

Concurrent Measurement of mRNA, PCR test and Detection of Antibodies

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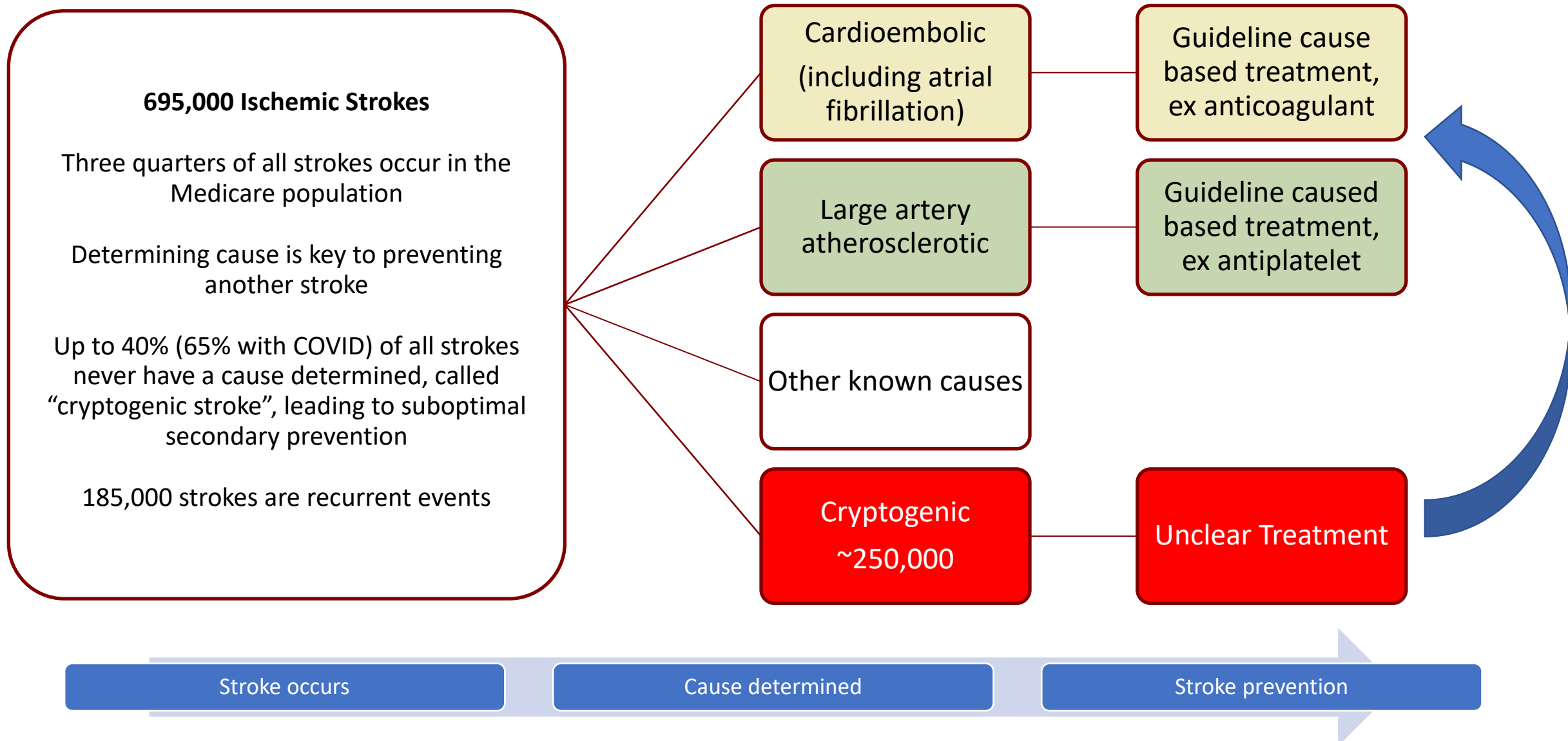
What is ISC-REST and what does it do?

The Ischemia Care Respiratory and Stroke Test Kit is novel and the only system in the world that uses blood testing for cause of stroke and respiratory status. Current status is 65% of ischemic strokes with COVID never have a cause determined (“cryptogenic”) leading to clinical inefficiency and increased risk for recurrent stroke. Understanding stroke cause and respiratory condition will increase utilization of appropriate secondary prevention of a more massive and debilitating recurrent stroke.

1. **Respiratory SARS-CoV-2 Panel**¹ is a multiplexed nucleic acid real-time PCR test intended for the qualitative detection and differentiation of nucleic acid from multiple respiratory viral and bacterial organisms, including the SARS-CoV-2 virus.
2. **Ischemia Care Dx (ISCDX)** is a test service, based upon micro array gene expression analysis, performed in a single laboratory, using whole blood as a source of mRNA, to aid in the diagnosis of cardio embolic and large artery atherosclerotic stroke, when hemorrhagic stroke is ruled out. The test could also be used as part of clinical evaluation and patient risk assessment. This test would be used in conjunction with standard clinical evaluation and will be used in the context of the patient's clinical history and other diagnostic test results.
3. **Access Anti-SARS-CoV-2 Total Test**¹ is a rapid, digital lateral flow serological test, using nanoparticle fluorescence, intended for qualitative detection of total antibodies to SARS-CoV-2 in human serum and plasma (heparin, EDTA).

¹ FDA cleared by Qiagen

Overview



How ISC-REST is used and procedural steps



Samples are collected in the hospital **(inpatient)** within 30 hours of symptom onset and sent to a CLIA laboratory, results stratify by cause and 13 respiratory conditions



First, testing reports cardioembolic (CE) or large artery athero (LAA) cause



Second, the testing reports on current respiratory status (including COVID-19) and previous COVID-19 antibodies.



Importance is COVID status (current and previous) in ischemic stroke is not obvious, complicating cause diagnosis, inefficient workflow, reducing optimal treatment, increasing hospital readmission risk.

Positive CE and negative COVID result

- **Atrial fibrillation (AF)** is a cardioembolic cause of stroke.
- Cryptogenic patients with undetected AF are at **5x greater likelihood of a recurrent stroke**.
- **Clinical improvement:** Identifying AF provides **60%+ risk reduction for recurrent stroke**


Positive LAA and negative COVID result


- **Vulnerable plaque** is a LAA cause of stroke.
- **Downstream testing** not routinely performed can confirm plaques as the underlying cause .
- **Clinical improvement:** **20% risk reduction for recurrent stroke**


Respiratory (COVID) impact


- **COVID positive + (LAA negative and CE negative)** investigate coagulopathy, hypercoagulable states, vasculitis, or venous thromboembolism
- **COVID negative + (LAA negative and CE negative)** investigate occult cancer, coagulation, hemostatic activation, or other non respiratory
- **COVID positive + CE positive** Investigate paradoxical embolism as cardioembolic, cardiomyopathy, consider Warfarin over DOACs
- **COVID positive + LAA positive** Investigate paradoxical embolism as in-situ clot formation as atheroembolic

Prior to COVID-19, Inefficiencies in current workflow contribute to delays in time to treatment, effective stroke prevention, and consistent patient evaluation


 Routinely performed standard

 Not routinely performed standard

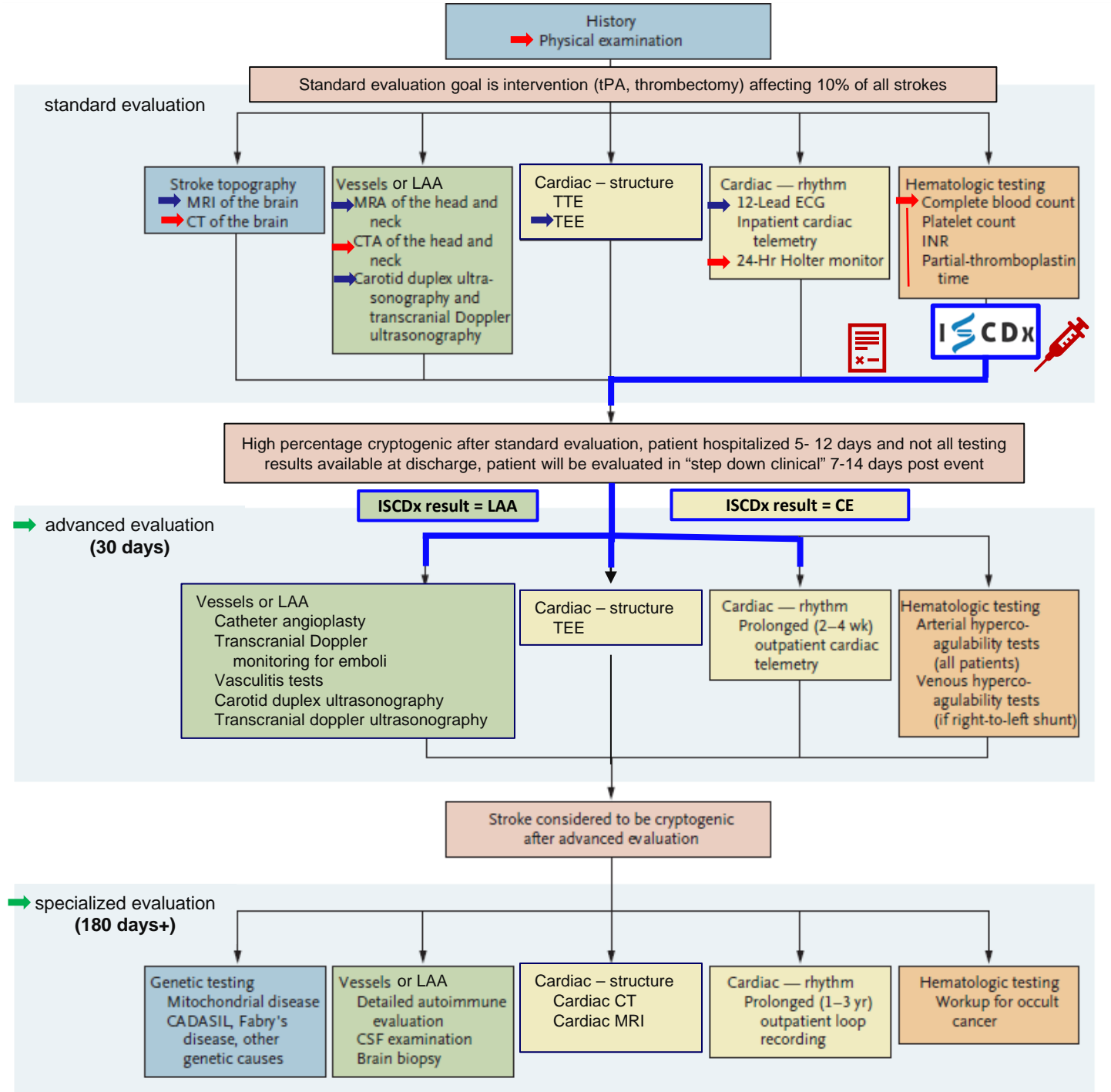
 CE clinical workflow procedures

 LAA clinical workflow procedures

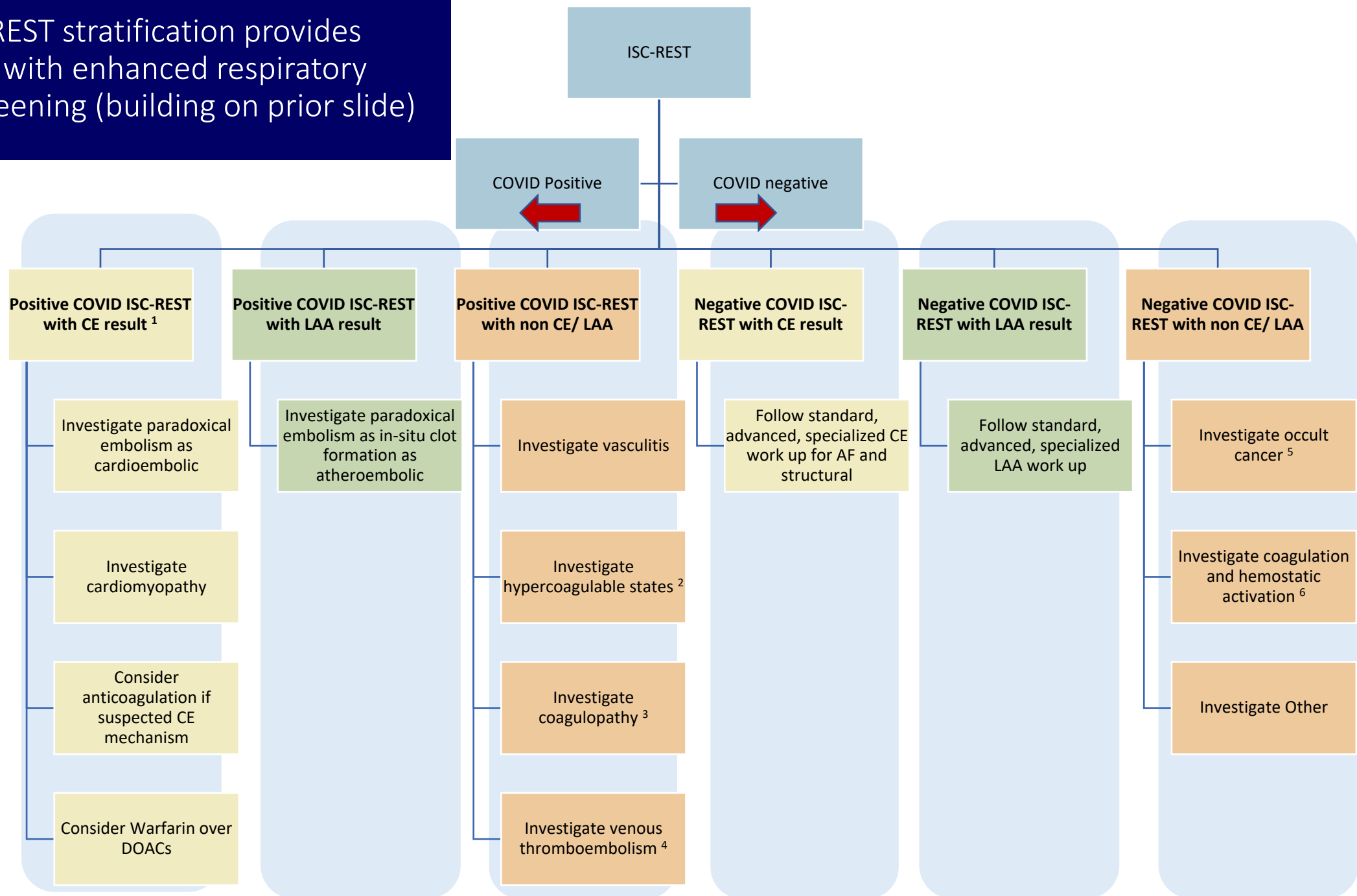
 ISCDx change in care

 Advanced and specialized evaluation not routine and may occur in-hospital or out of hospital

In a COVID-19 era the next slide builds on the importance of respiratory conditions in diagnosing and treating Ischemic Stroke

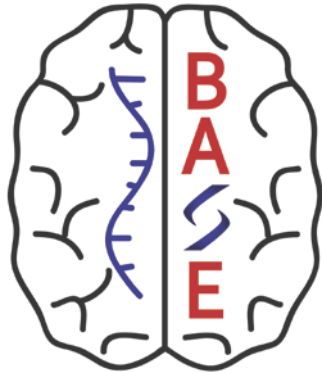


How ISC-REST stratification provides efficiency with enhanced respiratory status screening (building on prior slide)



BASE clinical trial and analytical validation data

Biomarkers of Acute Stroke Etiology ¹ (BASE) NCT02014896



To validate prior Federally funded research² based upon gene expression in RNA from whole blood as a means of predicting stroke etiology in acute ischemic stroke.

¹ Jauch, E.C., et al. Biomarkers of Acute Stroke Etiology (BASE) Study Methodology. Transl. Stroke Res. 8, 424–428 (2017). <https://doi.org/10.1007/s12975-017-0537-3>

² (Jickling, *Ann Neurol.* 2010;68:681–692)

Sensitivity	89.66%
Specificity	70.00%
Positive Likelihood ratio	2.99
Negative Likelihood ratio	0.15
Positive Predictive Value	89.66%
Negative Predictive Value	70.00%
Accuracy	84.62%

ISCDX is offered under the Clinical Laboratory Improvement Amendments (CLIA) program as a Laboratory Develop Test (LDT) governed by the Centers for Medicare and Medicaid Services (CMS) under the Food and Drug Administration (FDA)

Associated ischemic stroke and respiratory diagnosis related to ISC-REST

Ischemia Stroke	Respiratory	
Cardioembolic stroke		
Large Artery Atherosclerotic stroke		
Cryptogenic stroke		
Vasculitis		
Coagulopathy (including hypercoagulable states)		
Cardiomyopathy		
Venous thromboembolism		
Coagulation and hemostatic activation		
Occult cancer		
Atrial fibrillation		
Left atrial appendage		
Patent foramen ovale		
Small vessel disease		

Where would ISC-REST be documented in the medical record for individuals (medical coders) to identify

- In the laboratory tab of the EMR since it is a laboratory test(s).
- We do not believe there are different naming conventions for ISC-REST.

Permanent implantable devices – downstream from ISC-REST

- In cases where cause is undetermined (cryptogenic), clinicians may consider an implantable cardiac monitor (ICM)
- ICM was discovered to have an 86% false positive rate in cryptogenic populations
- ISC-REST will provide clinicians with quantitative data to aid in determining appropriate downstream utilization of ICM

Journal Of
Interventional Cardiology

Recommended progressing
directly to ICM because of
low yield on 30 day
ambulatory monitor

HeartRhythm



ICM 86% false positive rate in
cryptogenic stroke
populations

> Heart Rhythm. 2020 Jan;17(1):75-80. doi: 10.1016/j.hrthm.2019.07.015. Epub 2019 Jul 16.

**Incidence of false-positive transmissions during
remote rhythm monitoring with implantable loop
recorders**

Is the procedure performed in conjunction with another procedure or is it considered a stand alone

- The testing is standalone.
- However, the testing may stratify patients into downstream care pathways specific to cause.
- Downstream testing is time consuming, invasive, and may involve surgery just to determine cause.
- Delays in diagnosis of cause will delay treatment to prevent another stroke that is often more massive, debilitating, and place greater burden on patients, families and payors.

Examples of downstream testing appropriately used or avoided

Transesophageal echocardiogram (TEE)

Implantable cardiac monitoring

Hypercoagulable

Angiography (ex. cardiomyopathy)

Magnetic resonance imaging (ex vasculitis)

Cancer screening

Carotid duplex

Transcranial doppler

Genetic testing

Complications, sequela, or adverse events

- The risk to the patient for ISC-REST is a blood draw.
- The results are used by a clinician in conjunction with other clinical information used to evaluate cause of stroke and respiratory diseases.
- The ISC-REST may aid in reducing death and adverse events. For example, through screening patient populations to discover atrial fibrillation may reduce adverse events.

Negative clinical trials for treating cryptogenic with anticoagulant

Dabigatran trials come up short for stroke of unknown cause and cerebral venous thrombosis

<https://www.tctmd.com/news/dabigatran-trials-come-short-stroke-unknown-cause-and-cerebral-venous-thrombosis>

NAVIGATE ESUS: Rivaroxaban fails to prevent more recurrent cryptogenic strokes than aspirin

<https://www.nejm.org/doi/full/10.1056/nejmoa1802686>

Use case examples



According to Dr. Timothy Schoonover, Kettering Health Network Stroke Medical Director, on a single day in December 2020, 6 patients under the age of 45 were admitted with an ischemic stroke and 3 tested positive for COVID, and COVID history was unknown on all patients. All 6 were cryptogenic in nature.

Condition	Current practice	Future state
Cause is <u>unknown</u> after standard evaluation	Limited testing procedures past standard ¹ OR Extensive testing procedures past standard ²	Stratify into efficient workflow
Inefficiency in evaluation	Example: Implantable cardiac monitoring ³	Population enrichment

¹“We rarely test beyond standard evaluation because of low yield, if we guess at a pathway and it is negative (cardioembolic) it does not mean by default it was another (large artery)”

²“We should do everything possible to determine cause of stroke because it is in the best interest of patient care, no matter what because a recurrent stroke will be more massive and debilitating”

³“Implantable cardiac monitoring is given away like free cheese because of perverse financial incentives and not always in best interest of patient, there is a correct population, but when I sit down to counsel a patient it is difficult because of complications and surgery”

ISC REST Summary

1. Stroke is a large and complex problem.
Understanding cause enables guideline care to prevent a recurrent stroke.
 - Unknown cause ~ 40% , 65% in COVID
 - Recurrence rate ~ 25%
2. COVID and respiratory conditions have made diagnosing cause of stroke more difficult.
3. ISC-REST, the only clinically available molecular blood test for stroke and respiratory to stratify patients into down stream efficiencies, because when cause is known guideline care can significantly reduce recurrence risk.

