21 May 2021

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Standards Architecture of the Genomic Surveillance Enterprise

Marc Salit, JIMB

Coronavirus Standards Working Group

What should a Coronavirus Standards Working Group do?

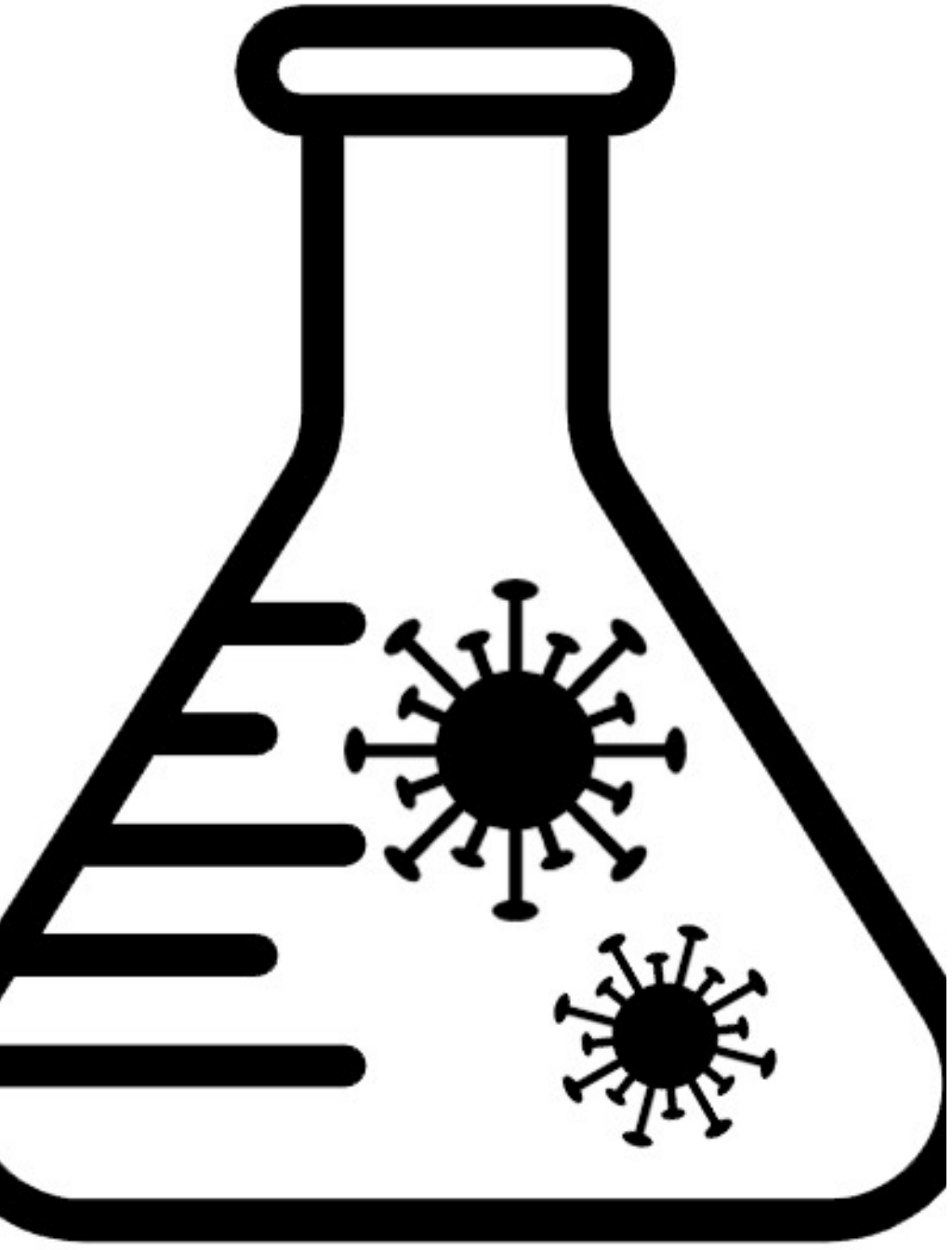
Assure development and availability of standards, controls, interlab testing, knowledge to support successful rollout & scaling of 2019-nCoV testing

Identify and develop critical infrastructure to support…

- confidence in test results
- interoperability
- scale-up
- long-term capacity

Identify best practices that should be institutionalized

Learn what we need to so next time we have a global network in place ready to make standards.



Agenda

Updates

- Viral RNA Harmonization

Standards Architecture

- Project with Rockefeller Foundation

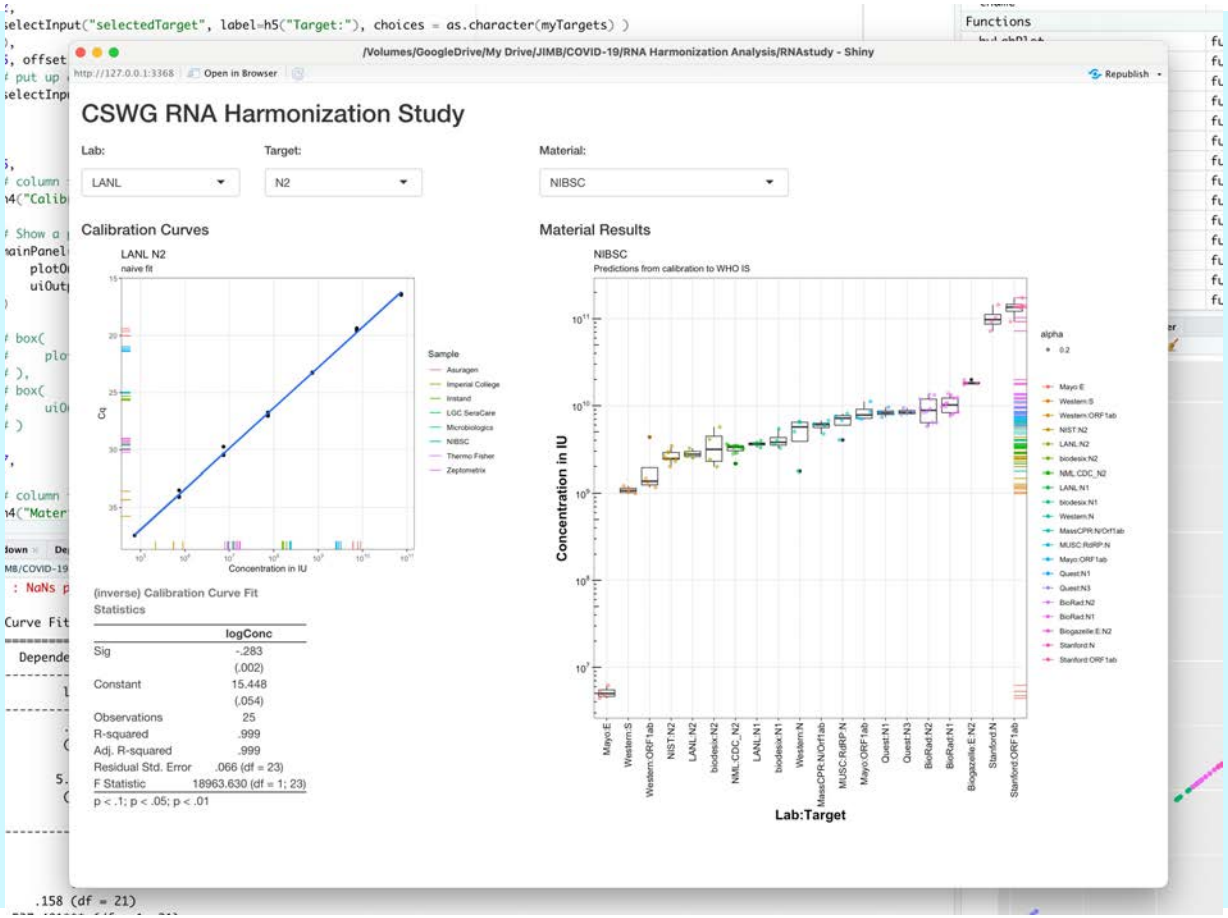
CSWG Viral RNA Harmonization Study Status

	NIST	NML/LGC	NIB (Slovenia)	Bio-Rad	Western	MUSC	Mayo	Labcorp	Quest	Biogazelle	MassCPR Diagnostics	Stanford Medicine	Los Alamos	biodesix
Panel Received	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑
Lab Metadata Entry Initiated	☑	☑	☐	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑
Lab Metadata Entry Complete	☑	☑	☐	☑	☑	☑	☑	☐	☑	☑	☑	☑	☑	☑
Lab Data Received	☑	☑	☐	☑	☑	☑	☑	☐	☑	☑	☑	☑	☑	☑
Data Summarized	☑	☑	☐	☑	☑	☑	☑	☐	☑	☑	☑	☑	☑	☑
Data Analyzed	☑	☑	☐	☑	☑	☑	☑	☐	☑	☑	☑	☑	☑	☑

Viral RNA Harmonization Study Data

- Data in from 12/14 labs
- Analysis tool being debugged
  - some artifacts in calculations for a few sites
- Need to compute value assignments with uncertainties
- Developing calibration selection capability

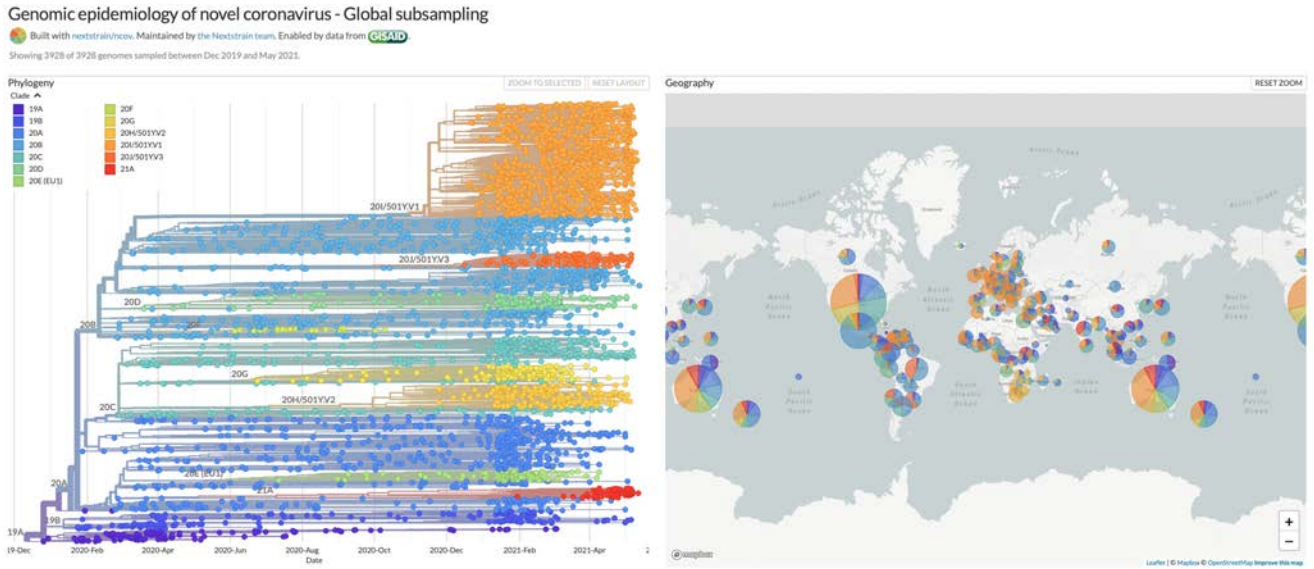
Viral RNA Harmonization Analysis https://msalit.shinyapps.io/RNAstudy/



- Shiny Web App to Analyze Study Data

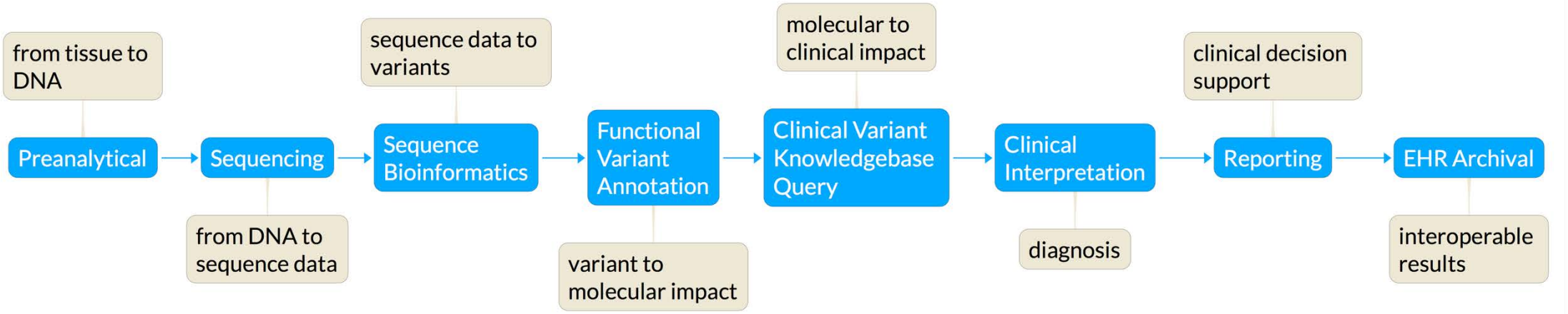
Genomic Surveillance of SARS-CoV-2

- Genomic epidemiology is at present disaggregated and artisanal
- Hybrid of public health entities, academic groups and centers, government agencies, commercial laboratory systems, informal and formal networks
- Can we do better by laying groundwork for enterprise-scale systematics?
  - consistency
  - reliability
  - transparency
  - interoperability



Nextgen Sequencing “Enterprise”

standards can play a role to develop confidence throughout…



NGS is a new kind of assay, and there's lots of room to establish confidence in results.

- Regulatory oversight can foster confident use of NGS in cancer detection and diagnosis.
- *"…a standards-based approach to analytical performance of NGS tests and the use of centralized curated databases containing up-to-date evidence to support clinical performance are under discussion."*

FDA workshop, Feb 20, 2015

PERSPECTIVE

REGULATORY SCIENCE

Unmet needs: Research helps regulators do their jobs

Russ B. Altman,[1] Natalia Khuri,[2,3] Marc Salit,[2,4] Kathleen M. Giacomini[3,5]*

A plethora of innovative new medical products along with the need to apply modern technologies to medical-product evaluation has spurred seminal opportunities in regulatory sciences. Here, we provide eight examples of regulatory science research for diverse products. Opportunities abound, par

Translational biomedical science has emerged as a critical research theme over the past decade and encompasses the spectrum of scientific activities from basic discovery to clinical trials to strategies for clinical implementation. Central to translational medicine is an understanding of the path that moves basic science discoveries toward improvements in clinical practice, which includes robust mechanisms for evaluating the safety and efficacy of potential new diagnostics and therapeutics—some of which are ultimately approved for human use. Under development are myriad new health care products derived from cutting-edge science, such as genomics-based diagnostics, interventional imaging techniques, combination devices with biological materials, and cell-based therapies, and regulators need to apply modern technological tools and make full use of scientific advances to evaluate the benefits and risks of generation medical products. "Regulatory science" refers to investigations that generate fundamental knowledge necessary for driving regulatory decision-making. Regulatory science is like all scientific research in its emphasis on hypothesis generation and experimentation, but it focuses on questions whose answers are of particular importance for regulatory decisions, including those related to food, veterinary products, drugs, diagnostics, devices, and medical software.

In the United States, the U.S. Food and Drug Administration (FDA) has long recognized the importance of regulatory science for its mission. A 2007 study of the FDA Sci-

cal Path Institute—have provided funding or developed programs specifically directed at research and training in regulatory sciences. FDA initiated a new program that provides funds to academic institutions for the building of Centers of Excellence in Regulatory Science and Innovation (CERSI) and has thus far made four awards, including three in the vicinity of FDA's White Oak campus (at Georgetown University, Johns Hopkins

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Table 2. NGS: Diagnostic enterprise from clinical sample through diagnosis, reporting, and data archival. Shown is (i) suggested evidence appropriate for the development of validation standards, which could then be used to establish that evidence, and (ii) critical stakeholders who can be convened to identify existing standards, create new standards, or establish the research agenda that would underpin the needed standards. VCF, variant call format; SOP, standard operating procedures; SDOs, study delivery operations specialists; HHS, health and human services.

Phase	Evidence needed	Standards and evidence-developing practices (examples)	Stakeholders for standards development	Knowledge gaps (examples)
Preanalytical: from tissue to DNA	• Representative sampling • Accurate (unbiased) extraction • Integrity of DNA	• Documentary standard to establish SOPs for sampling • Reference samples and interlaboratory studies to evaluate extraction and DNA integrity	• Clinical laboratories • Professional societies • Clinical SDOs	• Artifacts associated with extraction from archival tissue samples
Sequencing: from DNA to raw sequence data "Wet bench"	• Accurate (unbiased) sequencing • Fit-for-purpose characteristics	• Well-characterized genomic DNA reference materials • Documentary standard describing sequencing characteristics appropriate for different clinical indications	• Standards laboratories • Clinical laboratories • Sequencing technology developers • Academic laboratories developing methods • Genome centers	• Sequencing of "difficult" regions of the genome • Platform artifacts • High-quality benchmark genomes • Performance expectations (sensitivity, specificity thresholds)
Sequence bioinformatics: from raw sequence data to VCF "Dry bench"	• Unbiased processing of sequence data (mapping and assembly) • Accurate variant calling • Accurate and unambiguous variant representation • Interoperability of data representation	• Documentary standards describing protocols to critically evaluate processes, coupled to knowledge of technical platform idiosyncrasies • Data representation standards • Reference data, implementation: benchmark VCF files • Reference software to evaluate VCF files	• Standards laboratories • Clinical laboratories • Sequencing technology developers • Academic laboratories developing methods • Genome centers	• Assembly and mapping in "difficult" regions of the genome • Platform and algorithm artifacts • High-quality benchmark genomes • Performance expectations (sensitivity, specificity thresholds)
Functional variant annotation	• Accuracy of variant annotation, including establishing confidence in genomic landscape of the call	• Documentary standards for critical evaluation of processes, coupled to knowledge of technical platform idiosyncrasies • Data representation standards • Interlaboratory comparisons of annotation • Gold standard annotation of benchmark samples	• Clinical laboratories • Academic laboratories developing methods • Genome centers	• Development of genome-wide "gold standard" annotations
Clinical variant knowledge base (PharmGKB, ClinVar)	• Clinical scope, reliability, relevance, strength, applicability of data in knowledge base	• Documentary standards of evidence for inclusion in knowledge base • Documentary standards for critical evaluation of knowledge base contents, formatting, transaction accuracy • Knowledge base intercomparisons	• Clinicians • Professional societies • Academic laboratories	• Quantitative frameworks to assess knowledge of the strengths of associations of variants and disease • Quantitative framework to assess knowledge base curation/accuracy
Clinical interpretation	• Accurate interpretation of variants, including incidental findings and classification of pathogenicity • Accurate clinical findings	• Documentary standards describing best practices and methods of critical evaluation • Adjudicated benchmark case studies for interlaboratory comparisons of clinical interpretation	• Clinicians • Professional societies • Academic laboratories • Payers	• Quantitative framework to predict performance of clinical interpretation
Reporting	• Accurate and clear reporting of results to clinician in a standard format	• Documentary standards describing reporting guidelines • Interlaboratory comparisons and evaluations of reporting	• Professional societies • Clinicians • Genetic counselors • Clinical laboratories • Payers	• Communicate confidence in findings
EHR archival	• Accurate and interoperable representation of WGS, WES test results	• Data representation standards • Documentary standards describing data representation • Compliance test software to evaluate EHR formatting • Reference implementations	• Payers • Professional societies • HHS • Standards bodies	• No interoperable EHR standards in common practice

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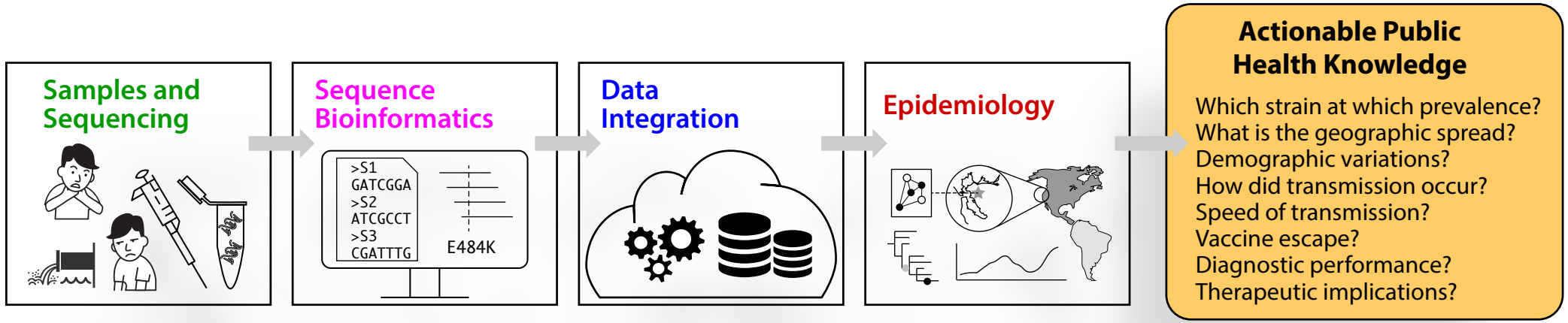
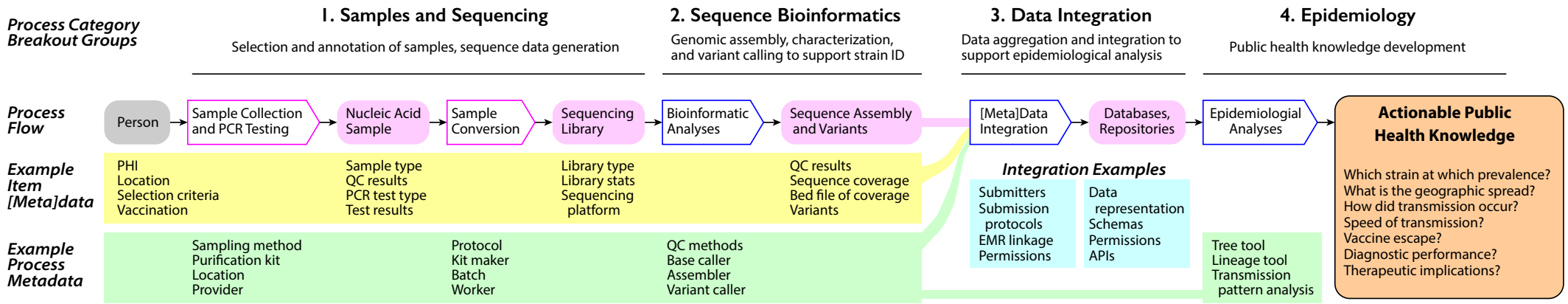
Standards Architecture

- Evidence to be developed
  - what sort of evidence do you need to establish the veracity of this process phase?
- Standards/Evidence Developing Practices
  - what sort of standards and practices help develop the evidence?
    - *standardized!*
      - comparable, transparent, evaluable
- Example Stakeholders
  - who cares about this phase, who's can help to establish standards?
- Example Knowledge Gaps
  - what are some of the things we don't know how to do?



Genomic Surveillance Workflow can be segmented…

- Note that the process needs to be considered from Samples to “So-what?”
  - must develop actionable Public Health Knowledge



Annotated genomic surveillance workflow

- This is our working draft, we're in process of consultations
- Open, public workshops 10-15 June
- Strawperson proposal distributed in advance
- 4 working groups, followed by synthesis plenary
- Will issue consensus report with prioritized standards projects

Architecture Table in development

Functional requirements	Key Questions	Standards, Interoperability Tools, Quality Tools	Who will make the Standards?	Existing Standards & Shared Resources
Sampling Strategy				
Sample processing and Sequencing				
Sequence Bioinformatics				
Data aggregation, integration, access				
Public Health Analytics				