THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Clumsy Coagulation Communication
Let's Blame the Lab!

George A Fritsma MS, MLS
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Lab Scientist–Clinician Communication

- Diagnostic errors—barriers and opportunities
- How does lab science improve patient experience?

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Total Testing Process

Lab Consult	Lab Consult	Lab	Lab Consult	Lab Consult
"Pre-pre" Analytical	**Pre-Analytical**	**Analytical**	**Post-analytical**	**"Post-post" Analytical**
Pt visits Dr with complaint	Collector addresses Pt, collects spec	Scientist performs assay	Lab personnel publish and deliver report	Dr & staff interpret results
Dr & staff select and order "labs"	Select tube, fill, invert, ID, manage spec	Validate, internal and external QC	Narrative, direct to electronic health record	Dr & staff treat Pt

- Ward-Cook KM, Lehmann CA, Schoeff LE, Williams RH. Clinical Diagnostic Technology—The Total Testing Process, 2004, AACC Press
- Laposata M. Clin Chem Lab Med 2007;45:712–9

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QC Error Rate Improvements

Era	Rate/Million	Comment
1947–90	162,116	Triggers first external QC
1996 Australia	20,000–300,000	Mostly transcription errors
1996 CAP	12,904	Automation, information technology, internal QC rules and training, improved external QC
1997 CAP	2700	

Plebani M. Exploring the iceberg of errors in laboratory medicine. Clinica Chimica Acta 2009; 404: 16–23.

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Quality Assurance in the 1990s

- Plebani; 1997 error rates, pre, 68%; analytical,13%; post,19%
- "The evil is in the boundaries," interface of lab and clinic
- Poor *extra-analytical* error attention & documentation
- Pre-analytical: *ID errors, poor tube-filling, blood/AC ratio, hemolysis*
- Post-analytical: data *receipt, reading, interpretation, usage*
- No lab scientist interpretation or consultation
- But isn't this outside the lab's control?

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Quality Improvement in the 1990s

- QI initiatives address extra-analytical errors
  - Reliable patient ID
  - Bar codes, require two data pieces
  - Quality criteria for specimen acceptance
- 1998: "patient-centered" clinical consults
  - Identify defects that can have negative patient impact
  - The "brain-to-brain loop"

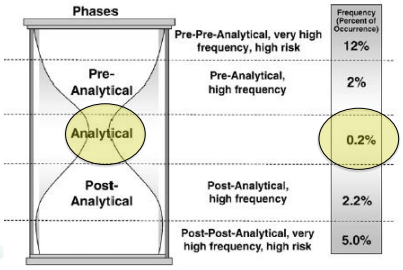
Lundberg GD. The need for an outcome research agenda for clinical laboratory testing. JAMA 1998;280:565–6.

Quality Care Indicators in 2003

- McGlynn surveyed 6712 adults, 12 metropolitan areas
- Addressed 439 quality care indicators
- 61% had the correct laboratory test ordered
- 55% received lab-recommended care

McGlynn EA, et al. N Eng J Med 2003; 348:2635–45

Where are the Errors Now?



Stroobants AK. Goldschmidt HM, Piebani M. Error budget calculations in laboratory medicine: linking the concepts of biological variation and allowable medical errors. Clin Chim Acta 2003;333:169–76.

Improvements in the 2000s

- Improving lab interest in patient safety, focus on how lab errors cause adverse patient events
- Improving failure analysis, error definitions
- Collecting evidence for "extra-analytical" errors
- Applying patient safety incentives, redundancy, and data backups to insure clinician response
- Recognizing that computers alone can't improve error rate
  - Computerized entry systems can actually raise error rate
- Developing lab-clinician interface
  - Emphasis on evidence-based practice: clinical trial data, standards
  - Diagnostic mgt team (DMT), M. Laposata, UTMB Galveston
  - Improve test selection, eliminate obsolete tests
  - Central POC testing QC

Challenges in the 2000s

- Laboratory service consolidation
  - Commoditization and outsourcing
  - Specimen mgt confounded by transport, storage, delay
- Professional staff reduction
  - Reduced retention, increased turnover, need to orient staff
  - Workload redirects staff attention from extra-analytical error
  - Adoption of lower-level staff in less demanding positions
  - Easy-to-use instruments don't improve error rate
  - Phlebotomist not responsible for the lab assay
- Emphasize cost-per-test over patient care
- Outcome: deterioration of service

Factors Driving Complexity

- Information explosion
  - 20,000 medical journals, thousands of DRGs
  - New drugs, "designer" drugs, TDM
- Health care reform
  - Millions of additional health care consumers
  - Focus on value: benefit/cost
- Laboratory provides best benefit/cost
  - Laboratory supports 70% of medical decisions
  - Laboratory spends 2% of CMS charges

Accountable Care Organizations

- Organization that ties alternative "capitation" payments to quality metrics and the cost of care.
- Coordinated health care providers accountable to patients and third-party payers for quality, appropriateness and efficiency of services.
- Targeted to Medicare patients.
- Measures of team coordination, reduced blood usage, early intervention, reduced redundancy, quality of life measures
- Electronic health records with hand-held devices

Fisher ES, Staiger DO, Bynum JPW, Gottlieb DJ. Creating accountable care organizations: the extended hospital medical staff. *Health Aff*. 2007; 26(:w44–w57.

Patient-Centered Medical Home

- Personal physician provides 1st contact, leads a team of practitioners who collectively take responsibility for comprehensive ongoing care.
- Care is coordinated or integrated among complex systems.
- Registries, EHR, and exchanges ensure patients receive culturally and linguistically appropriate care.
- Voluntary engagement in performance measurements to gauge quality improvement.
- Enhanced access: open scheduling, extended hours
- New options for communication: email, text, Skype.

H-160.919 "Principles of the Patient-Centered Medical Home." AMA Policy Finder. The AMA. Retrieved 9 June 2014.

Patient-Centered Medical Home Payment for…

- Time spent in care management outside F2F.
- Service coordination.
- Enhanced communication tools.
- F2F visits, not reduced by diversion of resources.
- Payment recognizes case mix differences in the patient population.
- Members share savings from reduced hospitalizations.

Diagnostic Errors

- Test order delay, dropped
- Failure to employ indicated tests
- Obsolete tests
- Test reporting error
- Failure to act on test results

Institute of Medicine: Crossing the quality chasm: a new health care system for the 21st century. Washington, DC: National Academy Press. 2001.
To Err is Human: Building a Safer Health, National Academy Press; www.nap.edu accessed 8-24-16

Primary Care Physician Lab Diagnosis Errors

- PCP test ordering error: 12.9%
- Results not returned to clinician: 24.6%
- Misfiling and poor chart availability: 17.6%
- Analytical errors: 0! (not reported to PCPs)

AMERICAN ACADEMY OF FAMILY PHYSICIANS
STRONG MEDICINE FOR AMERICA

Hickner J, Graham DG, Elder NC, et al. Testing practices: a study of the American Academy of Family Physicians National Research Network. Qual Saf Health Care 2008;17:194–200

Primary Care Practice Errors Malpractice Claim Review

- Adverse consequences of errors
  - No consequences, 26%; delay in care, 24%; financial loss, 22%; pain and suffering, 11%; other, 17%
- Malpractice claims of lab & imaging errors
  - Adverse physical outcomes, 58%; death, 30%
  - Missed diagnosis: cancer, 59%; infections, 5%; fractures, 4%, acute myocardial infarction (AMI), 4%
  - Failure to order appropriate test, 55%; ordered but not performed, 9%; lab performed incorrectly, 8%; PCP did not receive results, 12%; incorrect interpretation, 37%
- PCPs who monitor error reduce errors by 50%

Gandhi TK, Kachalia A, Thomas EJ, et al. Missed and delayed diagnoses in the ambulatory setting: a study of closed malpractice claims. Ann Intern Med 2006;145: 488–96.

Patient With Recent DVT/PE

From the AACC Consumer Web Forum, August 23, 2016: "After DVT/PE helped by TPA/Heparin and now on Xarelto 4 weeks, my first blood draw by new doctor shows factor VIII 228%, DRVVT screen 126 sec, confirmation 61 sec, normalized ratio 1.96, but hex phase phospholipid normal range and antiphospholipid normal range. Are any of these likely affected by clots still dissolving? Does any of this suggest long term clotting disorder just manifesting now? All other reports normal except slightly elevated liver enzymes."

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TPatient With Recent DVT/PE

Assay	Patient	RI
DRVVT Screen	126 s	0–52 s
DRVVT Confirm	61 s	0–34s
DRVVT normalized ratio	1.96	0.00–1.21
Factor VIII	228 u/dL	35–150 u/dL

Quoted from laboratory report:

- Abnormal screen is confirmed after addition of phospholipid.
- The normalized ratio is abnormal indicating the presence of lupus anticoagulant.
- However, note that oral anticoagulant therapy can yield false positive results.
- What would you say about these results?
- What follow-up is necessary?

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Choosing Wisely: Am Board of Internal Medicine Foundation and Consumer Reports American Society of Hematology

- Don't transfuse more than the minimum RBC units necessary to relieve symptoms of anemia or to return a patient to a safe HGB range—7–8 g/dL in stable, non-cardiac in-patients.
- Don't test for thrombophilia in adult patients with VTE in the setting of major transient risk factors—surgery, trauma, immobility.
- Don't administer plasma or PCCs for non-emergent reversal of Coumadin except in major bleeding, intracranial hemorrhage or anticipated emergent surgery.
- Don't anticoagulate for more than three months in a patient with a first VTE in the setting of a major transient risk factor.
- Don't test or treat for suspected heparin-induced thrombocytopenia (HIT) in patients with a low pre-test probability of HIT.

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A Personal Experience

CBC	Patient	RI
MCV	104 fL	80–100 fL
MCH	33 pg	26–32 pg
MCHC	34%	32–36%
Urinalysis	1+ bili	No bili
CBC, UA, chem panel, lipids WNL Repeated after 4 weeks, identical results. Would you follow up?		

- Liver enzymes normal
- Repeat CBC, same results, no blood film exam
- B12 and folate specimen neglected and discarded

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Survey of Primary Care Physicians and the Medical Laboratory, 2014

- 500,000,000 USA PCP patient visits per year
- 1800 PCPs, mean age 51, years in practice, 21, patients seen per week, 81
- Averaged 25 diagnostic lab tests/week, 31% of pts
- Uncertain about what test (s) to order: 14.7% of pts who needed diagnostic tests
- Uncertain about how to interpret results: 8.3%
- Potential ~23,000,000 incorrectly ordered or interpreted tests/year

Marques MB, Hickner J, Thompson PJ, Taylor JR. Primary care physicians and the laboratory; now and the future. Am J Clin Pathol 2014;142:738–40.

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How do PCPs Deal with Laboratory Ordering Uncertainty?

- Check e-references: 57% daily to weekly
- Review papers: 23%
- Refer patient to a specialist: 22%
- Check official guidelines: 21%
- Consult (curbside) fellow PCP: 14%
- Consult with lab professional: 6%
  - Laboratory scientist helpful 53% of time
  - Curbside consults helpful 75% of time

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What PCPs Hate about Labs

- Confusing test names
- Slow turnaround time
- Difficult to access prior results
- Reference interval variation
- Report info and format variation

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MB Marques, "I know for certain that most of my relevance as a member of the medical staff stems from my direct relationships and collaboration with physicians from other departments."

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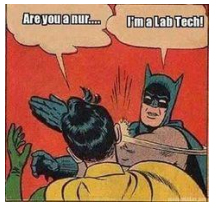
How do PCPs Deal with Laboratory Interpretation Uncertainty?

- Review patient history: 70%
- Follow up with patient: 66%
- Review e-references: 46%
- Order more lab tests: 34%
- Refer to a specialist: 29%
- Consult fellow PCP: 23%
- Check guidelines and references: 22%
- Repeat the same test: 19%
- Consult with lab professional: 6%
  - Helpful? 35%



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PCP Post-post Analytical Errors

- Diagnostic errors more frequent & cause more harm than Rx errors
- Types of post-post errors
  - Incorrect interpretation, 37%; inappropriate or inadequate follow-up, 45%; failure to refer, 26%
- Factors contributing to errors
  - Inadequate judgment, 70%; vigilance or memory, 59%; knowledge, 48%; patient-related, 46%; handoffs, 20%
  - Multifactorial: 54% of errors involve 3 process breakdowns; 29%, 4 or more
  - Multi-clinician: 43% of errors involve 2 or more physicians; 16% 3 or more

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Post-post Analytical Errors

- Duplicate health records
  - 400,000 HRs, 17,000 duplicates (4%), often single-entry
  - Labs: HGB A1c, TSH, LDL, vitamin B_{12}
  - Missed abnormal laboratory results, overall, 35%
  - 38% missed duplicate records compared to 28% in single
  - 18% abnormal results in secondary record
  - Odds ratio 1.44 of missing abnormal lab results in duplicated records
- Other reasons for missed lab results
  - Mass screening: OR 2.22
  - Old age: OR rises 1.15 per decade

Joffe E, Bearden CF, Byrne MJ, Bernstam EV. Duplicate patient records—implication for missed laboratory results. AMIA Annu Symp Proc. 2012; 2012: 1269–75.

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Reducing Diagnostic Errors

- Audit and resolve error and educate, don't punish
  - Disseminate practice guidelines & standards; provide clinical trial results instead of expert opinions
  - Enhance clinician knowledge of lab tests
- Improve systems
  - Modify laboratory test requisitions for easy ordering
  - Formulate *indication-based ordering* instead of test requests
  - Computerize decision-making strategies
  - Computerize order entry, check redundancy, duplicate records

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Cleveland Clinic Clinical Decision Support Tool (CDST)

- Computerized physician order entry (CPOE)
  - Reduces transcription error, provides real-time information
- Reduce duplicate lab testing
  - Unnecessary venipuncture, iatrogenic anemia, false positive follow-up
  - Costs: venipuncture, transport, analysis, resulting, clinical review
- 2010 "soft" stop with physician override
  - Reduced duplication of expensive tests like molecular diagnostics
  - Failed to reduce duplication of "routine" assays like *C. diff* PCRs


Gary Procop, MD

Procop GW, Yerian LM, Wyllie R, Harrison AM, Kottke-Marchant K. Duplicate laboratory test reduction using a clinical decision support tool. Am J Clin Pathol 2014;141:718–23.

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Why Are There Duplicate Orders?

- Physician can't afford time to check prior orders
- Physicians assume lab scientists catch duplicates
  - Doesn't help with venipuncture, transport, specimen management
- It would help if physician actually saw pending order list when placing orders in the CPOE


Robert Wyllie, MD

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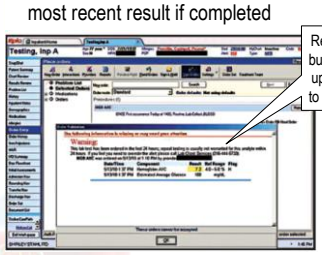
Cleveland Clinic CDST "Hard Stop" Assays

- Popup indicates test ordered same day and provides most recent result if completed



Results considered helpful but often overlooked. "Pop-up fatigue?" Many attempt to repeatedly reenter order.

Kandice Marchant, MD

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Assay Hard Stop Considerations

- What if controlled assay is part of a profile?
- Lab scientist must log duplicates (e. g. broken tube)
  - Internal override codes
- Institutional Review Board approval
- Test Utilization Committee agreement
- Bypass for medical necessity: phone Client Services
  - Physician name, test order, rationale
  - All bypasses recorded for statistical analysis
- Remove hard stop when proven inappropriate
- Broad participation, support from medical leadership

Lisa Yerian, MD

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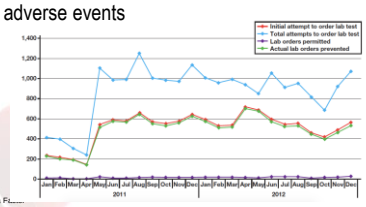
CDST Hard Stop Results

- Pilot, 13 assays; beta, 77; implementation, 1259
- In 2011–12, 12,204 hard stops employed, 414 overrides, saved $183,586 in materials and labor
- Savings excludes "soft" costs: phlebotomy, transport, accessioning, processing, assay results review
- No adverse events



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Cleveland Clinic Molecular Test Utilization CDST

- As of 2013, tests exist for >4000 genetic conditions
- Molecular assay costs rose 14% between 2008–10
- 8–30% of molecular assays ordered incorrectly
- Most physicians lack knowledge and experience
- Errors = diagnostic delays, inappropriate therapy

Riley JD, Procop GW, Kottke-Marchant K, Wyllie R, Lacbawan FL. Improving molecular genetic test utilization through order restriction, test review, and guidance. J Mol Diagn 2015;17:225–9.

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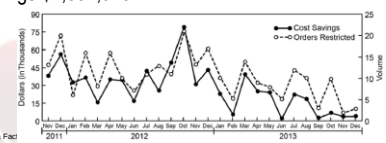
CDST Molecular Test Restrictions

- All inpatient molecular assay orders referred to laboratory-based genetic counselor
  - Criteria: requests for multiple genes or gene panels, discordance between specialty and type of test, discordance between the clinical diagnosis and test ordered, and cost >$1000
- Self-selected "deemed" users were physicians who used molecular testing regularly in their practice
- 2011–There were 13: 574 assays deferred, gross savings $1,531,913



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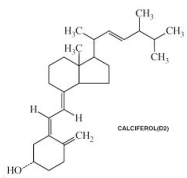
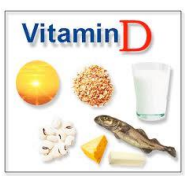
Pre-pre: Test Ordering

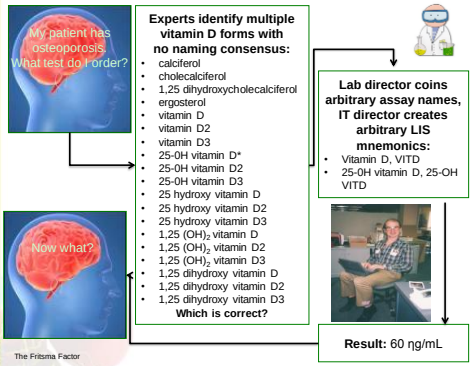
An order arrives with a serum-separator tube requesting "Vitamin D." How do you log it?





- Kleerekoper M, Schleicher RL, Eisman J, et al. Clinical applications for vitamin D assays: what is known and what is wished for. Clin Chem 2011;57:1227–32.
- Passiment E, Meisel JL, Fontanisei J, Fritsma GA, Aleryani S, Marques, M. Decoding laboratory test names: a major challenge to appropriate patient care. J Gen Intern Med DOI 10.1007/s11606-012-2253-8

"Pre-pre" Analytical Error: Test Selection



Choosing Wisely: Am Board of Internal Medicine Foundation and Consumer Reports American Society of Clinical Pathology

- Don't perform population-based screening for 25-OH-vitamin D deficiency.
- Avoid routine preoperative testing for low risk surgeries without a clinical indication.
- Don't use the bleeding time test to guide patient care.
- Don't ESR for acute inflammation in patients with undiagnosed conditions. Order a C-reactive protein (CRP).
- Don't test vitamin K levels unless the patient has an abnormal INR and does not respond to vitamin K therapy.
- Don't test for myoglobin or CK-MB in the diagnosis of acute myocardial infarction (AMI). Instead, use troponin I or T.

Pre-pre Naming Problems What's in a name?

Pre-pre Issues, Not Name-related

- PTT ordered for LMWH, fondaparinux, rivaroxaban?
- PTT interpretation in UFH Rx: 1.5–2.5 X MRI?
- Interpret PT and PTT when LA present?
- Lupus anticoagulant: what is it, lab diagnosis.
- What is in a thrombophilia profile?
- How to test for DOACs?
- What is in a VWD profile?

Pre-pre Issue: Pre-op Screen

Assay	Patient	RI
HGB	14.2 g/dL	13.5–15.6 g/dL
PTT	29 s	25–35 s
PT	12.4 s	9.8–12.6 s
BT	16.5 m	2–9 m
PLT count	310,000/µL	250–450,000/µL
Fibrinogen	270 mg/dL	150–400 mg/dL
D-dimer	190 ng/mL	110–240 ng/mL
No bleeding Hx, surgeon postpones procedure		

What do you recommend?

Choosing Wisely: Am Board of Internal Medicine Foundation and Consumer Reports American Society of Anesthesiologists

- Don't obtain baseline lab studies in patients without significant systemic disease undergoing low-risk surgery—CBC, metabolic panel, coag studies when blood loss (or fluid shifts) is expected to be minimal.
- Don't administer RBCs in a young healthy patient without ongoing blood loss and HGB of ≥ 6 g/dL unless symptomatic or hemodynamically unstable.

Pre-pre Issue: Pre-op Screen

Assay	Patient	RI
HGB	10.2 g/dL	13.5–15.6 g/dL
PTT	29 s	25–35 s
PT	12.4 s	9.8–12.6 s
PLT count	310,000/µL	250–450,000/µL
Fibrinogen	270 mg/dL	150–400 mg/dL
D-dimer	160 ηg/mL	110–240 ηg/mL
Hx: Easy bruising, chronic epistaxis, prolonged bleeding after shaving. Surgeon decides to go ahead with procedure.		

What do you recommend?

Pre-pre Issue: Pre-op Screen

Assay	Patient	RI
HGB	14.2 g/dL	13.5–15.6 g/dL
PTT	59 s	25–35 s
PT	12.4 s	9.8–12.6 s
PLT count	310,000/µL	250–450,000/µL
Fibrinogen	270 mg/dL	150–400 mg/dL
No bleeding Hx, surgeon postpones procedure		

What do you recommend?

Choosing Wisely
American Board of Internal Medicine Foundation and Consumer Reports: AABB

- Don't transfuse more units of blood than absolutely necessary.
- Don't transfuse red blood cells for iron deficiency without hemodynamic instability.
- Don't routinely use blood products to reverse warfarin.
- Don't perform serial blood counts on clinically stable patients.
- Don't transfuse O negative blood except to O negative patients and in emergencies for women of child bearing potential with unknown blood group.

Pre-pre: Thrombophilia Screen

Assay	Patient	RI
Protein C Activity	61%	>70%
Protein S activity	69%	>65%
Antithrombin activity	27%	78–126%
Factor VIII	125%	50–186%
APCR	2.4	>1.8
Factor II 20210	Wild-type	Wild-type
PTT-LA	34 s	30–40 s
Homocysteine	9 ηmol/L	>18 ηmol/L
50-YO man with DVT on heparin four days, physician ordered this thrombophilia profile		

What do you recommend?

Pre-pre: Thrombophilia Screen

Assay	Patient	RI
Protein C Activity	35%	>70%
Protein S activity	39%	>65%
Antithrombin activity	57%	78–126%
Factor VIII	125%	50–186%
APCR	2.4	>1.8
Factor II 20210	Wild-type	Wild-type
PTT-LA	39 s	30–40 s
Homocysteine	3.9 ηmol/L	<4.3 ηmol/L
60-YO woman, DVT; on Coumadin 3 weeks, physician ordered this thrombophilia profile		

What do you recommend?

Choosing Wisely
American Board of Internal Medicine Foundation and Consumer Reports

- American College of Chest Physicians
  - Don't order diagnostic tests at regular intervals (such as every day), but rather in response to specific clinical questions.
  - Don't transfuse RBCs in hemodynamically stable, non-bleeding ICU patients with a hemoglobin concentration greater than 7 g/dL.
- Society for Maternal-Fetal Medicine
  - Don't do an inherited thrombophilia evaluation for women with histories of pregnancy loss, intrauterine growth restriction (IUGR), preeclampsia and abruption.
- Society for Vascular Medicine
  - Don't order hypercoagulable testing for patients who develop first episode of DVT in the setting of a known cause.

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"Pre" Error: Specimen Management

- A phlebotomist collects a PT/INR using a "tiger-top" tube. The patient, who is on Coumadin, inquires about the tube; when she leaves, he transfers the specimen to a blue-closure tube and makes no note.
- What is in a tiger-top?
- What is the likely consequence?
- What really happened?

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Wrong Anticoagulant?

Data courtesy of Dorothy Adcock-Funk, MD, Esoterix Coagulation

Assay	Citrate	EDTA	Heparin	Serum
PTT	29s*	68s*	>180s	>180s
PT	12.4s*	23s*	>60s	>60s
FVII:Act	115%	116%	77%	308%
FVIII:Act	141%	4.5%	<1%	4.5%
FIX:Act	122%	115%	<1%	350%
VWF:Ag	122%	143%	70%	101%
VWF:RCo	114%	131%	37%	74%
PC:Act	111%	152%	<1%	<1%
PS:Act	96%	30%	<1%	21.6%
*Means				

Adcock, DM, Hoefner DM, Kottke-Marchant K. Collection, transport, and processing of blood specimens for testing plasma-based coagulation assays and molecular hemostasis assays; Approved Guideline−5th Edition, CLSI H21-A5; 2008.
Adcock-Funk DM, Lippi G, Favaloro EJ. Quality standards for sample processing, transportation, and storage in hemostasis testing. Semin Thromb Hemost 2012; 38: 576–85.

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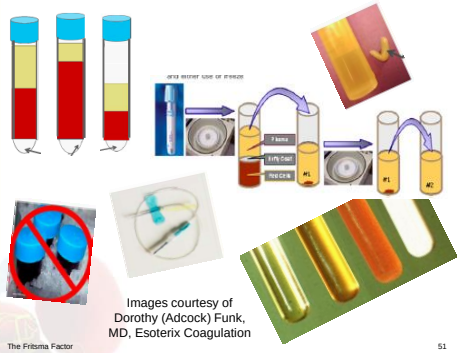
Pre-Analytical: Specimens



Images courtesy of Dorothy (Adcock) Funk, MD, Esoterix Coagulation

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Hemolysis: Cleveland Clinic ER

- At start, 18.5% moderately hemolyzed, 4.3% severe
- Most unit personnel are convinced specimens become hemolyzed in the lab.
- Straight stick in antecubital fossa is better than vascular access device in wrist
  - But no one in the ER will agree to stick twice
- Shorter tourniquet time, large bore needles
- Small vacuum tubes (syringes made no difference)
- At end, 2% hemolyzed specimen rate
- Instruments assay hemolysis, result unaffected assays, suppress affected assays. (IL "50" series)
- Ford A. Not fit to test: battling high hemolysis rates in the ED. CAP Today 2016, August, page 21.

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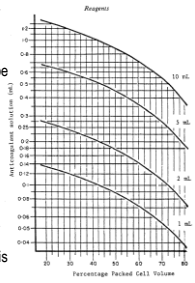
Pre: Adjust for HCT >55%

- $C = 1.85 \times 10^{-3} (100–HCT\%) V$
- Where…
  - C = final volume of anticoagulant in tube
  - HCT% = hematocrit
  - V = desired total volume of blood and anticoagulant
- Example, how much AC is needed to collect 2 mL blood from a patient with 70% HCT ?
  - $C = 1.85 \times 10^{-3} (30) \times 2 = 0.11$ mL
  - Remove 0.09 mL from 2 mL tube (is this possible?)



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Pre: Specimen Transport, No Ice

Two samples with originally >70% VWF:Rco, both held 6h at 4°C		
Assay	Sample 1	Sample 2
VWF:Ag	42%	68%
VWF:RCo	38%	30%
VWF:CB	12%	28%
Sample 1: false diagnosis of VWD type 1 in a normal subject Sample 2: false diagnosis of VWD type 2 in a normal subject		

- Cold precipitates large VWF multimers
- Cold activates platelets and FVII
- Refrigerate EDTA tubes up to 24 h for hematology to stabilize platelet count and HCT
- In clot tubes for clinical chemistry, cold raises serum K^+

- Favaloro E. Thromb Haemost 2001;86:1589–90
- Young D. Effects of preanalytical variables on clinical laboratory tests. AACC Press, 1997

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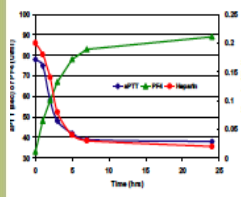
Pre: Specimen Storage



PPP stored 24h at 1–4°C			
Factor	Fresh	12h	24h
1. VIII	110%	102%	71%
2. VIII	60%	47%	39%
3. VIII	51%	50%	33%
FV	94%	93%	87%
PS	93%	97%	63%

Adcock D, Kressin D, Marlar RA. The effect of time and temperature variables on routine coagulation tests. Blood Coagul Fibrinolysis 1998;9:463–70.

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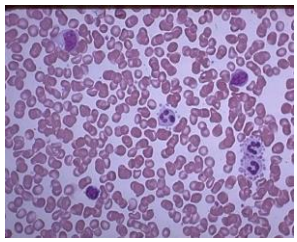
Pre: Thrombocytopenia

A CBC is collected on a 65-YO man during his annual physical and the PLT count is 59,000/μL. He reports no bleeding and his previous counts are normal. Suspecting ITP, the physician orders a bone marrow examination. What would you recommend?

Zandecki M, Genevieve F, Gerard J, Godon A. Spurious counts and spurious results on haematology analysers: a review. Part II: white blood cells, red blood cells, haemoglobin, red cell indices and reticulocytes. Int J Lab Hematol 2007;29:21-41.



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2016 New Phlebotomy Rules

- Phlebotomist must assemble materials in patient's sight
- Patient must spell full name, verbalize name and birth date.
- Patient must verify tube label.
- All tubes must be filled to stated volumes.
- Tube contents cannot be combined.
- Facilities must monitor blood volume totals, avoid iatrogenic anemia.

Clinical and Laboratory Standards Institute (CLSI). *Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard—Sixth Edition.* CLSI document GP41-A6 [ISBN 1-56238-650-0]. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2007.

CLSI GP41-A7 due 2016

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Analytical (Lab) Error: Thrombophilia Screen

Assay	Patient	RI
Protein C *antigen*	73%	>70%
Protein S *antigen*	99%	>65%
Antithrombin *antigen*	93%	78–126%
Factor VIII	125%	50–186%
APCR	2.4	>1.8
Factor II 20210	Wild-type	Wild-type
PTT-LA	39 s	30–40 s
Homocysteine	3.9 ηmol/L	<4.3 ηmol/L
45-YO woman, three DVTs in five years		

What do you recommend?

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Post-post: Thrombophilia Report

Assay	Patient	RI
Protein C activity	35%	>70%
Protein S activity	39%	>65%
Antithrombin activity	57%	78–126%
Factor VIII	125%	50–186%
APCR	2.4	>1.8
Factor II 20210	Wild-type	Wild-type
PTT-LA	39 s	30–40 s
Homocysteine	3.9 ηmol/L	<4.3 ηmol/L

- Triple heterozygote?
- Terminate pregnancy?
- Increase Coumadin?
- Start heparin?
- Consult with the lab?

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Post-post: Thrombophilia Report

Assay	Patient	RI
Protein C activity	35%	>70%
Protein S activity	39%	>65%
Antithrombin activity	57%	78–126%
Factor VIII	125%	50–186%
APCR	2.4	>1.8
Factor II 20210	Wild-type	Wild-type
PTT-LA	39 s	30–40 s
Homocysteine	3.9 ηmol/L	<4.3 ηmol/L

Or: "*Protein C, S, and AT appear deficient, probably Coumadin interference, reflex INR = 2.1, suggesting Coumadin is present. Other risk factor assay results are within reference interval. No evidence for thrombotic risk, repeat profile 2 weeks after discontinuing Coumadin.*"

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Post-post Issue: Pre-op Screen

Assay	Patient	RI
HGB	14.2 g/dL	13.5–15.6 g/dL
PTT	59 s	25–35 s
PT	12.4 s	9.8–12.6 s
TT	18.2 s	<21 s
PLT count	310,000/µL	250–450,000/µL
Fibrinogen	270 mg/dL	150–400 mg/dL
No bleeding Hx, surgeon postpones procedure		

- Heparin present?
- Risk: bleeding? Thrombosis?
- Repeat PTT until negative?
- Consult with laboratory?
- Laboratory immediate reflex to…

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Pre-op Screen: How About This?

Assay	Patient	RI
HGB	14.2 g/dL	13.5–15.6 g/dL
PTT	59 s	25–35 s
PT	12.4 s	9.8–12.6 s
TT	18.2 s	<21 s
PLT count	310,000/µL	250–450,000/µL
Fibrinogen	270 mg/dL	150–400 mg/dL
No bleeding Hx, surgeon postpones procedure		

"*Isolated prolonged PTT may indicate coagulation factor deficiency, coagulation factor inhibitor, or lupus anticoagulant. Normal TT indicates no heparin present. Laboratory reflex to PTT mixing study, results follow.*"

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Mixing Study: New Specimen, Next Day

Assay	Result	RI	Comment
PTT	57 s	25–35 s	Confirms prior PTT
PTT/control 1:1 immediate mix	38.5 s	Control 27.5 s	Commercial platelet-free normal control plasma

- Uncorrected?
- Should lab have done incubated mix?
- Do you send this result to the surgeon?
- Continue to delay surgery?
- Consult with laboratory?
- Laboratory immediate reflex to…

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Mixing Study: How About This?

Assay	Result	RI	Comment
PTT	57 s	25–35 s	Confirms prior PTT
PTT/control 1:1 immediate mix	38.5 s	Control 27.5 s	Commercial platelet-free normal control plasma

Interim report: "*Patient plasma mixed 1:1 with normal plasma, PTT performed immediately after mix remains prolonged (uncorrected). Presumptive evidence of lupus anticoagulant. LA profile follows.*"

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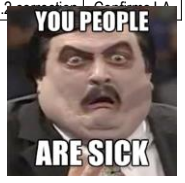
LA Profile: Third Day of Hospital Stay

Assay	Result	RI	Comment
PTT-LA	47.9 s	30–40 s	Confirms PTT
PTT-LA /control 1:1	38.5 s	Control 34.5 s	Possible LA
Staclot LA kit	12 s	> 8 s correction	Confirms LA
DRVVT	52.5 s	35–45 s	Possible LA
DRVVT confirm	1.4 ratio	> 1.2 correction	Confirms LA

- Send this result to the surgeon w/o comment?
- Delay surgery?
- Consult with laboratory?



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LA Profile: How About This?

Assay	Result	RI	Comment
PTT-LA	47.9 s	30–40 s	Confirms PTT
PTT-LA /control 1:1	38.5 s	Control 34.5 s	Possible LA
Staclot LA kit	12 s	> 8s correction	Confirms LA
DRVVT	52.5 s	35–45 s	Possible LA
DRVVT confirm	1.4 ratio	> 1.2 correction	Confirms LA

Or: "*Patient plasma tested using LA-sensitive PTT reagent and dilute Russell viper venom reagent, both prolonged, both corrected by high phospholipid neutralization reagent, confirming LA. No bleeding risk, may indicate thrombosis risk if LA is chronic. Repeat after 12 weeks to determine persistence.*"

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Pre-op Coags: Same as Before

Assay	Result	RI
PT	14.2 s	12.6–14.6 s
PTT	42.5 s	25–35 s
TT	17.5 s	< 21 s
PLT	245,000/µL	150–450,000/µL

- Heparin present?
- Risk: bleeding? Thrombosis?
- Repeat PTT until negative?
- Consult with laboratory?
- Laboratory reflex to…

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Pre-op Coags Same as Before How About This?

Assay	Result	RI
PT	14.2 s	12.6–14.6 s
PTT	42.5 s	25–35 s
TT	17.5 s	< 21 s
PLT	245,000/µL	150–450,000/µL

Or: "*Isolated prolonged PTT may indicate coagulation factor deficiency, coagulation factor inhibitor, or lupus anticoagulant. Normal TT indicates no heparin present. Laboratory reflex to PTT mixing study, results follow.*"

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Mixing Study: How About This?

Assay	Result	RI	Comment
PTT	42.5 s	25–35 s	Confirms previous PTT
PTT/control 1:1 mix immediate	31.1 s	Control 27.5 s	Commercial platelet-free normal control plasma
PTT/control 1:1 mix 2 h at 37°C	33.4 s	Control 31.3 s	Control is incubated alone and with mix

- Corrected?
- Send results to surgeon w/o comment?
- Delay surgery?
- Consult with laboratory?
- Laboratory reflex to…

Or: "*Patient plasma was mixed 1:1 with normal plasma, PTT is within 10% of normal plasma immediately and after incubation—corrected. Presumptive evidence of factor deficiency, factor assays follow.*"

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VWD Profile

Assay	Result	RI	Comment
FVIII	40%	50–150%	Mildly decreased
VWF:Ag	37%		VWD type 1
VWF:RCo	45%		
VWF:Act	48%		
VWF:CBA	37%		

- Send this result to the surgeon w/o comment?
- Delay surgery?
- Consult with laboratory?

Or: "*Results indicate von Willebrand disease type 1, risk of mucocutaneous bleeding may require pre-operative corrective therapy.*"

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Consultative Lab Testing

- "Indication-based" clinical query ordering
- Reduce cost by selecting correct assays
- Specimen management SOP
- Initial profile with algorithm-based reflex additions
- Assess causes for long PT or PTT: Hx of bleeding or thrombosis, interfering drugs, summarize results
- Conclude about abnormalities efficiently
- Reduce repeat orders
- Shortened TAT and inpatient stay
- Narrative interpretations, indicating cause and significance of the coagulation abnormality, bleeding and thrombotic risk, recommendations for therapy

Kandice Marchant, MD, PhD; Cleveland Clinic; Cleveland, Ohio

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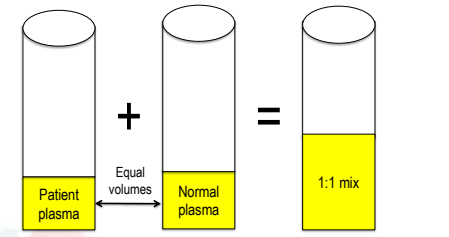
PTT Mixing Study



PTT 42.5 s

PTT 30 s

Manufacturer's value confirmed by laboratory QA supervisor

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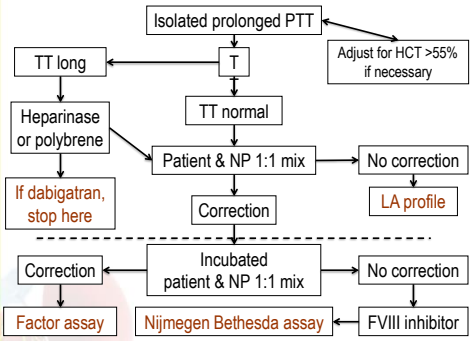
Acute Care Mixing Study Algorithm



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Choosing Wisely: Am Board of Internal Medicine Foundation and Consumer Reports Am College of Medical Genetics and Genomics

- Don't order a duplicate genetic test unless there is uncertainty about the validity of the existing test result.
- Don't order MTHFR genetic testing for the risk assessment of hereditary thrombophilia.
- Don't order HFE genetic testing for a patient without iron overload or a family history of HFE-associated hereditary hemochromatosis.
- Don't order exome or genome sequencing before obtaining consent that includes the possibility of secondary findings.

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The Fritsma Factor 75

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