The Role of Informatics in the Era of Precision Medicine

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Berlin, Germany

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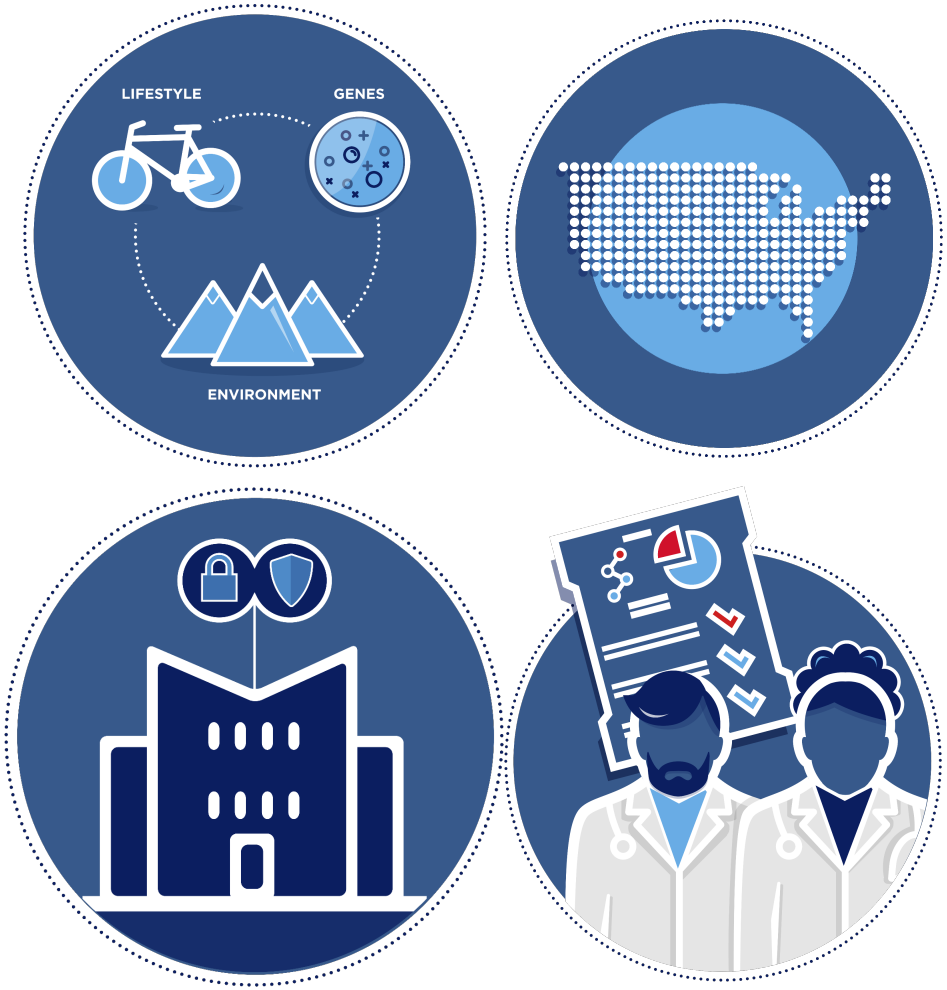
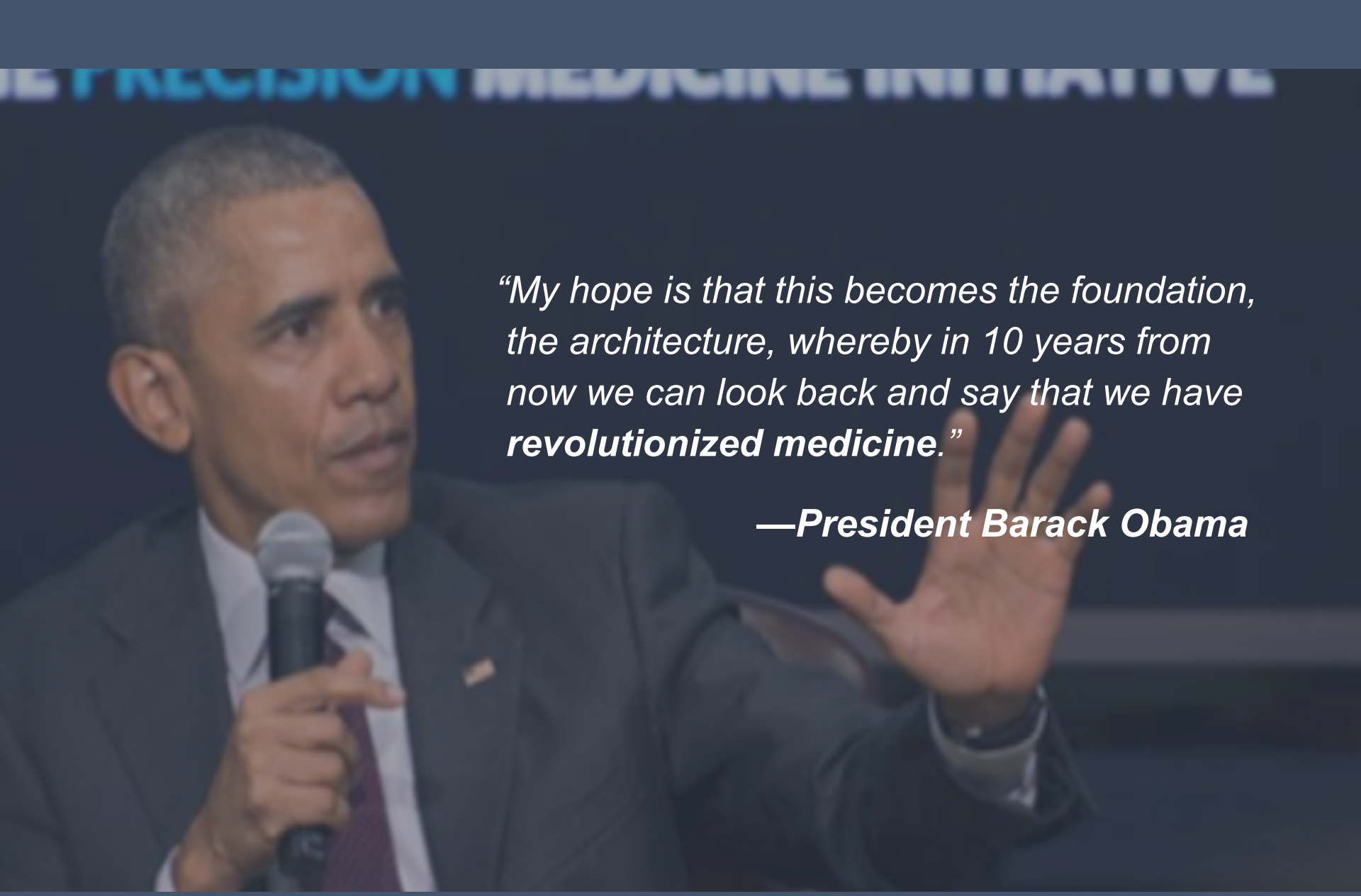
What is Precision Medicine?

- **Precision medicine** is an emerging approach for disease treatment and prevention that takes into account individual variability in lifestyle, environment, and genes.
- It is a radical shift in how each of us can receive the best care possible based on our unique makeup.



The Precision Medicine Initiative (PMI®)

- Announced by President Barack Obama in his 2015 State of the Union address
- **MISSION:** To enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized care



*"My hope is that this becomes the foundation, the architecture, whereby in 10 years from now we can look back and say that we have **revolutionized medicine**."*

—President Barack Obama

The *All of Us*℠ Research Program

- The cornerstone of the larger PMI – led by the NIH
- One million or more volunteers, reflecting the broad diversity of the U.S.
- Opportunities for volunteers to provide data on an ongoing basis
- Data shared freely and rapidly to inform a variety of research studies

All of Us℠ THE FUTURE OF HEALTH BEGINS WITH YOU | The Precision Medicine Initiative®

PMI Budget for the *All of Us*℠ Research Program

$130M

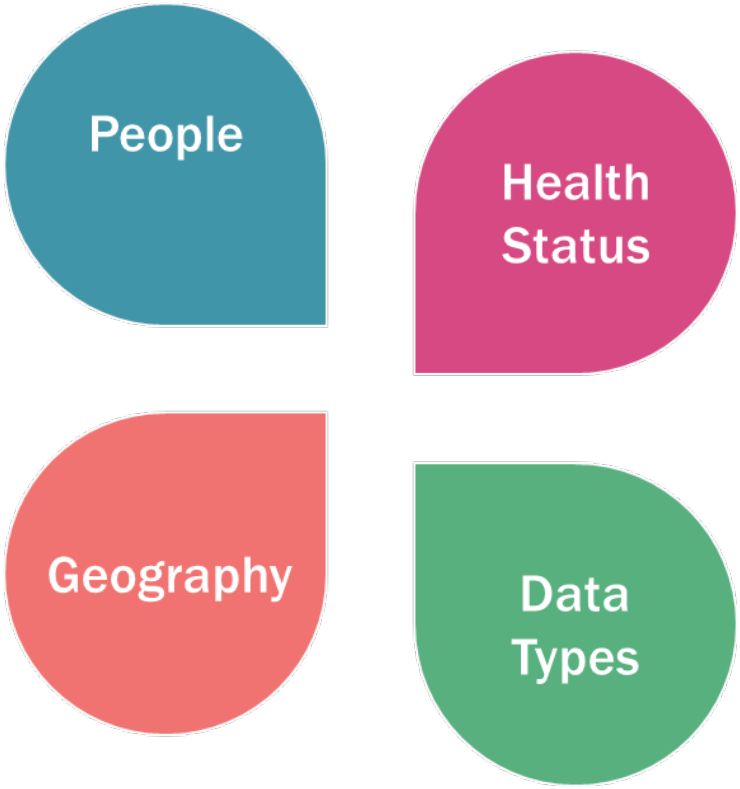
FY16 ENACTED

$230M

FY17 PRESIDENT'S REQUEST

A Transformational Approach to Diversity

- Reflecting the country's rich diversity to produce meaningful health outcomes for historically underrepresented communities

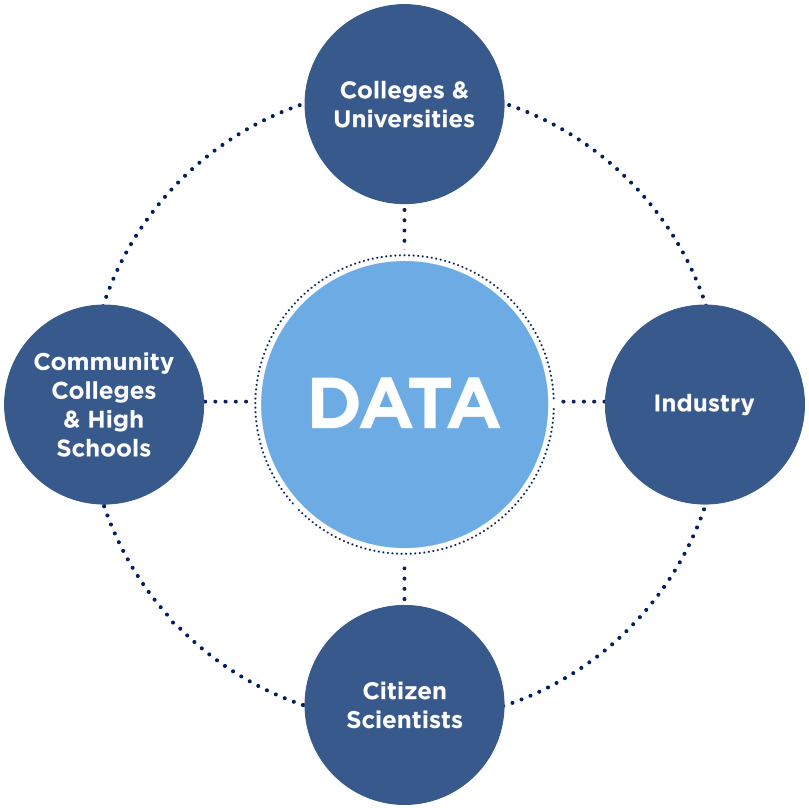


A Transformational Approach to Participation

- Participants in the *All of Us*℠ Research Program will be true partners—not patients, not subjects—in the research process
- Involved in every step of program development
  - What data we collect
  - What lab analyses we do
  - What research is conducted
  - How data gets returned

A Transformational Approach to Data Access

- Data sharing will be swift to both researchers and participants
- Participants will have access to study information and data about themselves
- Data collection will start small and will grow over time
- Privacy and security will adhere to the highest standards
- Will invest to level the playing field so diverse researchers can play



All of Us℠ Research Program Data

- The Program will start by collecting a limited set of standardized data from sources that will include:
  - Participant questionnaires
  - Electronic health records
  - A baseline physical evaluation
  - Biospecimens (blood and urine samples)
  - Mobile/wearable technologies
  - Geospatial/environmental data
- Data types will grow and evolve with science, technology, and trust.

Selected Scientific Opportunities

- Develop quantitative **estimates of risk** for a range of diseases by integrating environmental exposures and genetic factors.
- Identify the causes of individual variation in response to commonly used therapeutics = **pharmacogenomics.**
- Discover **biological markers** that signal increased or decreased risk of developing common diseases.
- Develop **solutions to health disparities.**
- Use **mobile health technologies** to correlate activity, physiological measures, and environmental exposures with health outcomes.
- Empower **study participants** with data and information to improve their own health.
- Create a platform to enable **trials of targeted therapies.**

Established Program Infrastructure

DATA AND RESEARCH SUPPORT CENTER (DRC)

Vanderbilt University Medical Center
with the Broad Institute and Verily

BIOBANK

Mayo Clinic

PARTICIPANT TECHNOLOGIES CENTER (PTC)

Scripps Research Institute
with Vibrent Health

HEALTH CARE PROVIDER ORGANIZATIONS (HPOs)

Regional Medical Centers, Health Centers
(including Federally Qualified Health Center pilots),
VA Medical Centers

HPOs: Regional Medical Centers (RMCs)

- Able to enroll diverse patient populations
- Strong electronic health record capacity
- Geographic spread
- Capacity to enroll 35,000 a year

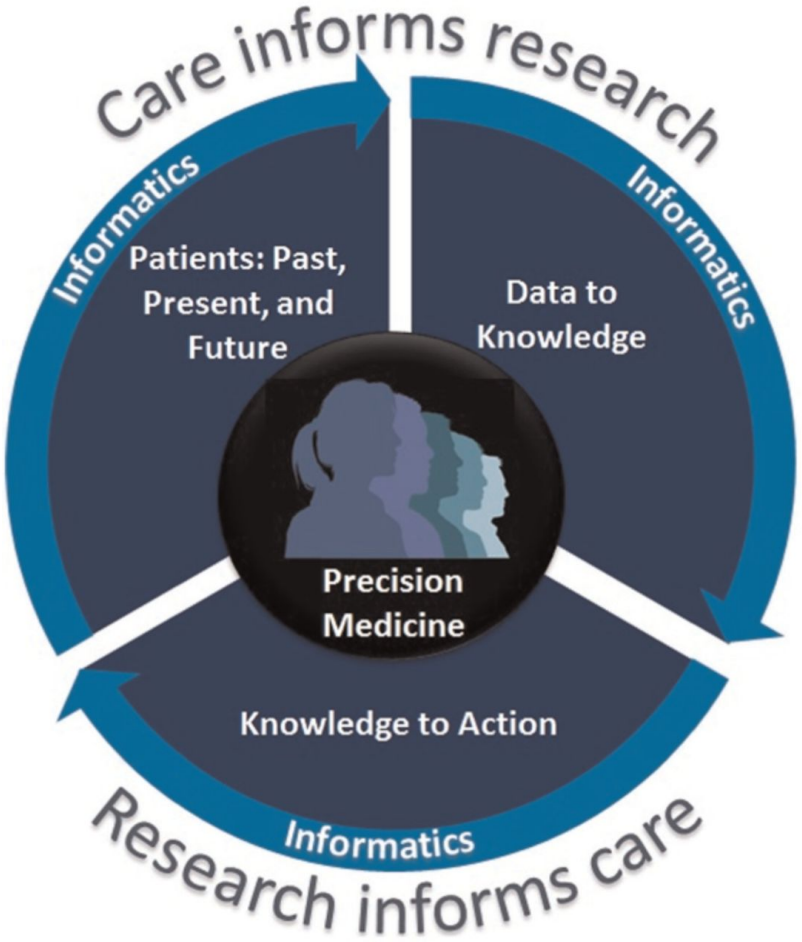
HPOs: Federally Qualified Health Centers (FQHCs) – Pilot Sites

- Develop and pilot health center approaches for enrolling underserved populations, especially those historically underrepresented in biomedical research
- A collaboration with the Health Resources and Services Administration (HRSA) and the MITRE Corporation

HPOs: Veterans Affairs (VA) Medical Centers

- Invite veterans to enroll in the *All of Us*℠ Research Program at participating VA medical centers
- A collaboration with the Department of Veterans Affairs and the Million Veteran Program, a national, voluntary research program studying how genes affect health
- 20 participating sites anticipated

Role of informatics in PMI®



[Tenenbaum et al. JAMIA 2016]

Key informatics research agenda for PMI®

1. Facilitate electronic consent and specimen tracking
   - Machine-readable, and standardized consent forms
   - Infrastructure to enable participant engagement after enrollment
   - Infrastructure to perform role-based distributed queries over cohorts and sample collections

[Tenenbaum et al. JAMIA 2016]

Key informatics research agenda for PMI®

2. Develop and deploy standards for data privacy, security and integrity
   - Methods for de-identification, encryption and sharing of genomic and personal health record data
     - EHR data sharing is even more rare
   - Privacy-preserving data mining and computation
   - Mechanisms and policies for addressing data breach

[Tenenbaum et al. JAMIA 2016]

Key informatics research agenda for PMI®

3. Develop and deploy standards for data integration and exchange
   - Don't create more standards…re-use and expand existing ones
   - EHR and other clinical data mapped to common data models
     - Expand to include omics, environmental and social data
   - Federated querying capabilities
   - Sharing of health care data

[Tenenbaum et al. JAMIA 2016]

Key informatics research agenda for PMI®

4. Advance methods for biomarker discovery and translation
   - Computational phenotyping
     - Standardized phenotype definitions
   - Functional characterization of genes and pathways related to the biomarker for clinical utility
   - Variant annotations with actionable clinical information
   - Frameworks for evaluating clinical actionability

[Tenenbaum et al. JAMIA 2016]

Key informatics research agenda for PMI®

5. Processes and protocols for capturing and exchanging metadata and data provenance
   - Tools that enable implementation of standard operating procedures (SOPs) for data processing, analysis, and interpretation
   - Policies for responsible, reproducible, and reusable science
   - Metadata management capabilities for research protocols, databases, software code etc.

[Tenenbaum et al. JAMIA 2016]

Key informatics research agenda for PMI®

6. Build a precision medicine knowledge base
   - Comprehensive knowledge base that contains information about disease subtypes, disease risk, diagnosis, therapy, and prognosis
   - Machine- and human-readable representation
   - Federated querying and inferencing
   - New methodologies for updating and maintaining the integrated knowledge base

[Tenenbaum et al. JAMIA 2016]

Key informatics research agenda for PMI®

7. Enhance EHRs to promote precision medicine
   - Computational phenotyping
   - Integrate discrete genomic findings and interpretations in machine-readable format
   - Clinical decision support knowledge base for genome-based risk predictions, prognoses, and drug-dosing at the point of care
   - Patient portal and return of results

[Tenenbaum et al. JAMIA 2016]

Key informatics research agenda for PMI®

8. Facilitate consumer engagement
   - Collect information about person's environment and lifestyle choices
   - Address ethical, legal and social issues on data use and re-use

[Tenenbaum et al. JAMIA 2016]

Precision Medicine Informatics activities at Weill Cornell Medicine

EHR-driven phenotyping

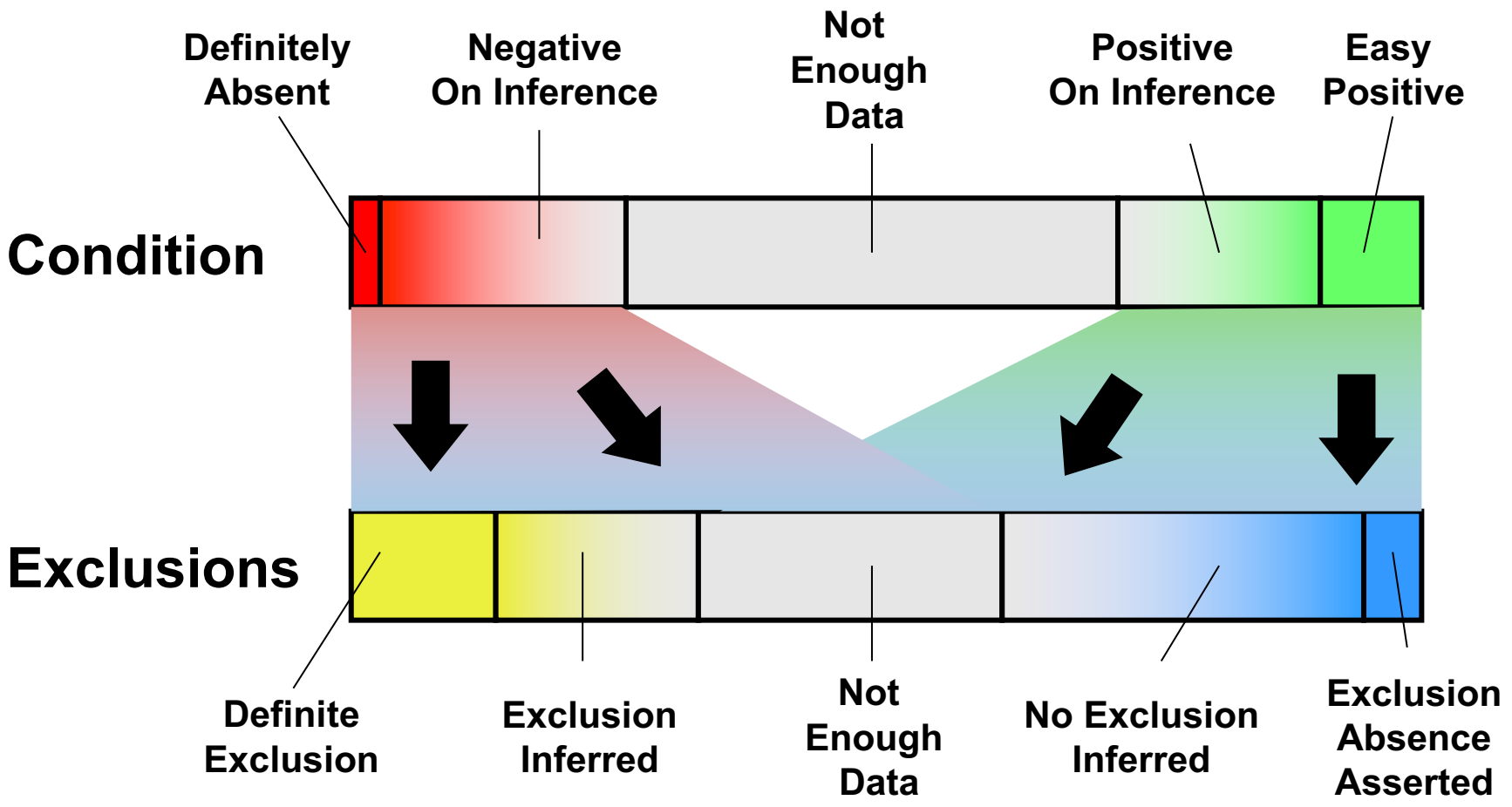
- Goal: To develop high-throughput semi-automated techniques and algorithms that operate on normalized EHR data to identify cohorts of potentially eligible subjects on the basis of disease, symptoms, or related findings

- Application areas:
  - Biomarker discovery
  - Quality reporting
  - Clinical decision support
  - Clinical trial recruitment

What is the goal of Phenotyping?

Maximize # subjects with accuracy

Common phenotypes → PPV
Rare phenotypes → Sensitivity with reasonable PPV

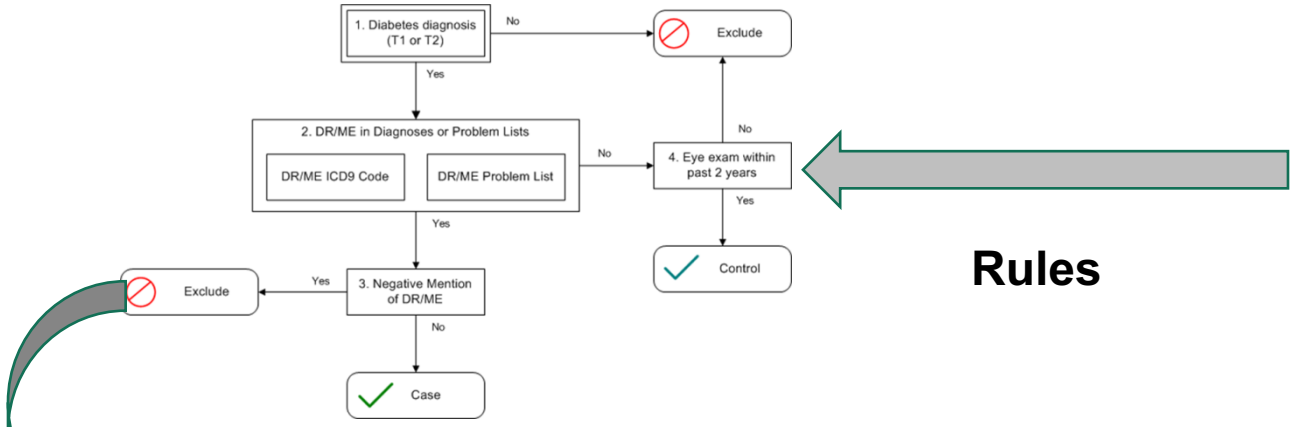


EHR-driven Phenotyping Algorithms - I

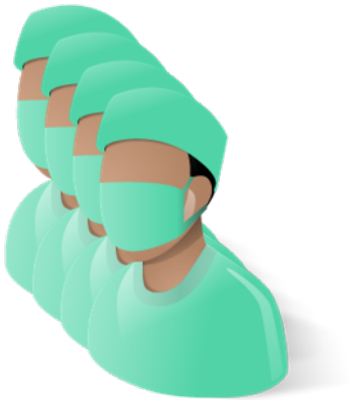
- Typical components
  - Billing and diagnoses codes
  - Procedure codes
  - Labs
  - Medications
  - Phenotype-specific co-variates (e.g., Demographics, Vitals, Smoking Status, CASI scores)
  - Pathology
  - Radiology
- Organized into inclusion and exclusion criteria

[eMERGE Network]

EHR-driven Phenotyping Algorithms - II



Rules



Phenotype Algorithm

Evaluation

Visualization

Transform

Transform

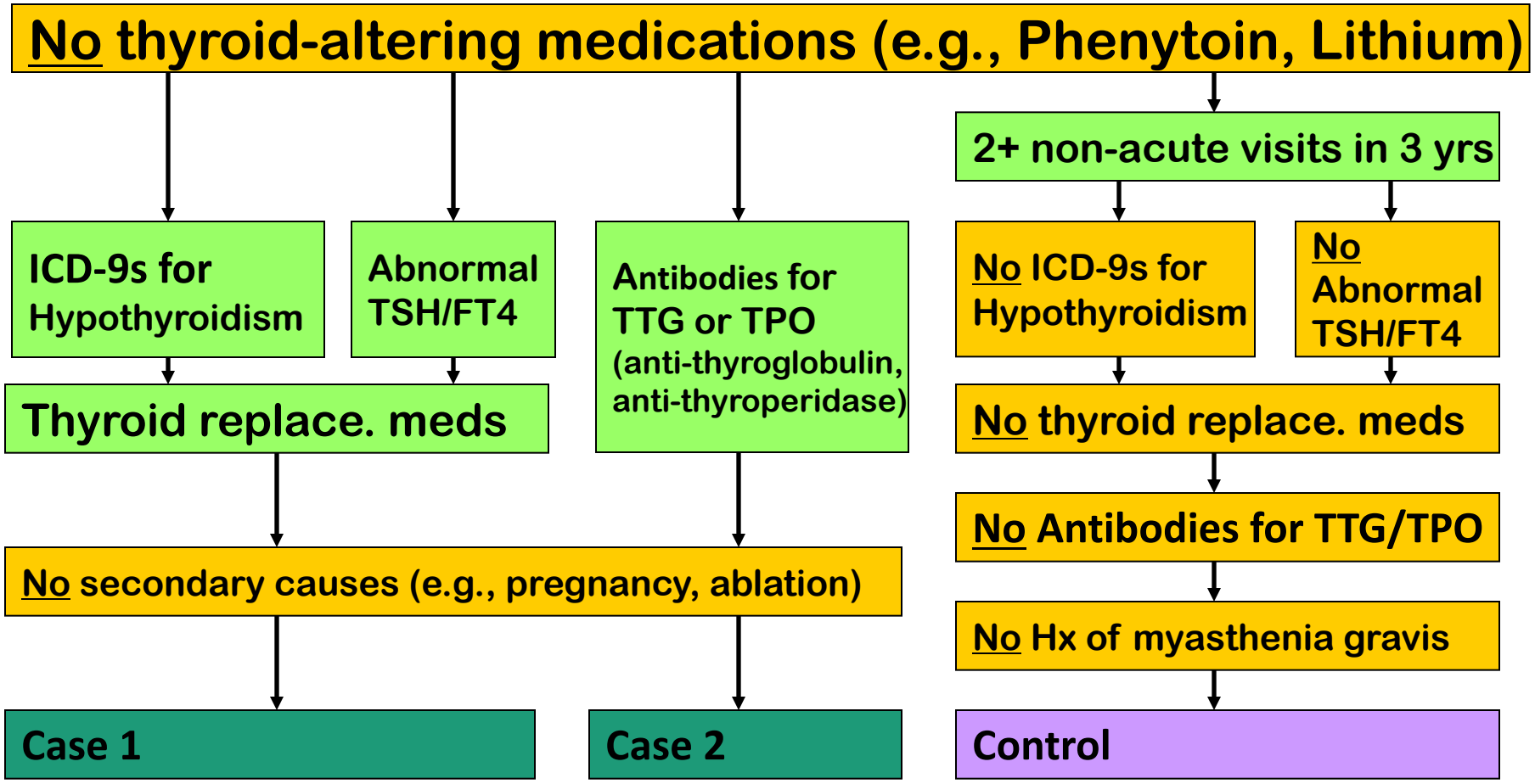
Data

Mappings

NLP, SQL

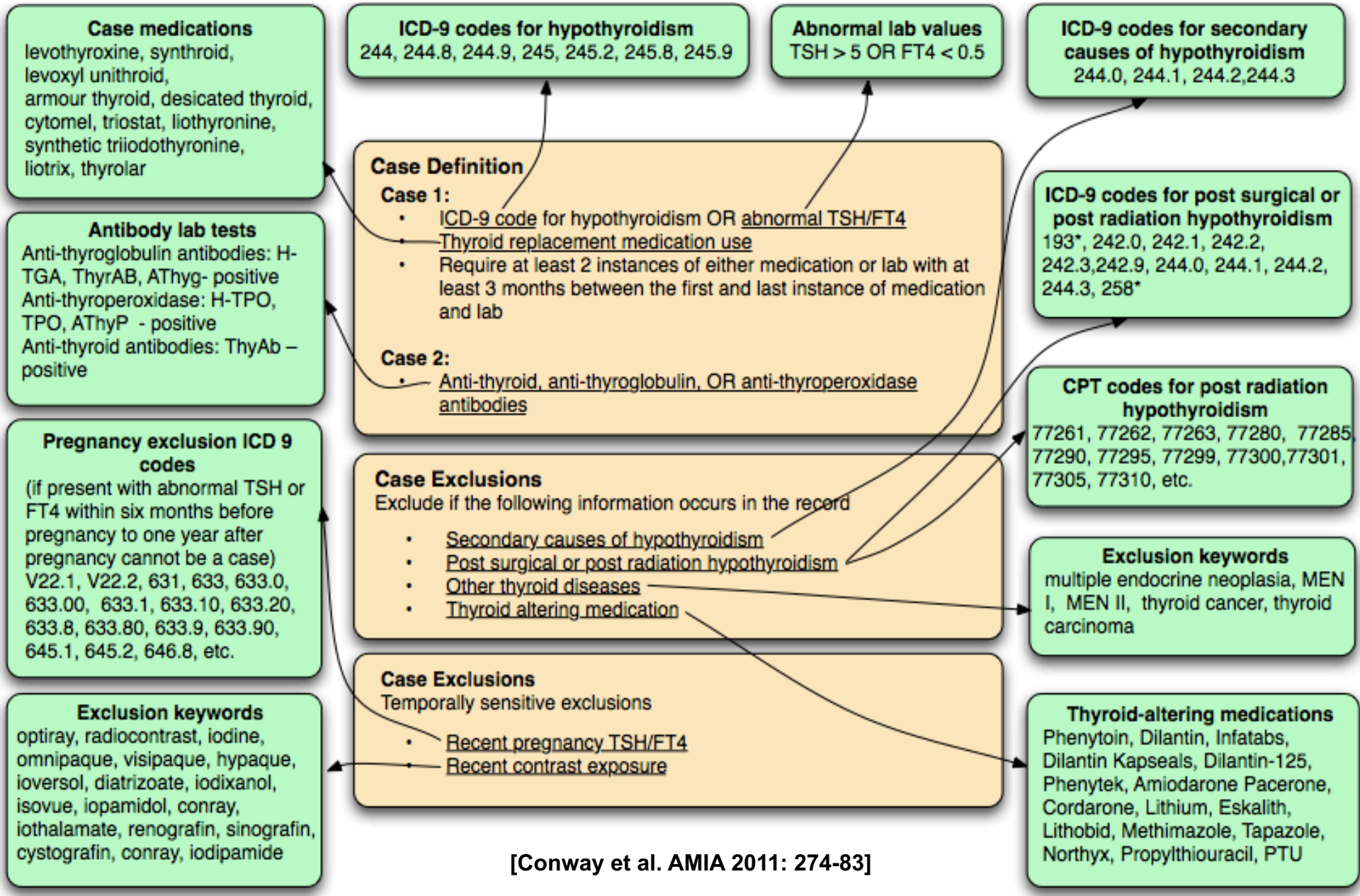
[eMERGE Network]

Example: Hypothyroidism Algorithm



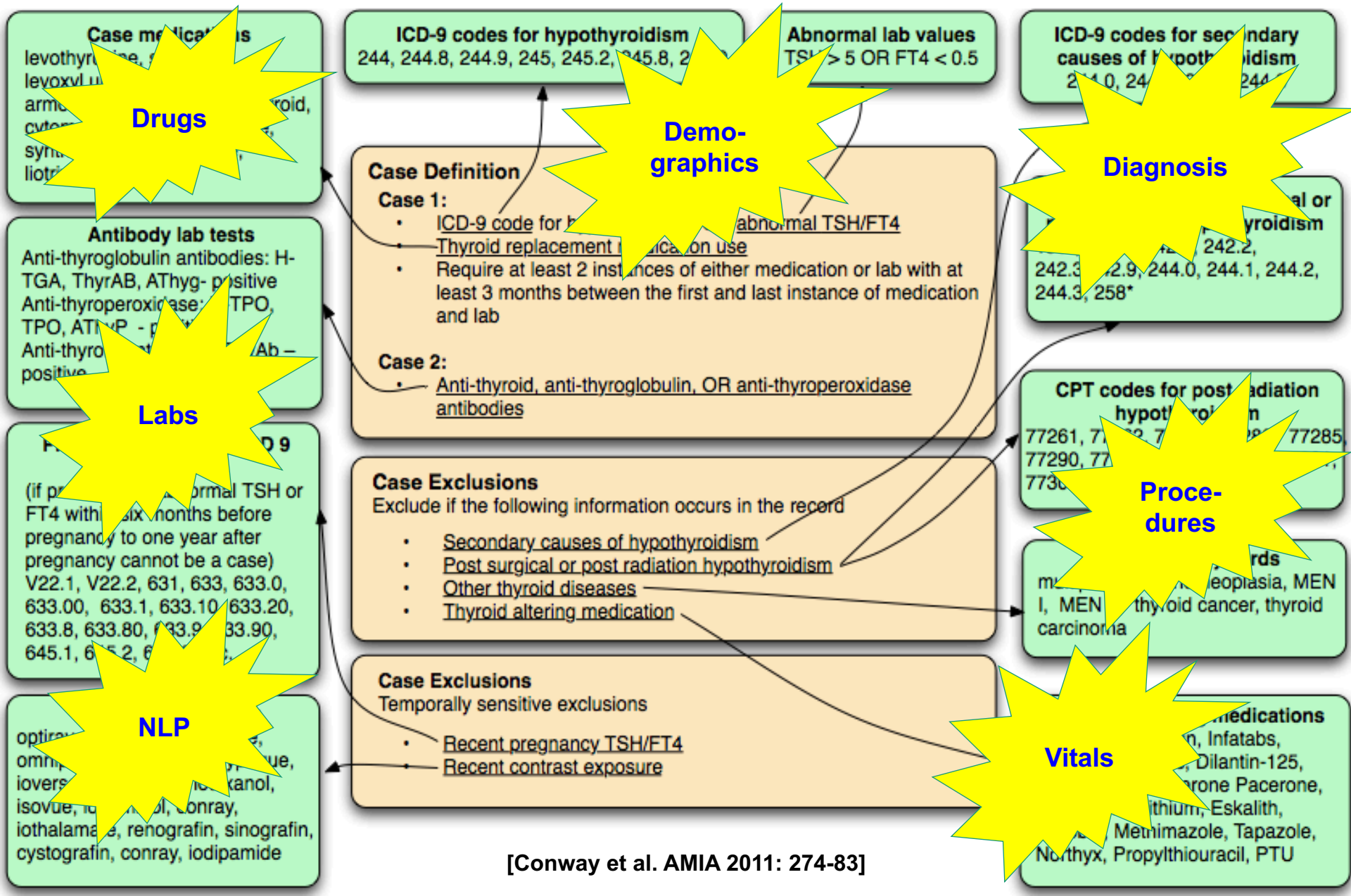
[Denny et al., ASHG, 2012; 89:529-542]

Example: Hypothyroidism Algorithm



[Conway et al. AMIA 2011: 274-83]

Example: Hypothyroidism Algorithm

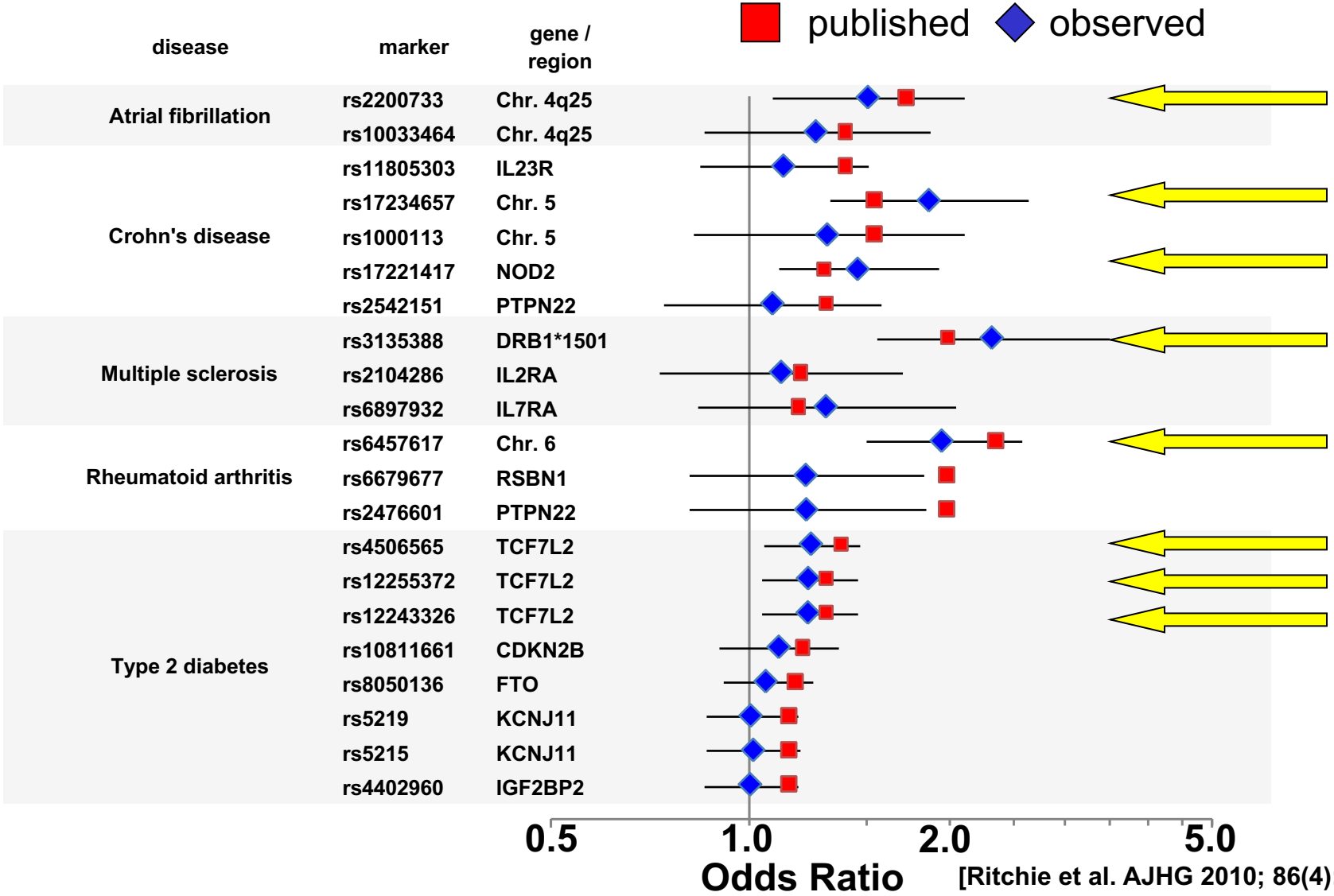


[Conway et al. AMIA 2011: 274-83]

Phenotyping Algorithms	Data Categories used to define EHR-driven Phenotyping Algorithms			
	Clinical gold standard	**EHR-derived phenotype**	**Validation (PPV/NPV)**	**Sensitivity (Case/Cntrl)**
Alzheimer's Dementia	Demographics, clinical examination of mental status, histopathologic examination	Diagnoses, medications	73%/55%	37.1%/99%
Cataracts	Clinical exam finding (Ophthalmologic examination)	Diagnoses, procedure codes	98%/98%	99.1%/93.6%
Peripheral Arterial Disease	Clinical exam finding (ankle-brachial index or arteriography)	Diagnoses, procedure codes, medications, radiology test results	94%/99%	85.5%/81.6%
Type 2 Diabetes	Laboratory Tests	Diagnoses, laboratory tests, medications	98%/100%	100%/100%
Cardiac Conduction	ECG measurements	ECG report results	97% (case only algorithm)	96.9% (case only algorithm)

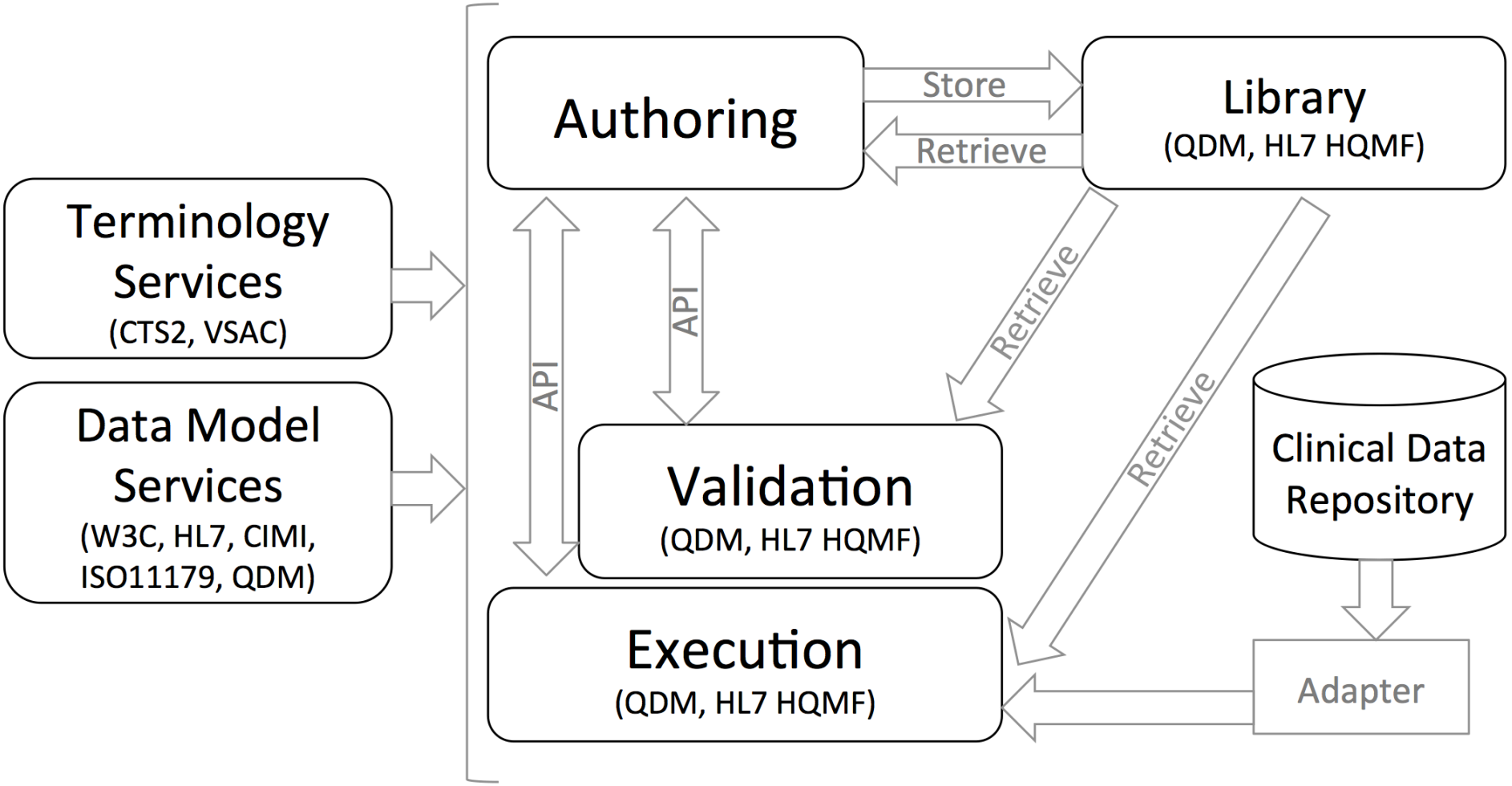
[eMERGE Network]

Genotype-Phenotype Association Results



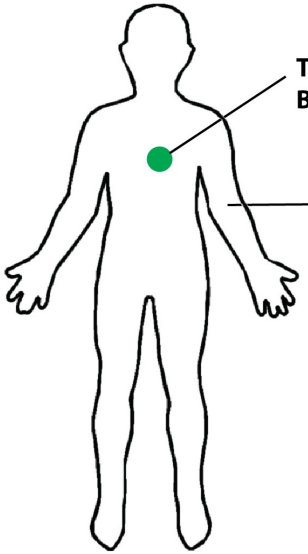
[Ritchie et al. AJHG 2010; 86(4):560-72]

Phenotype Execution and Modeling Architecture (PhEMA)



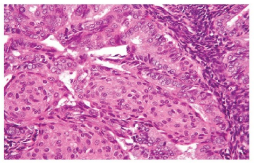
[Rasmussen et al. AMIA 2015]

Precision Oncology at Weill Cornell Medicine

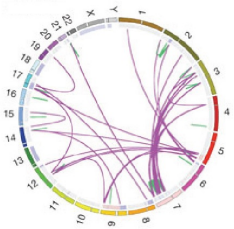


Advanced cancer patient

Pathology

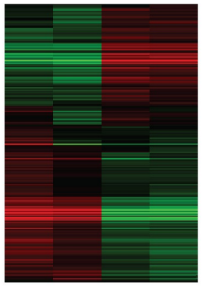


DNA



Tumor and normal
Genome/exome Seq
Genotyping (SNP arrays)
copy number alterations
point mutations
rearrangements
indels

RNA



RNA-seq
Gene expression
Gene fusions

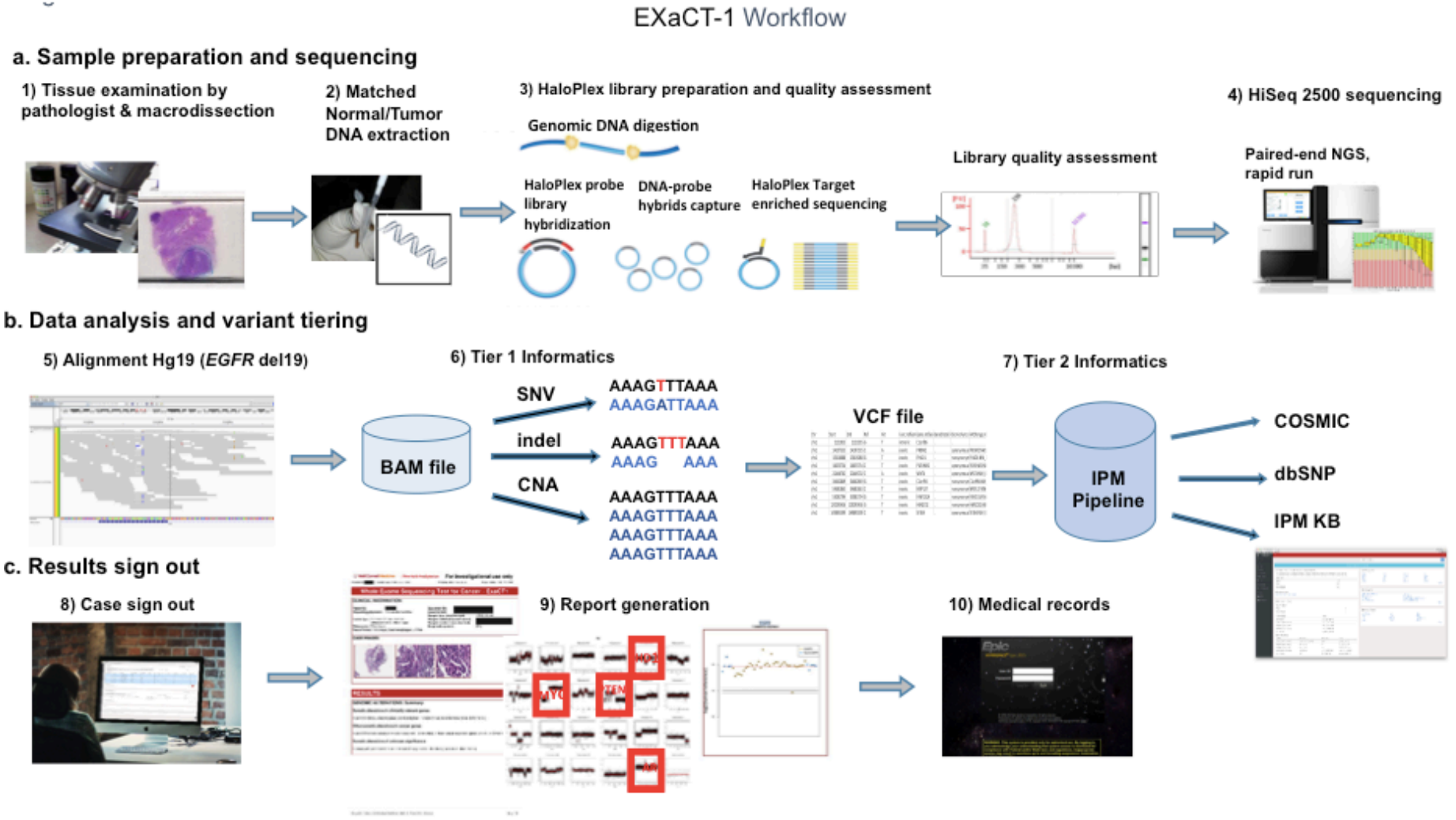
Integration of Data

Sequencing Tumor Board

Patient Specific Clinical Report

[Rennert et al. 2016]

CLIA-approved whole-exome sequencing test queries >21,000 genes



[Rennert et al. 2016]

npj | Genomic Medicine

www.nature.com/npjgenmed

ARTICLE OPEN

Development and validation of a whole-exome sequencing test for simultaneous detection of point mutations, indels and copy-number alterations for precision cancer care

Hanna Rennert[1,2], Kenneth Eng[1,3], Tuo Zhang[1,4], Adrian Tan[1,4], Jenny Xiang[1,4], Alessandro Romanel[5], Robert Kim[1,2], Wayne Tam[2], Yen-Chun Liu[2], Bhavneet Bhinder[1], Joanna Cyrta[1], Himisha Beltran[1,6], Brian Robinson[1,2], Juan Miguel Mosquera[1,2], Helen Fernandes[1,2], Francesca Demichelis[5], Andrea Sboner[1,2,3], Michael Kluk[1,2], Mark A Rubin[1,2,7] and Olivier Elemento[1,3,7]

We describe Exome Cancer Test v1.0 (EXaCT-1), the first New York State-Department of Health-approved whole-exome sequencing (WES)-based test for precision cancer care. EXaCT-1 uses HaloPlex (Agilent) target enrichment followed by next-generation sequencing (Illumina) of tumour and matched constitutional control DNA. We present a detailed clinical development and validation pipeline suitable for simultaneous detection of somatic point/indel mutations and copy-number alterations (CNAs). A computational framework for data analysis, reporting and sign-out is also presented. For the validation, we tested EXaCT-1 on 57 tumours covering five distinct clinically relevant mutations. Results demonstrated elevated and uniform coverage compatible with clinical testing as well as complete concordance in variant quality metrics between formalin-fixed paraffin embedded and fresh-frozen tumours. Extensive sensitivity studies identified limits of detection threshold for point/indel mutations and CNAs. Prospective analysis of 337 cancer cases revealed mutations in clinically relevant genes in 82% of tumours, demonstrating that EXaCT-1 is an accurate and sensitive method for identifying actionable mutations, with reasonable costs and time, greatly expanding its utility for advanced cancer care.

npj Genomic Medicine (2016) **1,** 16019; doi:10.1038/npjgenmed.2016.19; published online 20 July 2016

INTRODUCTION

Identification of genetic alterations by next-generation sequencing (NGS) has become the standard of care in genomic medicine.[1] Currently, numerous NGS assays and platforms are growing set of known clinically relevant mutations but also identify novel or unexpected important variations, including constitutional mutations in cancer predisposing genes, pharmacogenomics variants impacting therapy and discovery of MHC

NewYork-Presbyterian
Weill Cornell Medical Center

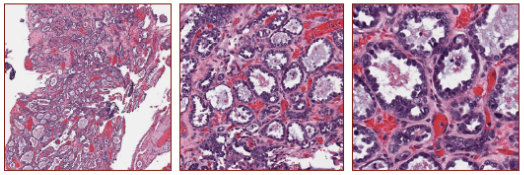
Institute for Precision Medicine Report - Preliminary

Patient ID: PM266 **Diagnosis:** Clear cell carcinoma **Report date:** Dec. 05, 2014

CLINICAL INFORMATION

Patient ID:	PM266	**Sample type (case/control):**	FFPE / FFPE
Physician:	Himisha Beltran M.D.	**Sample collected (case/control):**	(3/18/2014) / (3/18/2014)
Diagnosis:	Clear cell carcinoma	**Sample received (case/control):**	(11/14/2014) / (11/14/2014)
Site:	Pelvic mass	**Neoplastic content:**	56.6%
Specimen IDs (case/control)	PM266_ZA2_1_Case_HALO PM266_ZC2_1_Ctrl_HALO		

CASE IMAGES



RESULTS

GENOMIC ALTERATIONS: Summary

Somatic alterations in clinically relevant genes

A set of 49 clinically relevant genes was investigated. 2 alterations were found in these genes (listed below).

Somatic alterations of unknown significance in known cancer genes

A set of 509 known cancer genes was investigated. 8 alterations in these cancer associated genes were found (listed below).

Somatic alterations of unknown significance

13 gene(s) with point mutations or indels and 41 copy number alteration(s) were found (listed below).

Clinically relevant genomic alterations

These alterations occur in genes that are deemed clinically relevant because: they are targets of drugs, they confer resistance or susceptibility to treatment, or for other clinically relevant reasons (see Appendix).

Gene name	FDA approved drugs with indication (if any)	Interpretation
PIK3CA p.H1047L VAF:72.67%	none	Mutations in PIK3CA may be associated with sensitivity to PI3K inhibitors. However these inhibitors are currently undergoing clinical trials and their efficacy and/or lack of toxicity has not yet been demonstrated.

NewYork-Presbyterian
Weill Cornell Medical Center

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Patient ID: P

CLINICAL INFORMATION

Patient ID: PM266
Physician: Himisha Beltran M.D.
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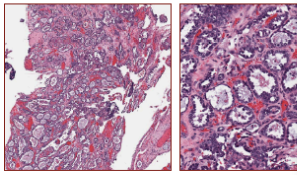

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Institute for Precision Medicine - Mark A. Rubin, M.D.

NewYork-Presbyterian
Weill Cornell Medical Center

Institute for Precision Medicine Report - Preliminary

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Gene name	FDA approved drugs with indication (if any)	Interpretation
FGFR3 focal amplification	none	FGFR3 amplification may be associated with response to the multitargeted tyrosine kinase inhibitor pazopanib (Liao et al, 2013, Cancer Res).

VAF: variant allele frequency

Notes

The status of alterations in gene(s) **KRAS** is indeterminate because the coverage was below the optimal levels of this method (<10 reads). Hence, analysis of the alteration(s) with an independent methodology will be performed.

Genomic alterations of unknown significance in cancer genes

These alterations occur in genes that are cancer associated, but their impact on the disease is unknown (see Appendix).

Copy number alterations

Gene name	Description	Classification of alteration	Altered region
FH	fumarate hydratase	LARGE SCALE AMPLIFICATION	chr1:223,533,597-249,212,519
H3F3A	H3 histone, family 3A	LARGE SCALE AMPLIFICATION	chr1:223,533,597-249,212,519
BCL7A	B-cell CLL/lymphoma 7A	FOCAL AMPLIFICATION	chr12:122,468,644-123,419,896
STAT3	signal transducer and activator of transcription 3 (acute-phase response factor)	FOCAL AMPLIFICATION	chr17:40,039,428-40,673,093
YWHAE	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide (14-3-3 epsilon)	FOCAL AMPLIFICATION	chr17:649,687-1,968,405
AKT2	v-akt murine thymoma viral oncogene homolog 2	FOCAL AMPLIFICATION	chr19:39,759,400-40,947,690
WHSC1	Wolf-Hirschhorn syndrome candidate 1(MMSET)	FOCAL AMPLIFICATION	chr4:1,316,228-2,160,908

Genomic coordinates are based on human reference GRC37/hg19. Large scale alterations involve at least 50 genes.

Somatic mutations and indels

Gene name	Gene description	Classification	Reference Allele	Tumor Allele 1	Tumor Allele 2	AA change	Tumor (Normal) read depth	Tumor VAF
ARID1A chr1:27094361	AT rich interactive domain 1A (SWI-like)	nonsense	G	G	A	p.W1024 *	53 (55)	41.5%

AA: amino-acid; VAF: variant allele frequency; Genomic coordinates are based on human reference GRC37/hg19 and are 1-based.

Genomic alterations of unknown significance

These alterations are not known to have any effect on the disease, but are here reported in the event that in the future progress in scientific knowledge could determine their role (see Appendix).

Somatic mutations and indels

Gene name	Classification	Reference Allele	Tumor Allele 1	Tumor Allele 2	AA change	Tumor (Normal) read depth	Tumor VAF
WWC1 chr5:167881029	inframe deletion	GGA	-	-	p.V861_nofs	54 (44)	100.0%

NewYork-Presbyterian
Weill Cornell Medical Center

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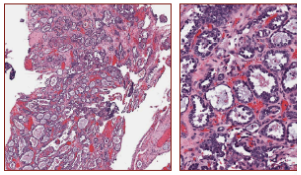

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Gene name	FDA approved drugs with indication (if any)	
FGFR3 focal amplification	none	FGFR3 tyrosine

VAF: variant allele frequency

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Genomic alterations of unknown s

These alterations occur in genes that are cancer associat

Copy number alterations

Gene name	Description
FH	fumarate hydratase
H3F3A	H3 histone, family 3A
BCL7A	B-cell CLL/lymphoma 7A
STAT3	signal transducer and activator of transcription 3 (acute-p factor)
YWHAE	tyrosine 3-monooxygenase/tryptophan 5-monooxygenas protein, epsilon polypeptide (14-3-3 epsilon)
AKT2	v-akt murine thymoma viral oncogene hom
WHSC1	Wolf-Hirschhorn syndrome candidate 1(MM

Genomic coordinates are based on human reference GRC37/hg19. Large

Somatic mutations and indels

Gene name	Gene description	Classifi
ARID1A chr1:27094361	AT rich interactive domain 1A (SWI-like)	nonse

AA: amino-acid; VAF: variant allele frequency; Genomic coordinates are b

Genomic alterations of unknown s

These alterations are not known to have any effect on the scientific knowledge could determine their role (see Appe

Somatic mutations and indels

Gene name	Classification	Reference Allele
WWC1 chr5:167881029	inframe deletion	GGA

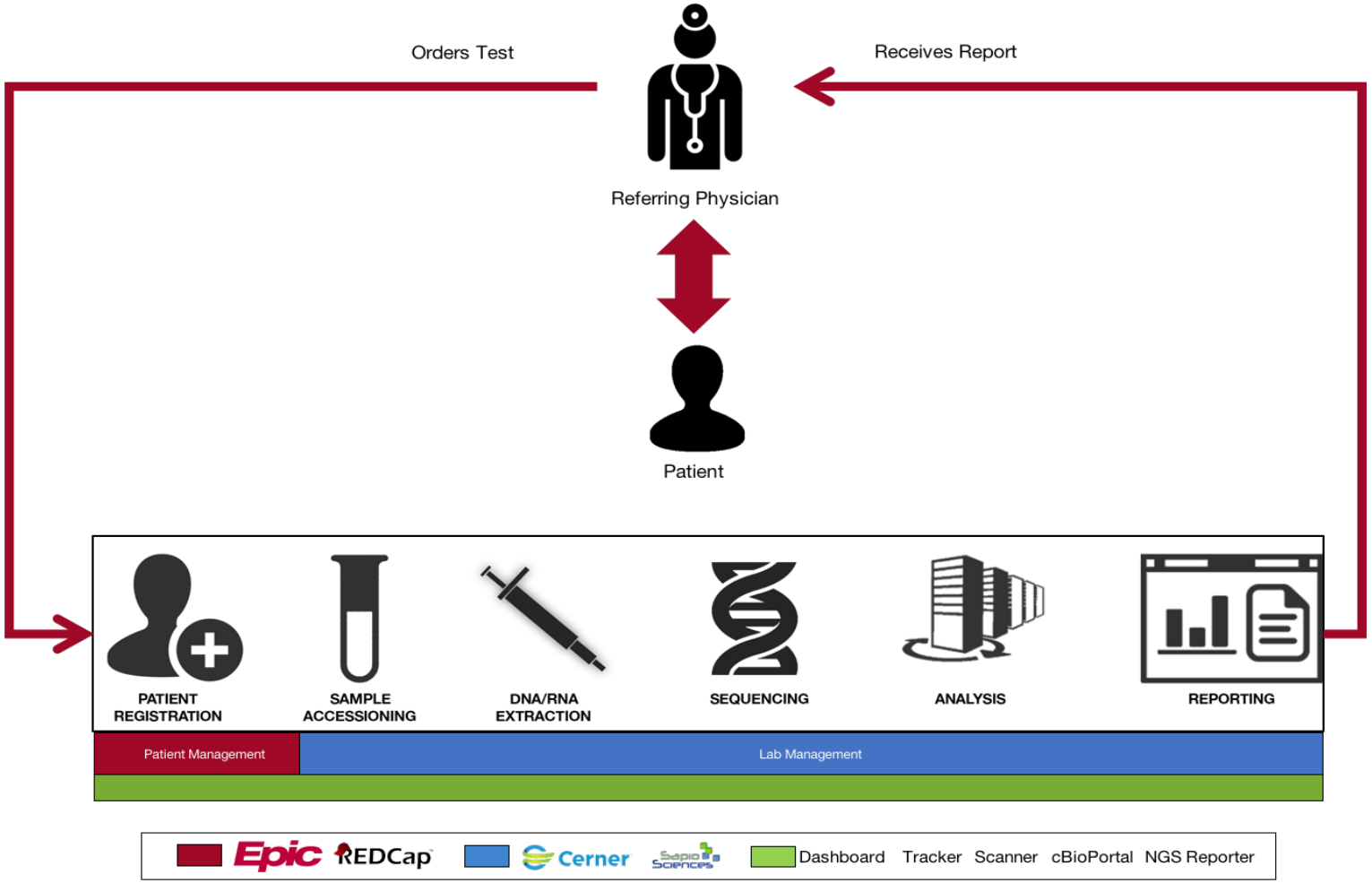
Gene name	Classification	Reference Allele	Tumor Allele 1	Tumor Allele 2	AA change	Tumor (Normal) read depth	Tumor VAF
PCDHA7 chr5:140215766	missense	G	G	T	p.D600Y	80 (159)	32.5%
LCE6A chr1:152816181	missense	G	G	A	p.R62H	52 (34)	38.5%
DNAJB7 chr22:41257666	missense	G	G	T	p.F111L	63 (67)	34.9%
HNRNPH3 chr10:70101354	missense	T	T	C	p.I263T	109 (104)	43.1%
PRRC2A chr6:31597056	missense	T	T	G	p.L2222W	66 (62)	34.8%
AMMECR1 chrX:109445692	missense	C	C	T	p.E258K	105 (119)	28.6%
PTX3 chr3:157160185	missense	G	G	A	p.R188H	35 (22)	85.7%
ATP10B chr5:160018093	missense	G	G	T	p.S1206R	93 (156)	26.9%
IKBKAP chr9:111679850	missense	G	G	A	p.P281S	161 (189)	36.6%
NABP1 chr2:192543814	missense	G	G	T	p.G64C	187 (200)	41.7%
INPPL1 chr11:71949090	missense	C	C	A	p.P1186Q	51 (89)	33.3%
ACACA chr17:35603828	missense	G	G	A	p.R792C	75 (115)	28.0%

AA: amino-acid; VAF: variant allele frequency; Genomic coordinates are based on human reference GRC37/hg19 and are 1-based.

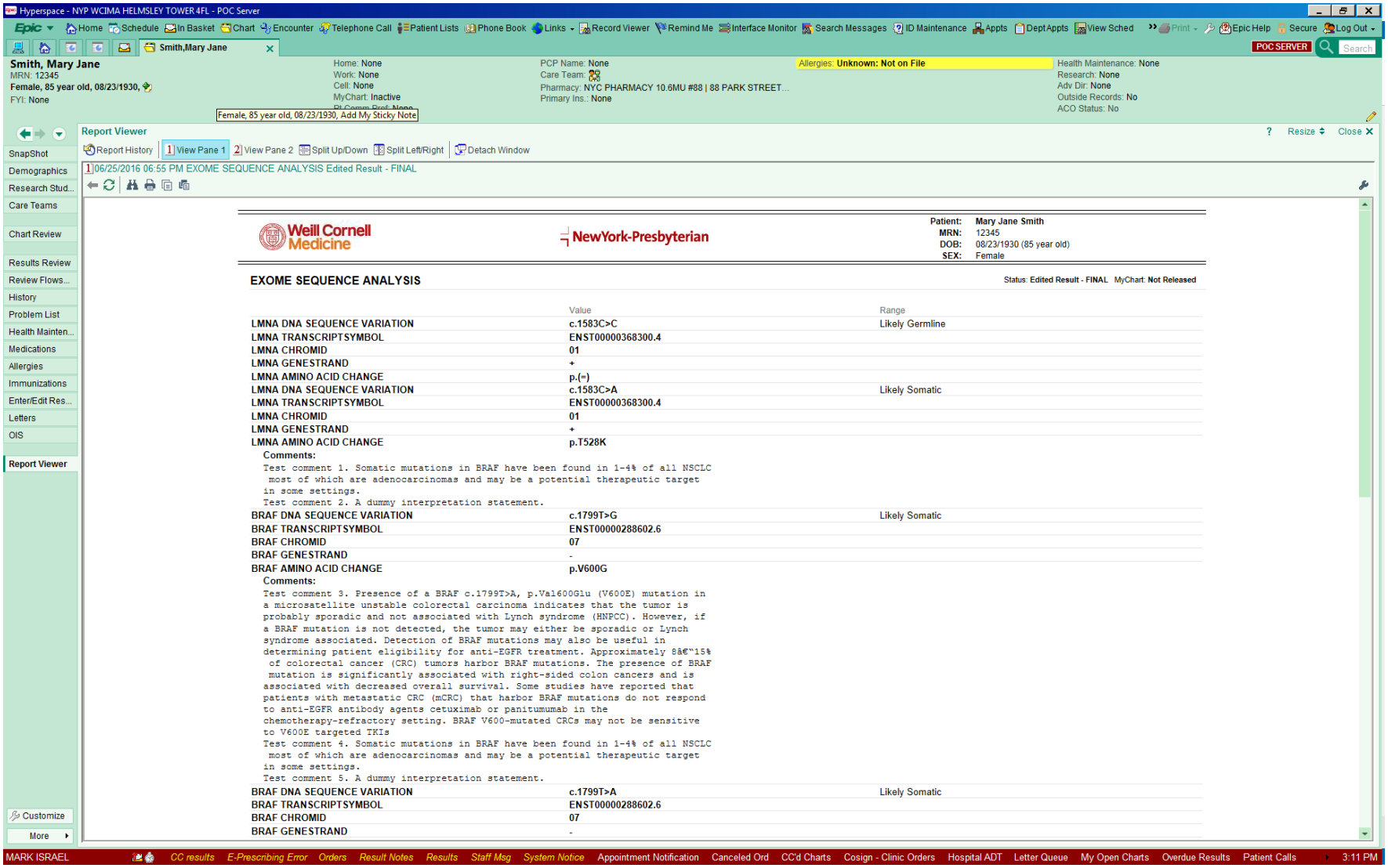
Copy number alterations

Location (Chr:Start-End)	Type	Number of genes	Gene names (if less than 6)
chr1:108,303,451-108,313,302	FOCAL AMPLIFICATION	1	VAV3
chr1:1,451,428-1,534,985	FOCAL AMPLIFICATION	4	ATAD3A; TMEM240; C1orf233; SSU72
chr1:176,103,007-176,118,174	FOCAL AMPLIFICATION	1	RFWD2
chr1:179,955,350-180,366,693	FOCAL AMPLIFICATION	6	too many to show
chr1:182,491,189-183,471,466	FOCAL AMPLIFICATION	13	too many to show
chr1:201,104,865-201,358,357	FOCAL AMPLIFICATION	5	TNNT2; IGFN1; TMEM9; PKP1; LAD1
chr1:21,139,689-21,151,640	FOCAL AMPLIFICATION	1	EIF4G3
chr1:223,533,597-249,212,519	LARGE SCALE AMPLIFICATION	228	too many to show
chr1:28,586,401-28,920,568	FOCAL AMPLIFICATION	12	too many to show
chr1:46,511,673-46,736,392	FOCAL AMPLIFICATION	5	LURAP1; PIK3R3; POMGNT1; RAD54L; TSPAN1
chr10:133,107,486-133,748,005	FOCAL DELETION	3	TCERG1L; FLJ46300; PPP2R2D

High Level Workflow for EHR integration



EHR (Epic) integration



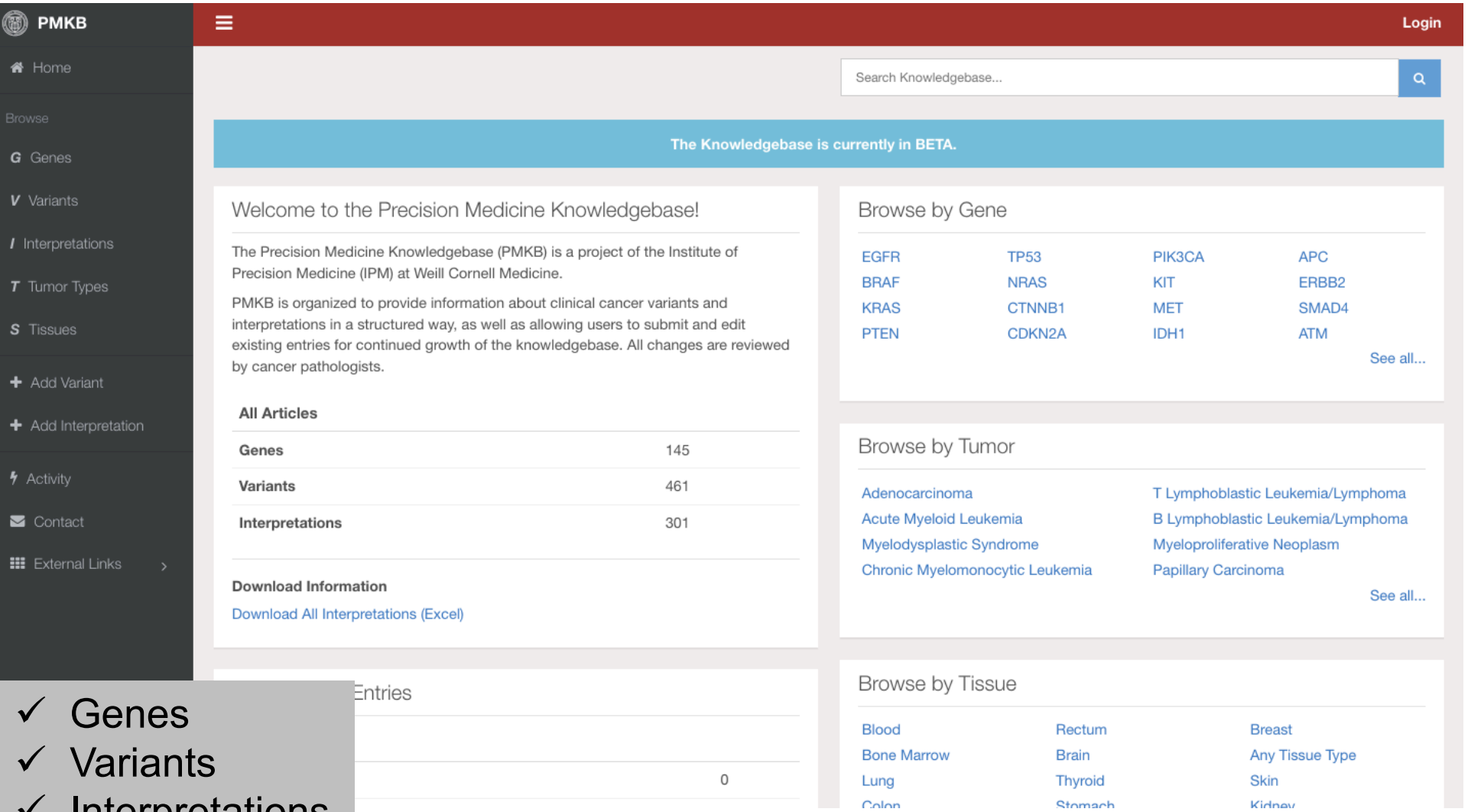
Data to be discretely stored and presented to Clinicians

- Primary Site
- Tissue Site
- Source of Material
- Gene Name
- Gene Position
- Copy Number Anomaly (CNA) (Broad vs Focal qualifier if available to be displayed here)
- Exon Number
- Coding Nucleotide Change
- Amino Acid Change
- Variant Allele Frequency (VAF)
- Interpretation
- Hyperlink to PDF report from IPM

Controlled Vocabularies for results

- Result components will be built using elements described by the Genomic Information System (GIS) and will be associated with a LOINC number where possible
- Primary site, tissue type, histology will use SNOMED Morphology codes
- Integration with additional annotation and information from Precision Medicine Knowledge Base (PMKB) – next slide

Precision Medicine Knowledge Base (PMKB)

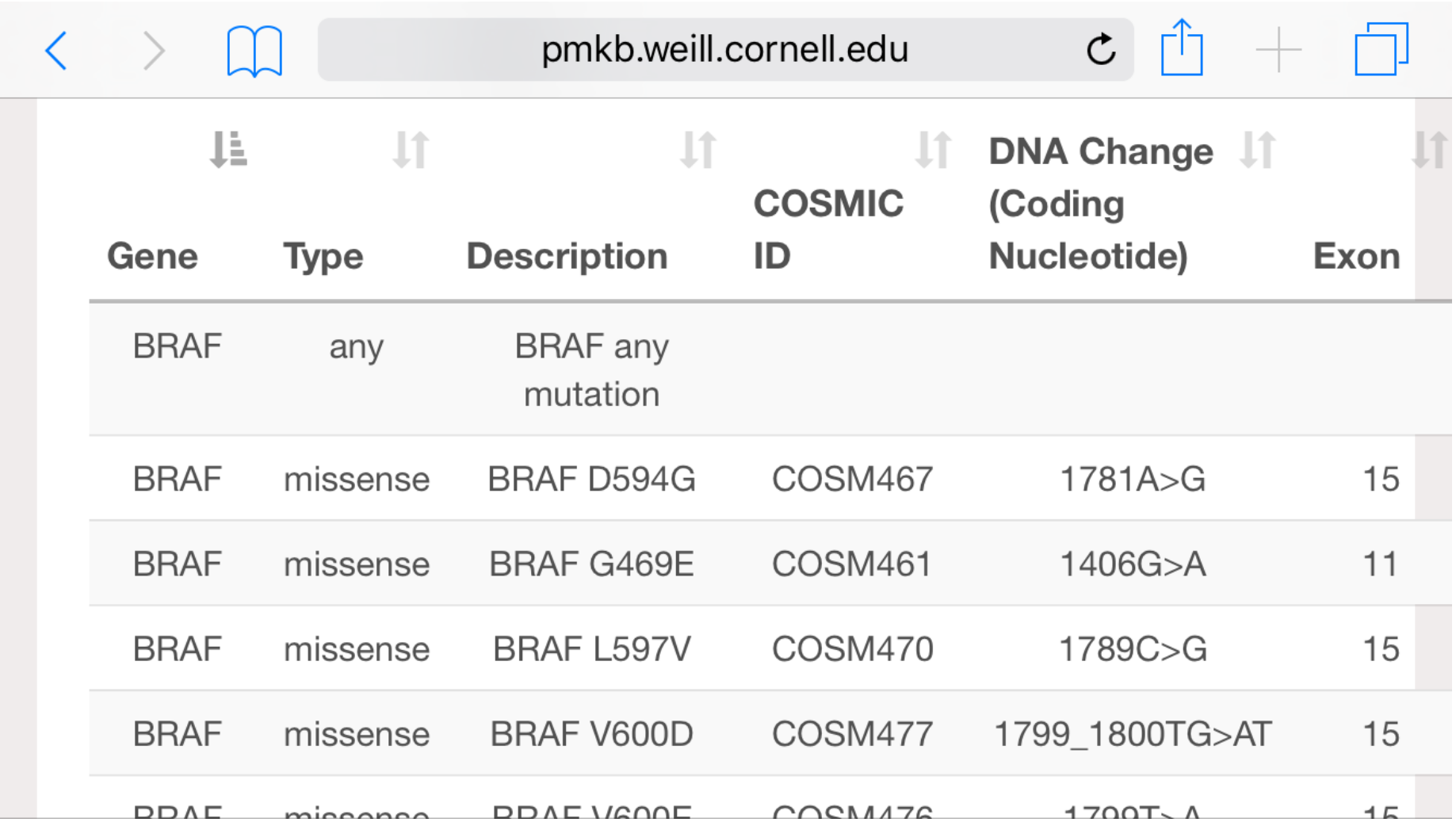


- ✓ Genes
- ✓ Variants
- ✓ Interpretations
- ✓ Tumor Types
- ✓ Tissue Types

[Huang et al. 2016]

https://pmkb.weill.cornell.edu/

PMKB – BRAF Gene Variants



Gene	Type	Description	COSMIC ID	DNA Change (Coding Nucleotide)	Exon
BRAF	any	BRAF any mutation			
BRAF	missense	BRAF D594G	COSM467	1781A>G	15
BRAF	missense	BRAF G469E	COSM461	1406G>A	11
BRAF	missense	BRAF L597V	COSM470	1789C>G	15
BRAF	missense	BRAF V600D	COSM477	1799_1800TG>AT	15
BRAF	missense	BRAF V600E	COSM476	1799T>A	15

https://pmkb.weill.cornell.edu/

PMKB – EFGR Interpretation 278

Interpretation 278

Information | View History | Suggested Revisions

Variant(s)	EGFR E709_T710delinsD EGFR exon(s) 18 indel EGFR exon(s) 18 deletion
Tumor(s)	Adenocarcinoma Non-Small Cell Lung Carcinoma
Tissue(s)	Lung
Tier	1

Interpretation

Somatic mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) gene are present in approximately 80% of the lung adenocarcinomas that respond to first and second generation EGFR inhibitors (eg, gefitinib, erlotinib and afatinib). Two types of mutations account for approximately 80-90% of all EGFR mutations: short in-frame deletions in Exon 19 and a point mutation in exon 21 at codon 858 (L858R). Other less common mutations in exons 18, 20, and 21 are found in 10-20% of EGFR-mutated cases. EGFR Exon 19 deletions, EGFR Exon 21 L858R mutations correlate strongly with sensitivity to specific EGFR inhibitors and the response rate to therapy with TKIs has been reported to be up to 80% in such cases. The T790M mutation in exon 20 is associated with resistance to some EGFR inhibitors. However, third generation TKI (eg, osimertinib) can specifically target T790M. EGFR exon 18 mutations account for 3.6% of all the EGFR mutations in lung adenocarcinomas. Of these, G719 mutations account for the majority of them and are sensitive to anti-EGFR inhibitors. Exon 18 deletions are rare (<0.1%) and but they are potentially responsive to anti-EGFR TKIs in some small clinical case studies. Of note, they appeared to be more sensitive to second-generation TKIs, especially afatinib and neratinib, than to first- and third-generation TKIs based on in vitro experiments.

Citations

Ackerman A, et al. EGFR delE709_T710insD: a rare but potentially EGFR inhibitor responsive mutation in non-small-cell lung cancer. J Thorac Oncol 2012;7(10):e19-20

Kobayashi Y, et al. EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Augmented

OncoKB
Precision Oncology Knowledge Base
Annotation of Somatic Mutations in Cancer

Precision Medicine KnowledgeBase
Weill Cornell Medicine

CIViC
Clinical Interpretations of Variants in Cancer

Cancer bioMarkers-db

CANCER GENOME INTERPRETER

...

Global Alliance for Genomics & Health

Variant Interpretation for Cancer

- Gene
- Variant
- Cancer subtype
- Clinical implication: drug sensitivity, drug resistance, adverse response, diagnostic, or prognostic
- Source (e.g., PubMed identifier)
- Curation group

Audacious Goals to Help Make This Happen

- Through the ***All of Us*℠ Research Program** and **Institute of Precision Medicine** activities at Weill Cornell, we aim to generate:
- **A new model of research** based on collaboration among researchers, providers, and participants
- **A rich resource of data**, including biospecimens, to help accelerate research advances
- **Increased knowledge** leading to individualized care and improved health for future generations

It takes a village…

Acknowledgment

- *All of Us*[SM] research team at Cornell, Columbia and Harlem Hospital
- Weill Cornell Institute of Precision Medicine
- Members of Project PhEMA
- Members of eMERGE network

Thank You!

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http://pathaklab.com

We're hiring:

http://hpr.weill.cornell.edu