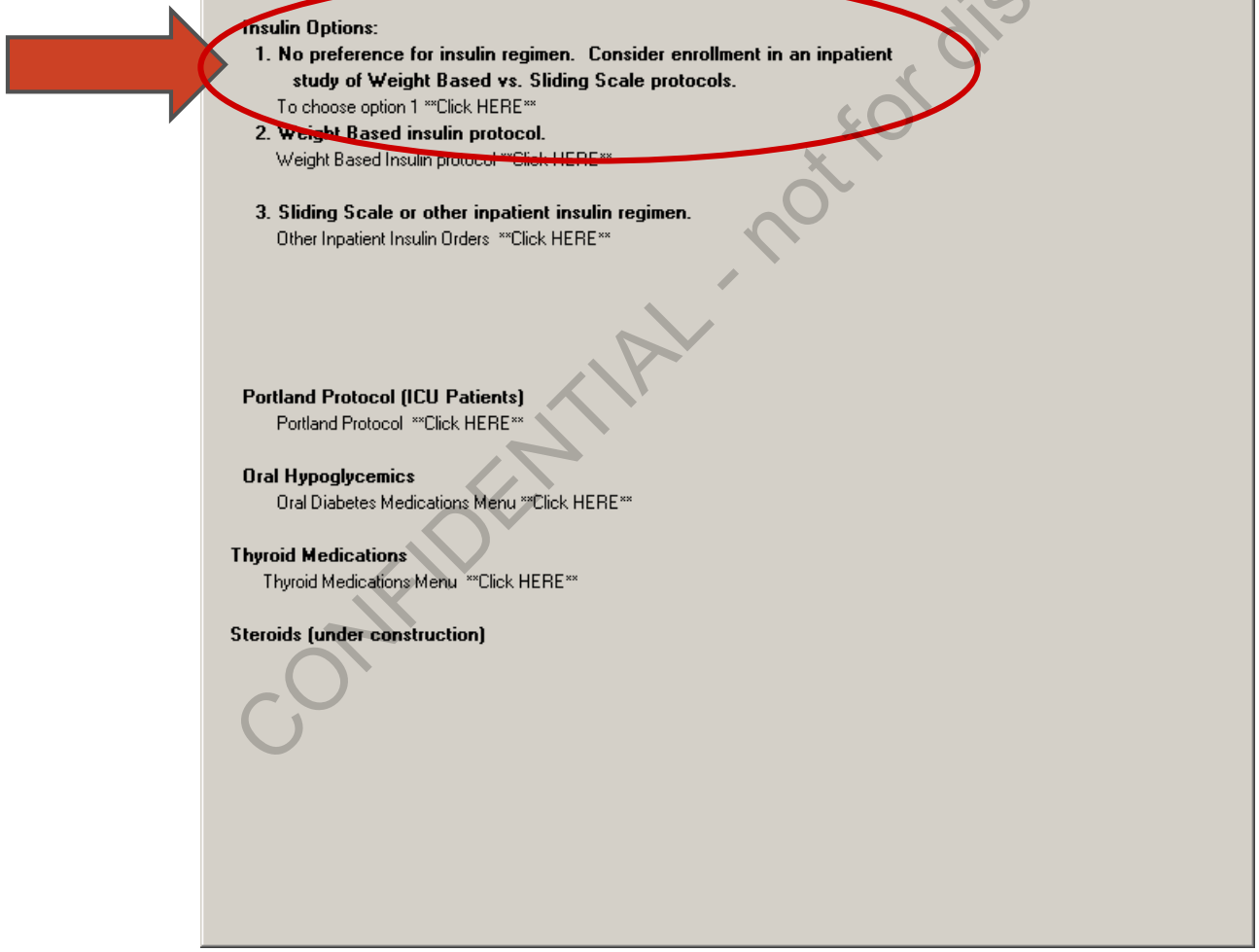
Clin Trials. 2011 Apr;8(2):183-95. doi: 10.1177/1740774510395635

# Use of EHR Application Layer

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Annals of Internal Medicine

IDEAS AND OPINIONS

# Chlorthalidone Versus Hydrochlorothiazide: A New Kind of Veterans Affairs Cooperative Study

Frank A. Lederle, MD; William C. Cushman, MD; Ryan E. Ferguson, ScD, MPH; Mary T. Brophy, MD, MPH; and Louis D. Fiore, MD, MPH

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Ann Intern Med. 2016 Nov 1;165(9):663-664. doi: 10.7326/M16-1208. Epub 2016 Sep 16.

# Spinal Stenosis Study

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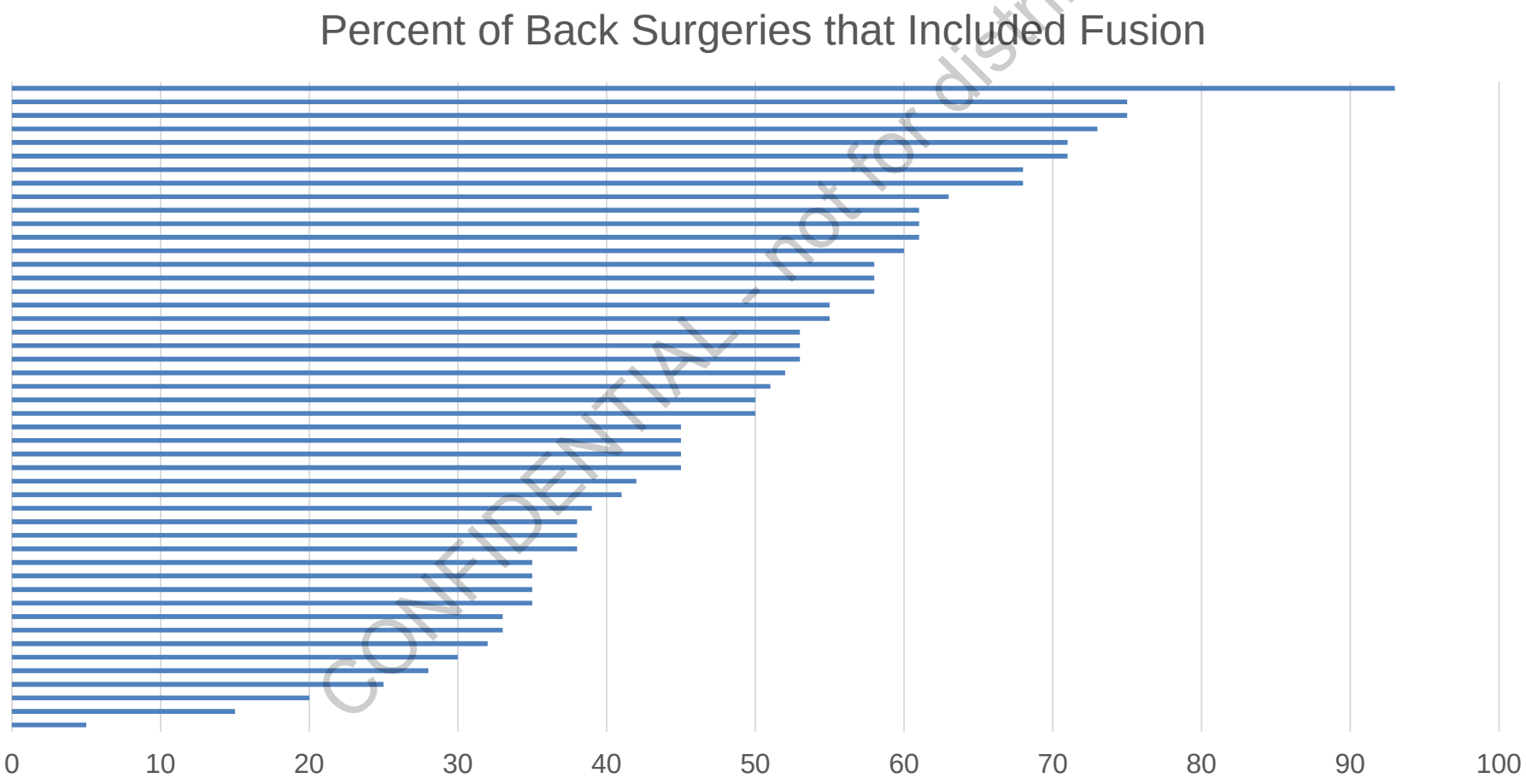
# Fusion Rate by VA Facility

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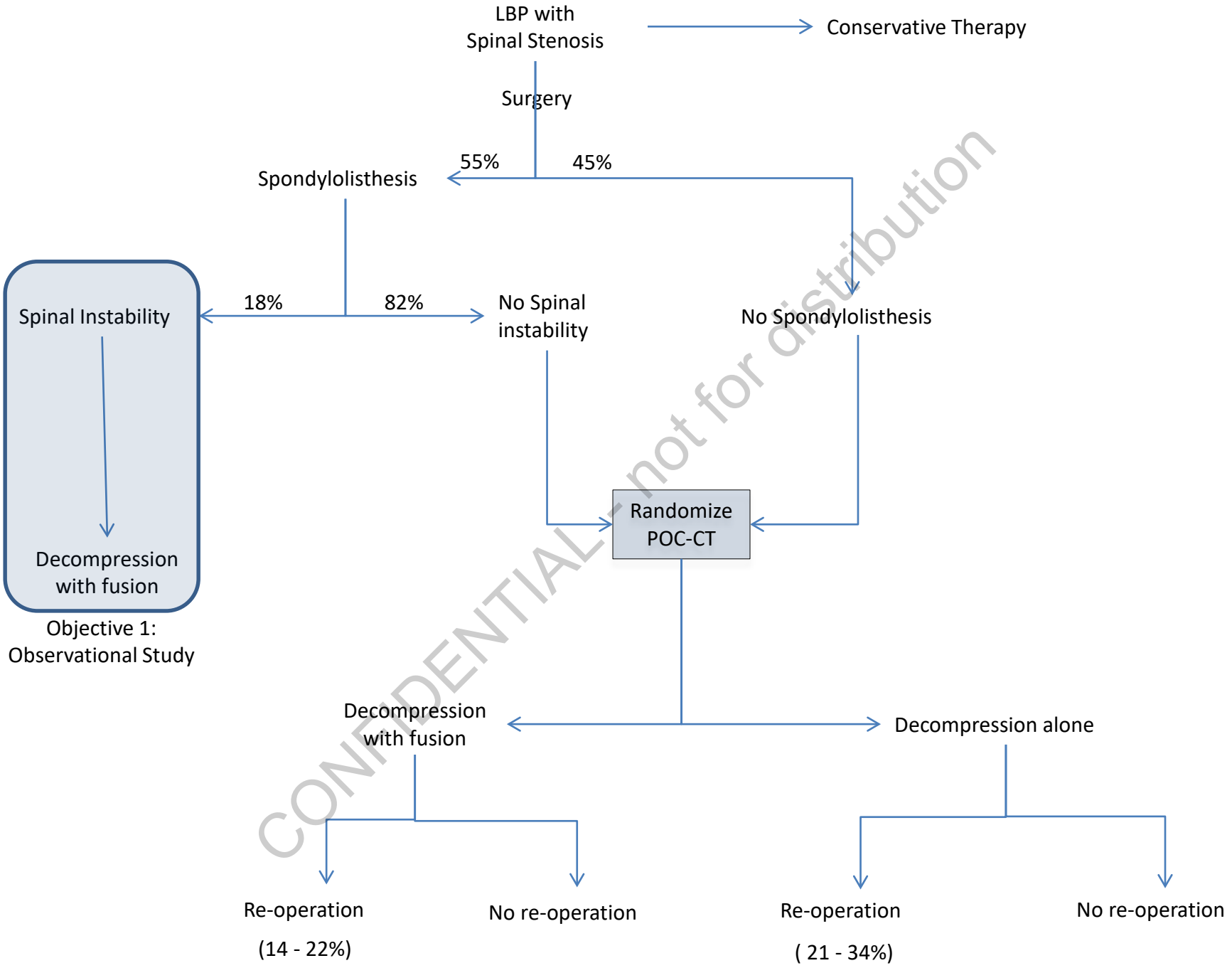


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# Spinal Stenosis Study Design Features

- Outcomes ascertained in randomized and non-randomized patients
- Surgical approach not controlled
- Continuous feedback of study results to healthcare providers
  - –Educational activity
- No inclusion/exclusion  criteria
  - –Evolving study population

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# Chapter 4: The Biomarker Story

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COMMENTARY

# Detours on the Road to Personalized Medicine

## Barriers to Biomarker Validation and Implementation

Louis D. Fiore, MD, MPH
Leonard William D'Avolio, PhD

### Current Clinical Research Models

For evaluation of most diagnostic tests and therapeutic interventions, studies with well-described, homogeneous populations of patients will usually suffice, and in trials involv-

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JAMA. 2011 Nov 2;306(17):1914-5. doi: 10.1001/jama.2011.1605.

nature genetics

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# Precision oncology for acute myeloid leukemia using a knowledge bank approach

Moritz Gerstung[1,2,9], Elli Papaemmanuil[1,3,9], Inigo Martincorena[1], Lars Bullinger[4], Verena I Gaidzik[4], Peter Paschka[4], Michael Heuser[5], Felicitas Thol[5], Niccolo Bolli[1,6], Peter Ganly[7], Arnold Ganser[5], Ultan McDermott[1], Konstanze Döhner[4], Richard F Schlenk[4], Hartmut Döhner[4,10] & Peter J Campbell[1,8,10]

**Underpinning the vision of precision medicine is the concept that causative mutations in a patient's cancer drive its biology and, by extension, its clinical features and treatment response. However, considerable between-patient heterogeneity in driver mutations complicates evidence-based personalization of cancer care. Here, by reanalyzing data from 1,540 patients**

the belief that therapeutic choices made on the basis of these causative events will be biologically sound. Applications of genomics in cancer medicine include enhanced diagnostic accuracy through molecular characterization, personalized forecasts of a patient's prognosis and support for choosing among different therapeutic options[3,4]. There are, however, complications to this narrative: only a few cancer

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# Learning Healthcare System Domains (Opportunities for Participation)

Quantification – Phenotyping and Biomarker qualification (Biobanking)

Computation – Data sharing and analysis platforms (Computer Science)

Knowledge Engineering – Translational models (Data Science)

Validation – Longitudinal observational studies and POC clinical trials

Implementation – Decision support platforms (Tumor Board Application)

Education – Training programs and knowledge dissemination

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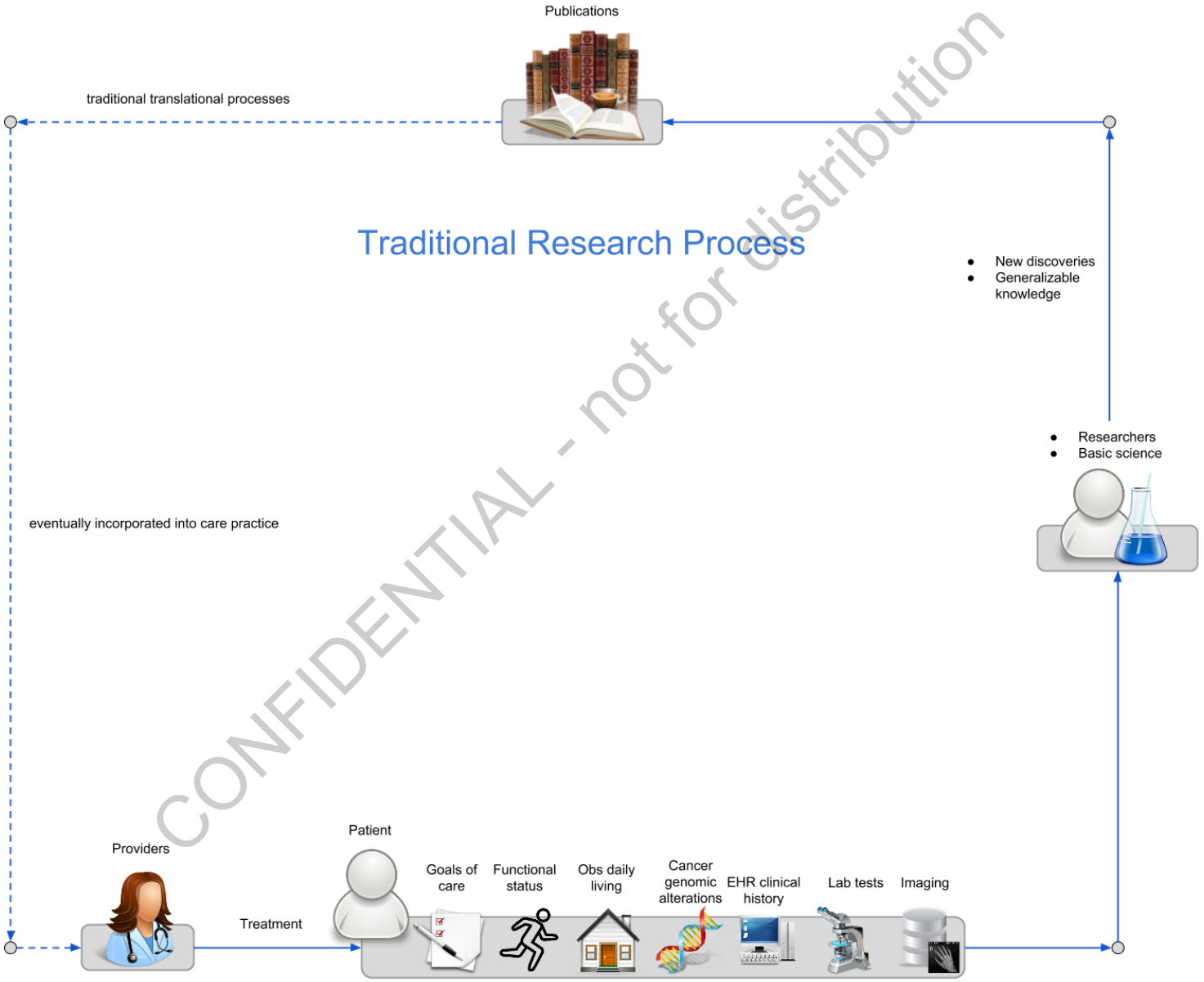
Adapted from:
Cohen Veterans Bioscience Programs: https://www.cohenveteransbioscience.org/programs/roadmap/

T2 gap

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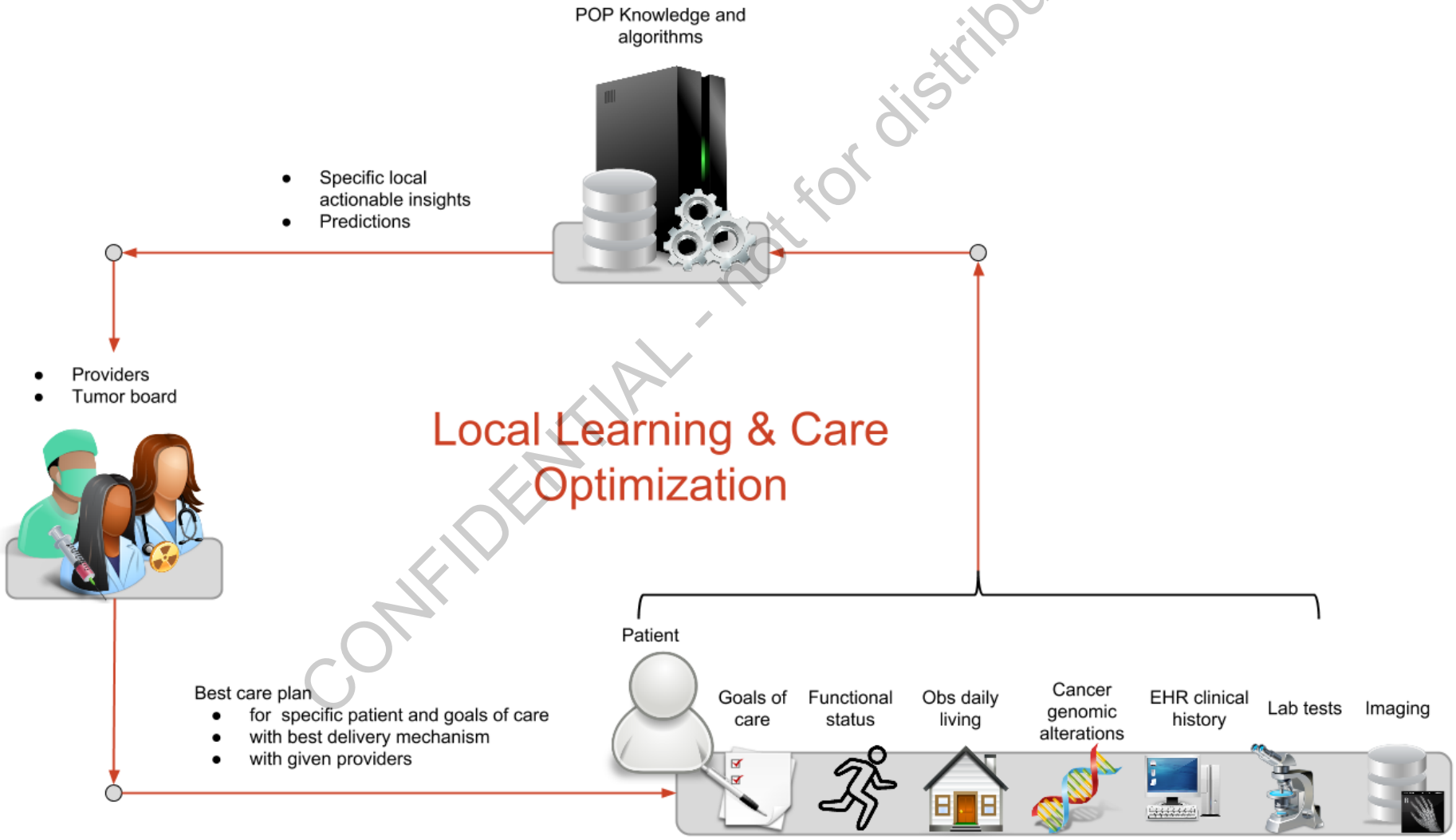
# Local Learning and Care Optimization

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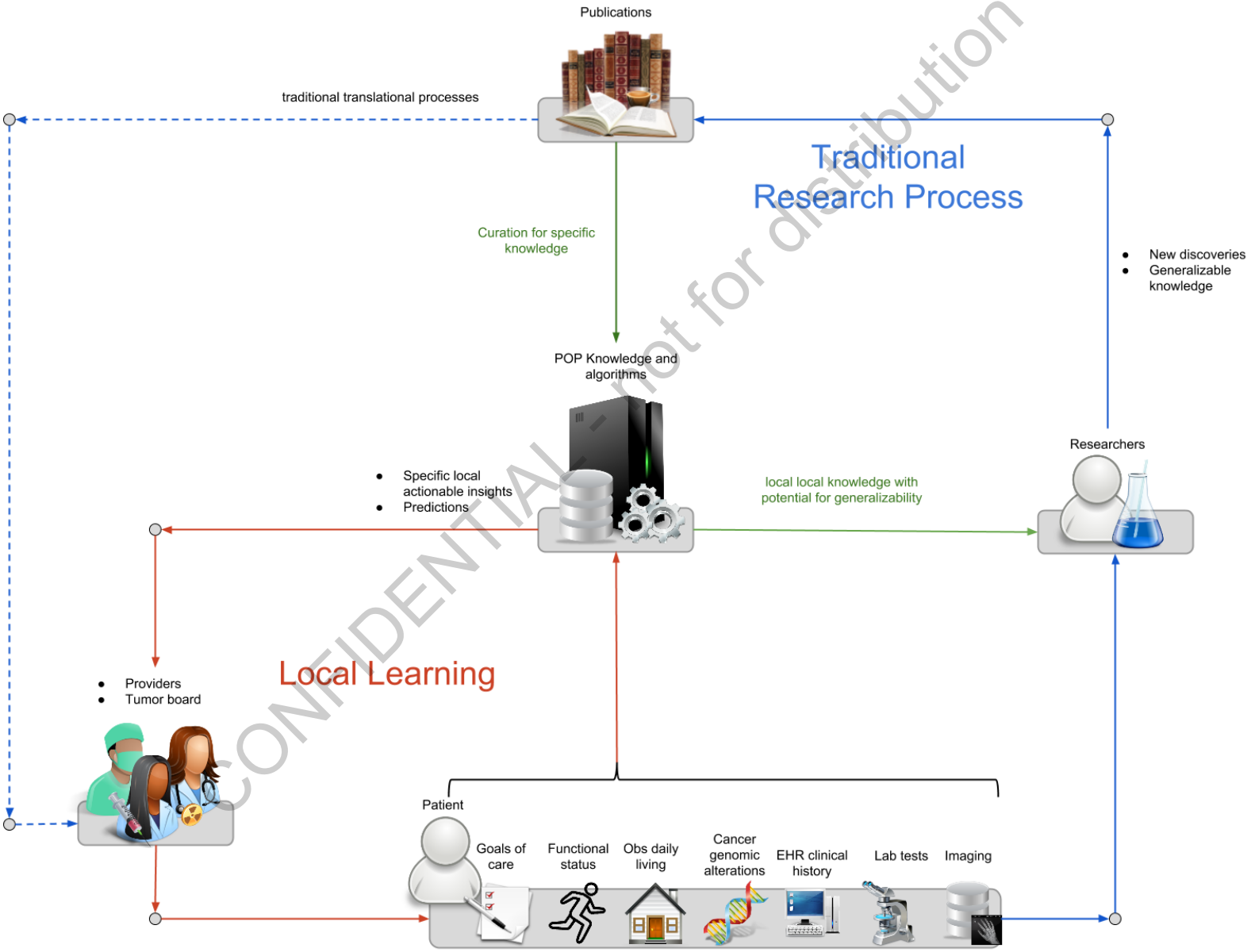


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# Chapter 5: The VA Precision Oncology Program

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# Implementation of a Precision Oncology Program as an Exemplar of a Learning Health Care System in the VA

Louis Fiore, MD, MPH; Ryan E. Ferguson, PhD, ScD, MPH; Mary Brophy, MD, MPH; Valmeek Kudesia, MD, MS; Colleen Shannon, MPH; Andy Zimolzak, MD, MMSc; Karen Pierce-Murray, RN; Sara Turek, MPH; and Philip Lavori, PhD

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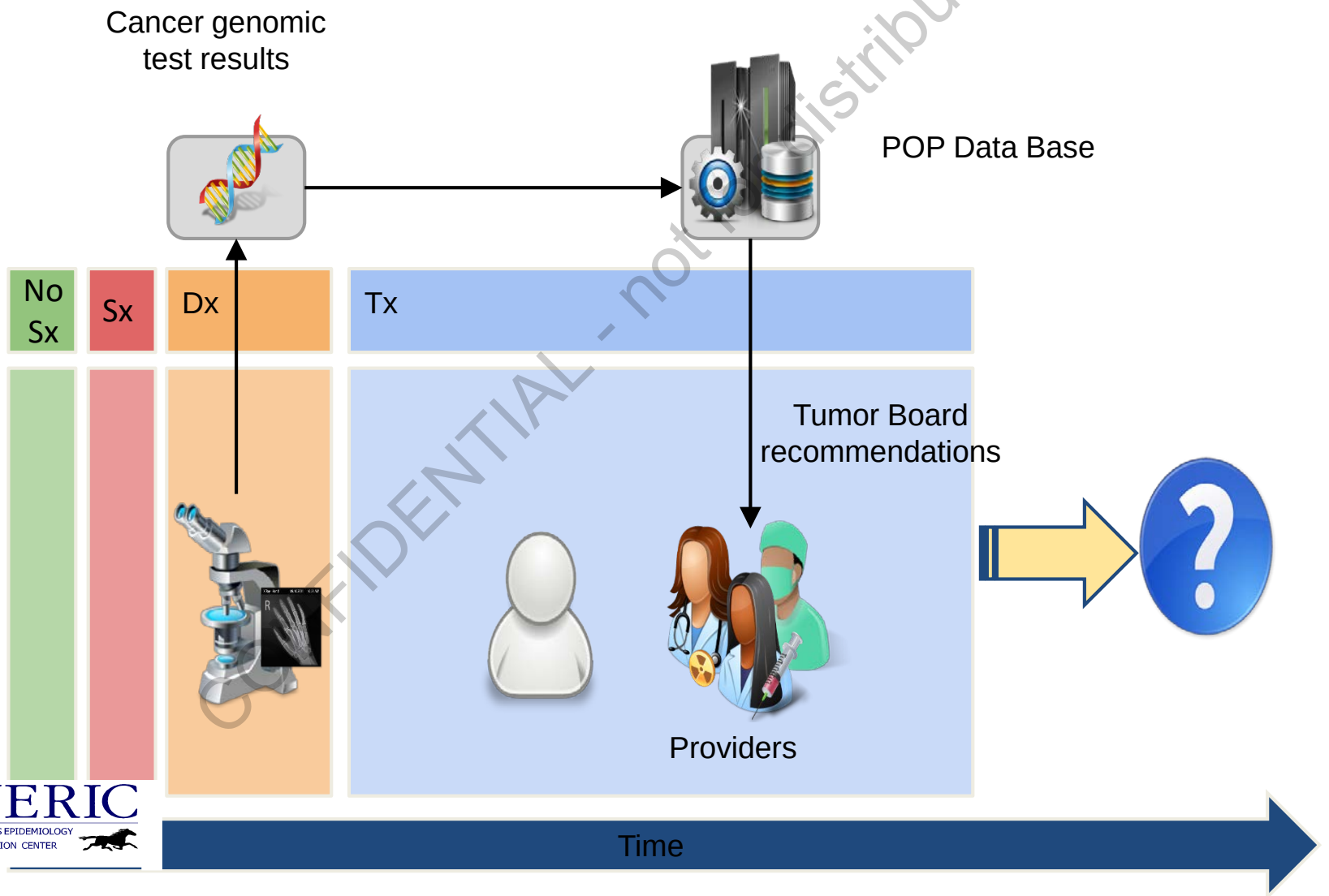
Fed Pract. 2016 February;33(suppl 1):26S-30S

# Current 'Local Learning'

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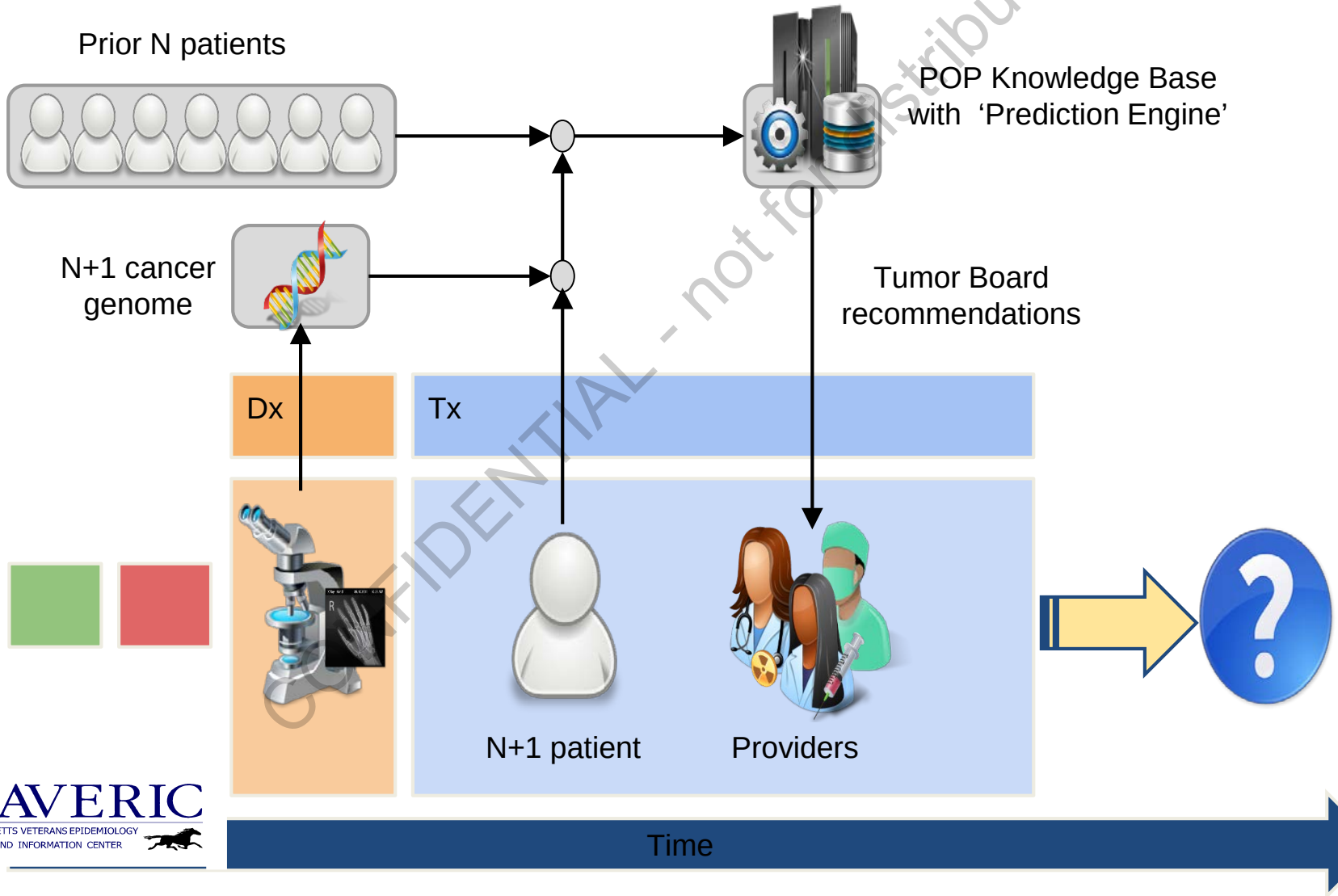
# Local Learning Through Observations

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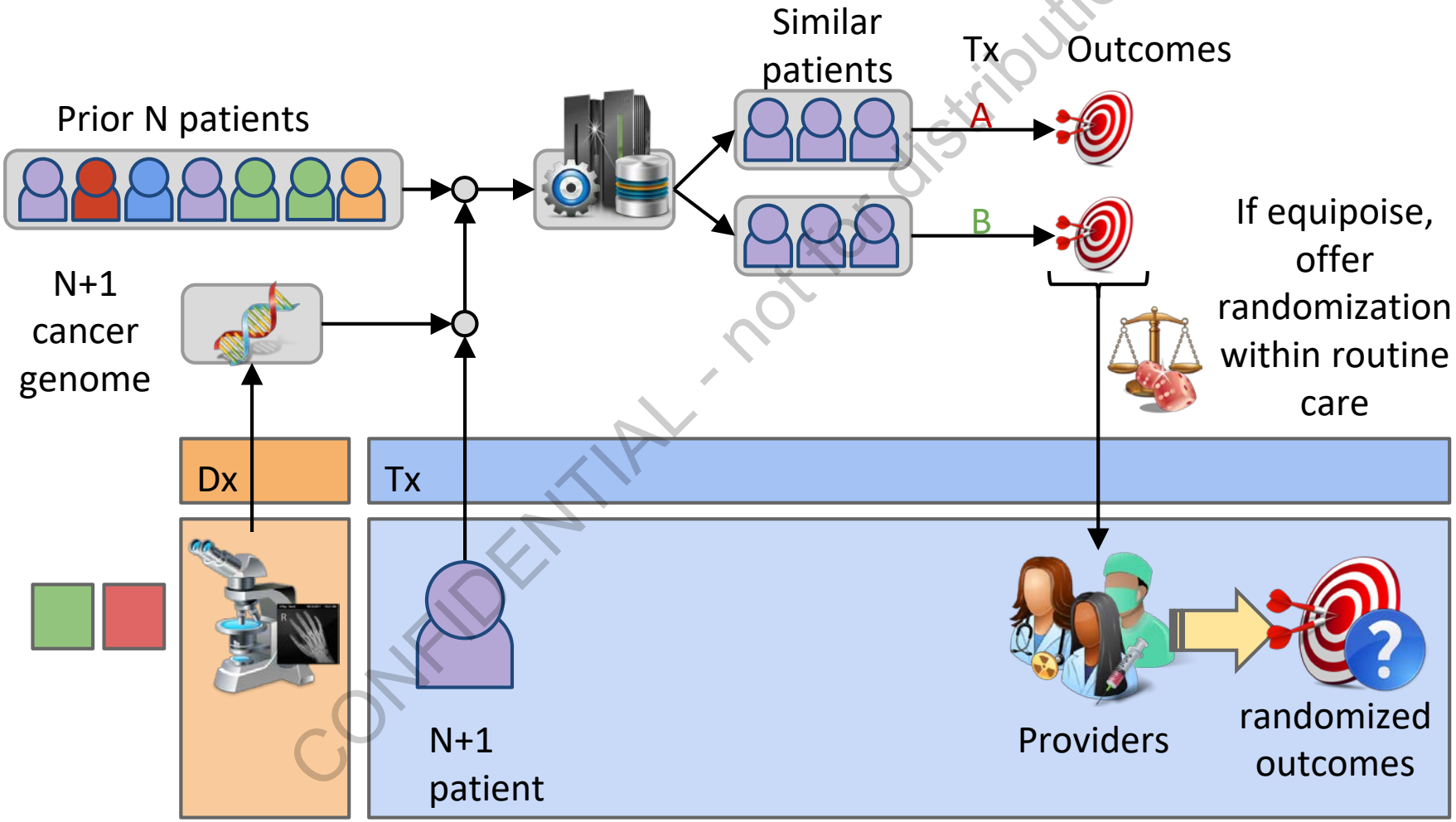
# Local Learning Through Experiments

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U.S. Department of Veterans Affairs

# Precision Oncology Program

*Precision cancer care as unique as your DNA*

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## The Crossroads of Clinical Care and Research

Louis Fiore
Mary Brophy

# Precision Oncology

- Individual patient tumor tissue is molecularly profiled
- Cancer treatment guided by results of the profile
- Therapies are less toxic, potentially more effective
- Molecular profiling and targeted therapies are expensive and benefit unsure

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# The VA National Precision Oncology Program

- Turnkey processes established for molecular profiling
- National contracts to reduce costs
- Consultation service to assist clinicians
- New drugs made available to patients through research partnerships
- Patient data aggregated for learning and research purposes

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# Goals

- Define and disseminate precision oncology best practices
- Provide standardized high quality care
  - –Reduce disparities
  - –Facilitate providers
  - –Engage patients
- Utilize program data to:
  - –Understand cost and effectiveness
  - –Generate knowledge on what works and what does not
  - –Provide opportunities for clinical trial participation
  - –Realize economies of scale for laboratory and drug costs

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# Learning and Research in POP

- Codependence of clinical care and research programs
  - –Molecular profile has value only if targeted therapies exist
  - –Targeted therapy development requires access to patients who have been profiled
- Heterogeneity introduced by categorization of patents based on their molecular profiles results in:
  - –Difficulties in learning through experience in a high dimensional space
  - –Recruitment barriers for clinical trials that enroll based on specific molecular profiles
  - –Need for a large numbers of patients to acquire knowledge

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# Traditional Research Opportunities

- Creation of a clinical data repository to include patient demographics and self reported data, tumor features and molecular profile results, treatments, outcomes
- Intramural and sponsored clinical trials opened nationally to enable broad patient access
  - –Structure provided by the VA Cooperative Studies Program and the Central IRB
  - –Intellectual capital provided by VA clinicians and external stakeholders
  - –Clinical trials encouraged as the standard of care in VA
  - –Patients matched to clinical trials through data repository
- Appeal to potential sponsors of partners
  - –Rapid enrollment into clinical trials due to size of the VA
  - –Cost effective participation given VA infrastructure and programs
  - –Potential for participation in Cancer Moonshot Programs

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# Rapid Learning Opportunities

- Analytics applied to the data repository predict expected outcomes for patients based on past experience
- This knowledge is used by providers, tumor boards, researchers and Program sponsors for:
  - –Decision support
  - –Practice guidelines refinement
  - –Determination of Program effectiveness
  - –For publication if knowledge is generalizable

*The POP is an exemplar of a "Learning Healthcare System" where traditional clinical and research silos are replaced by systematic learning using scientific methodology in the clinical care ecosystem*

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# Beneficiaries

- VA Patients - State-of-the-art cancer care is delivered in a standardized fashion nationally without geographical disparity
- VA Cancer Care Providers – Burden is reduced by centralization of operational activities including facilitated access to novel therapeutics
- VA Healthcare System – Delivers the “Best Care Anywhere” with cost and benefit insight to facilitate ‘business intelligence’ management
- Pharma – Patients are matched to clinical trials nationally to accelerate the pace of clinical trial execution
- NCI and other basic scientists – The data repository and virtual tissue bank can be mined for scientific discovery and validation
- Non-VA Healthcare Networks – Generalizable knowledge generated is shared through publications

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# Players and Stakeholders

- VHA Leadership – Maintain highest quality of care within VA
- VHA Clinical Care Services – Facilitate providers and offer research opportunities for patients
- VHA Cooperative Studies Program – Provides clinical trial infrastructure, support and intellectual input
- Pharma – Supply emerging targeted and immunotherapies
- NCI – Sponsored researchers can re-use artifacts of the Program
- FDA – New models of clinical trial enrollment can be studied such as ‘Distributed Enrollment’ and ‘Point of Care’ studies
- Non-VA Healthcare Systems – Through participation in VA sponsored research activities

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# Barriers

- Slow adoption of Precision Oncology by the clinical community
  - –Overcome by establishment of best practices, creation of centralized work processes to facilitate implementation, and provision of access to novel therapeutics
- Medical center support
  - –Funding for tumor sequencing and program implementation must be recognized as clinical responsibilities
- Research community “Balkanization”
  - –Researchers must collaborate on efforts and share resources (data) to enhance healthcare while creating generalizable knowledge
- Current clinical trial regulatory and operational bottlenecks
  - –Novel approaches are required in an era of more effective or less toxic therapies and smaller eligible patient sample sizes

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