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Clumsy Coagulation Communication
Let's Blame the Lab!

George A Fritsma MS, MLS
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Lab–Clinician Communication

- Barriers and opportunities
- Where are the errors made?
- How do we enhance patient experience?

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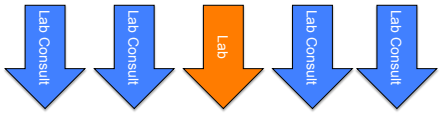
Total Testing Process



"Pre-pre" Analytical	Pre-Analytical	Analytical	Post-analytical	"Post-post" Analytical
Patient visit	Specimen collection	Assay performed	Assay result published and delivered	Doctor interprets result
Dr. writes lab order: correct test selection	Tube selection, fill, mix, ID, specimen management	Validation, lot-to-lot, internal & external QC	Written report to chart, electronic delivery	Doctor treats patient

- 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

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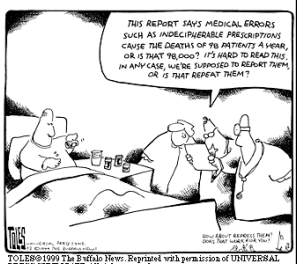
IOM: Quality Domains

- Patient-centeredness
- Effectiveness
- Timeliness
- Efficiency
- Safety
- Equity

Institute of Medicine: Crossing the quality chasm: a new health care system tor the 21st century. Washington, DC: National Academy Press. 2001.



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Quality Assurance in the 1990s

- 1996–7: CAP error rate improvements
  - Improved internal and external QC approaches
  - Automation reduced errors
- Plebani; 1997 error rates, confirmed 2007: pre, 68%; analytical,13%; post,19%
  - "The evil is in the boundaries," interface of lab and clinic
  - Poor *extra-analytical* error rate attention & documentation
  - Pre-analytical: ID errors, poor tube-filling, blood/AC ratio
  - Post-analytical: gaps in data *receipt, reading, interpreting, usage*
  - No assay interpretation and consultation
  - Indiscriminate adoption of POC testing

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

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Quality Improvement in the 1990s

- QI initiatives address extra-analytical errors
- Reliable patient ID
  - Bar codes, use of two data pieces
- Quality criteria for specimen acceptance
- 1998: "patient-centered" clinical consults
  - Any defect 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.

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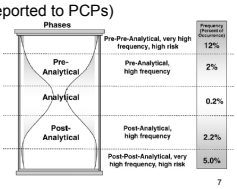
Quality Assurance in the 2000s

- Hazard Analysis and Critical Control
  - Stroobants: "Pre-pre" error rate 12%, post-post 5%
- Primary care physician errors: Hickner
  - Test ordering: 12.9%
  - Reporting results to clinician: 24.6%
  - Misfiling and poor chart availability: 17.6%
  - Analytical errors: 0 (not reported to PCPs)

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.
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



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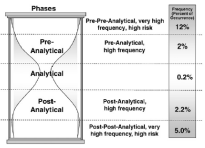
Quality Assurance in the 2000s McGlynn Study

- 6712 adults in 12 metropolitan areas
- 439 quality care indicators
- 61% had the correct laboratory test ordered
- 55% received recommended care



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

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Primary Care Practice Errors

- Adverse consequences of errors
  - No consequences, 26%; delay in care, 24%; financial and time 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%
- PCP practices that monitor cut errors 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.

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PCP Post-post Analytical Errors

- Dx errors cause more harm and are more frequent than drug or treatment errors
- 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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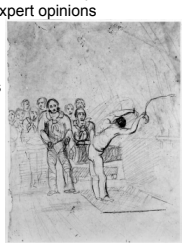
Reducing Diagnostic Errors

- Resolve error and educate, don't punish
  - Enhance clinician knowledge of lab tests
  - Disseminate practice guidelines & standards; provide clinical trial results coupled with expert opinions
  - Audit errors
- Improve systems
  - Modify laboratory test requisitions
  - Formulate *clinical queries* in place of test requests
  - Computerize order entry, check redundancy and decision-making strategies



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Cleveland Clinic Test Utilization Committee

Order Duplication Review

- In 2010, of 4,326,387 selected inpatient tests, 27,549 (0.64%) were ordered more than once a day
- Created list of tests that shouldn't be ordered more than once a day, confirmed with medical staff
- Implemented "hard stops" for attempted duplicate orders
- Means for the caregiver to still order the test, but with documentation and lab approval

Marchant C, Procop G; Test Utilization Committee

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Cleveland Clinic Test Utilization Committee "Hard Stop" Assays

- Quantitative transplant viruses: CMV, EBV, BKV
- Molecular thrombosis markers: FVL, FII 20210
- Total cholesterol, HDL, LDL, triglyceride
- *Clostridium difficile* EIA
- Thrombophilia panel
- Reticulocyte count
- CRP, HGB A1C
- Hepatitis panel
- Iron and TIBC
- Will expand list and extend time intervals

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Improvements in the 2000s

- Improving lab interest in patient safety, focus on how lab errors cause adverse patient events
- Improving error definitions, failure mode analysis
- Collecting evidence for extra-analytical errors
- Applied patient safety incentives, redundancy, and data backups to insure clinician response
- Recognize that IT alone can't improve error rate
  - Computerized entry systems can raise error rate
- Developing lab-clinician interface
  - Emphasis on evidence-based practice: clinical trial data, standards
  - The diagnostic management team (DMT), M. Laposata, Vanderbilt
  - Improve test selection, eliminate obsolete tests
  - Develop narrative interpretations
  - Control POC testing

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Challenges in the 2000s

- Laboratory service consolidation
  - Commoditization and outsourcing
  - Less emphasis on extra-analytical variation
  - Specimen management confounded by distance, time, storage
- Professional staff reduction
  - Workload redirects staff attention from extra-analytical error
  - Reduced retention, higher turnover, need to educate staff
  - 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
  - Outcome: slow deterioration of service
- Point-of-care devices
  - High CVs, personnel require education and supervision
- Balance cost-per-test with patient care value

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Factors Driving Complexity

- Information explosion
  - 20,000 medical journals, thousands of DRGs
  - Increasing number of drugs, personalized drugs
- Health care reform
  - Millions of additional health care consumers
  - Focus on value: benefit/cost
- USA Today 9.24.12: "Accountable Care Organizations Experience Record Profits"
  - Accountable care measures: smoking, weight loss, exercise, reduce blood usage, early intervention, redundancy
  - Electronic medical records with hand-held devices
- Laboratory provides best benefit/cost
  - Laboratory supports 70% of medical decisions
  - Laboratory spends 2% of CMS charges

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Lab-centered Enhancements

- *Clinical queries* in place of test selection
- Two patient identifiers at collection
- Label verified by patient after collection
- Simple SOPs for specimen management
- Evidence-based specimen acceptance criteria
- Rapid transmission of critical results with read-back protocols, especially to ER
- Reliable IT
- Interpretive narrations (or narrative interps)

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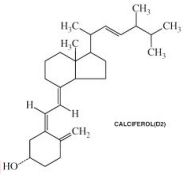
Pre-pre: Test Ordering

An order arrives with a serum-separator tube requesting "vitamin D." What exact test is this, and how do you log the order?



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.

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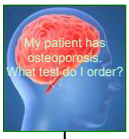
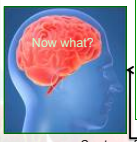
"Pre-pre" Analytical Error: Test Selection



Experts identify multiple vitamin D forms with no naming consensus:

- calciferol
- cholecalciferol
- 1,25 dihydroxycholecalciferol
- ergosterol
- vitamin D
- vitamin D2
- vitamin D3
- 25-0H vitamin D*
- 25-0H vitamin D2
- 25-0H vitamin D3
- 25 hydroxy vitamin D
- 25 hydroxy vitamin D2
- 25 hydroxy vitamin D3
- 1,25 $(OH)_2$ vitamin D
- 1,25 $(OH)_2$ vitamin D2
- 1,25 $(OH)_2$ vitamin D3
- 1,25 dihydroxy vitamin D
- 1,25 dihydroxy vitamin D2
- 1,25 dihydroxy vitamin D3

Which is correct?



Lab director coins arbitrary assay names, IT director creates arbitrary LIS mnemonics:

- Vitamin D, VITD
- 25-0H vitamin D, 25-OH VITD

Result: 60 ng/mL

Courtesy of Elissa Passiment, EVP, ASCLS and Julie Taylor, CDC; in press, J Gen Intern Med

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

FX PTT FVIII AT INR PC FV PT VWF

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Pre-pre Issues, Not Name-related

- PTT ordered for LMWH or fondaparinux
- PTT interpretation in UFH Rx: 1.5–2.5 X MRI
- INR for coagulopathy, do you want a PT?
- Interpret PT and PTT when LA present
- What is in a thrombophilia profile?
- Lupus anticoagulant: what is it, what do you do?
- What is in a VWD profile?

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Pre-pre: 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?

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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 ng/mL	110–240 ng/mL
Hx: Easy bruising, chronic epistaxis, prolonged bleeding after shaving. Surgeon decides to go ahead with procedure.		

What do you recommend?

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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?

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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 UFH 4 days, physician ordered this thrombophilia profile

What do you recommend?

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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 w, physician ordered this thrombophilia profile

What do you recommend?

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Pre: Specimen Management

- A phlebotomist collects a PT/INR specimen using a “tiger-top” tube. The patient inquires about the cap; when she leaves, he transfers the specimen to a blue-top and makes no note of his actions.
- What is in a tiger-top?
- What is the likely consequence?

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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%
*Mean values				

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.

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Pre-Analytical: Specimens

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

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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 used 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 draw tube (possible?)

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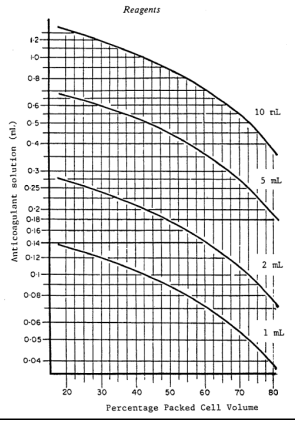
Pre: Adjust for HCT >55%



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Pre: Specimen Transport, No Ice

Two samples with originally >70% VWF:Rco, 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 type 1 VWD patient		

- Cold activates platelets and coagulation factor VII
- 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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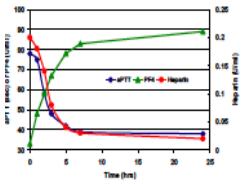
Pre: Specimen Storage



PPP stored 24h at 1–4°C			
Factor	Fresh	12h	24h
VIII	110%	102%	71%
VIII	60%	47%	39%
VIII	51%	50%	33%
V	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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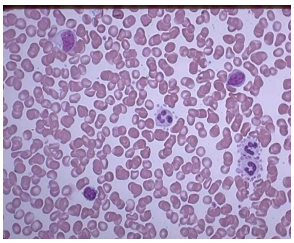
Pre: Thrombocytopenia

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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71 YO Female, Atrial Fibrillation 30 Years of 7.5 mg/day Coumadin

- Monday: INR 11, no bleeding symptoms
  - Target range 2–3
  - Hx: when INR 5–6: bruising, bleeding gums, epistaxis
  - Just started on statin
    - Total cholesterol: 263 mg/dL
    - Triglycerides: 319 mg/dL (lipemia?)
- Tuesday repeat collection: INR 11
  - Vitamin K 10 mg IV push, D/C Coumadin
- Thursday collected fasting: INR 1.5
  - Fasting, resume Coumadin 7.5 mg/day
  - Was it the vitamin K or lipemia?
- Monday: INR 2.5: lost follow-up

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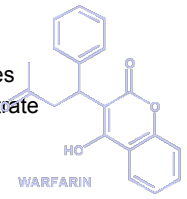
71-YO Female: Coumadin Indications

- Cardiac insufficiency 2° to acute coronary syndrome with ejection fraction <30%
- Venous thromboembolism (VTE)
  - Deep venous thrombosis (DVT)
  - Pulmonary embolism (PE)
- Atrial fibrillation
  - Prevent secondary stroke
- Prosthetic heart valves
- Did this problem illustrate a pre-analytical or an analytical error?



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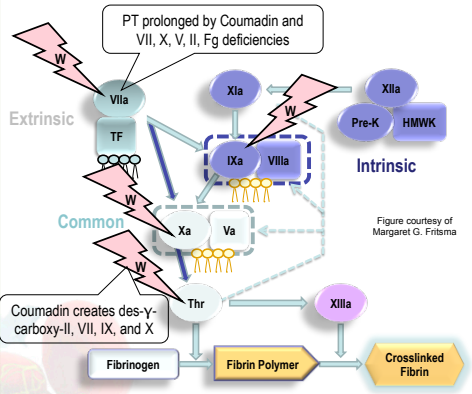

Figure courtesy of Margaret G. Fritsma

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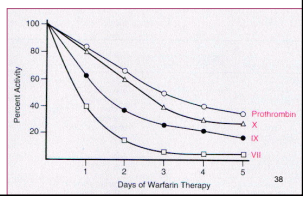
Is the PT/INR All it Could Be?

- INR invalid in first five days of therapy
- Optical coagulometers affected by lipemia
- PT falsely prolonged by lupus anticoagulant
- INR invalid during transition from direct thrombin inhibitors (argatroban) to coumadin
- POC INR adjusted to match plasma INR

Rosborough TK, Jacobsen JM, Shepherd MF. Relationship between chromogenic factor X and INR differs during early warfarin initiation compared with chronic warfarin administration. Blood Coagul Fibrinolysis 2009 20:433-5.



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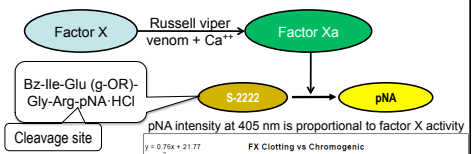
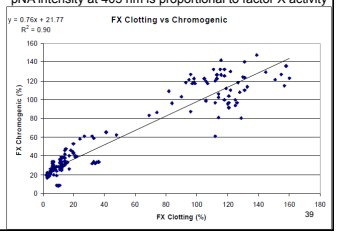
Chromogenic Factor X (CFX)



pNA intensity at 405 nm is proportional to factor X activity



diaPharma

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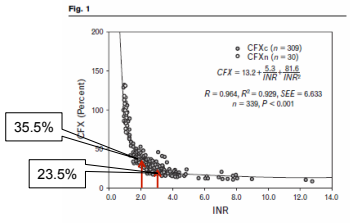
Chromogenic X In Place of PT?



A good model fit between INR and CFX when expressed as a second order inverse function ($n = 339$, $R^2 = 0.929$; $P < 0.001$). Open circles represent samples from normal control group (CFXn) and closed circles from patients receiving Coumadin therapy (CFXc). CFX, chromogenic factor X; INR, international normalized ratio.

McGlasson DL, Romick BG, Rubal BJ. Comparison of a chromogenic factor X assay with INR for monitoring oral anticoagulation therapy. Blood Coag Fibrinolys 2008;19:513–17

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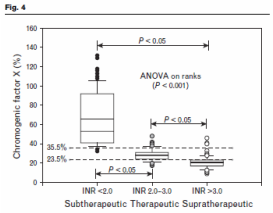
Chromogenic X in Place of PT?



Box plots (median: solid line, mean: dotted line, whiskers: 10th and 90th percentile) for CFX values categorized by INR therapeutic ranges. Significant differences were noted between all groups. Dashed lines indicate the CFX range (23.5–35.5%) is equivalent to the INR therapeutic range (INR 2.0–3.0). ANOVA, analysis of variance; INR, international normalized ratio.

"The data suggest the CFX can be a useful tool for monitoring oral anticoagulation in patients in which INR confounders are present."

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INR & Chromogenic X With Lupus Anticoagulant

- INR & CFX assayed in 44 control coumadin patients and 46 coumadin patients with LA
  - All were in therapeutic range for CFX 22–40% = INR 2–3
- 4 (9%) of controls had INR >3.0, none >4.0
- 18 (39%) LA patients had INR >3.0, 5 (11%) >4.0
- Monitoring Coumadin therapy by CFX in LA patients avoids LA-induced INR artifact

Rosborough TK, Shepherd MF. Unreliability of international normalized ratio for monitoring warfarin therapy in patients with lupus anticoagulant. Pharmacotherapy. 2004;24:838–42.

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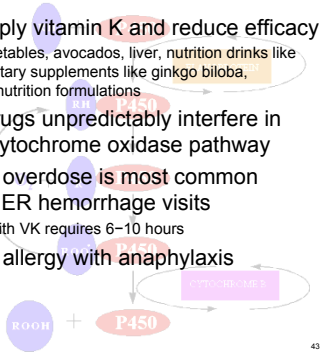
Coumadin Limitations

- These supply vitamin K and reduce efficacy
  - Green vegetables, avocados, liver, nutrition drinks like Ensure, dietary supplements like ginkgo biloba, parenteral nutrition formulations
- Over 80 drugs unpredictably interfere in CYP2C9 cytochrome oxidase pathway
- Coumadin overdose is most common reason for ER hemorrhage visits
  - Reversal with VK requires 6−10 hours
- Coumadin allergy with anaphylaxis



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Three Polymorphisms Raise Activity

CYP2C9*2, CYP2C9*3, VKORC1-1639 G>A

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes*

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

*Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the Table. VKORC1 -1639 G→A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3 and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

Caldwell MD, Awad T, Johnson JA. CYP4F2 genetic variant alters required warfarin dose. Blood 2008;111: 4106-12.

71-YO Female, Afib 30 Y

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Coumadin Resistance

- Coumadin resistance
  - VKORC1-3730 G>A variant raises dose 1 mg/d
  - CYP4F2 variant raises dose 1 mg/d
- Coumadin receptor insufficiency
  - Require dosages of 25 mg/d or more
  - What accounts for the rest?

Cini M, Legnani C, Cosmi B, Guazzaloca G, et al. A new warfarin dosing algorithm including VKORC1 3730 G > A polymorphism: comparison with results obtained by other published algorithms. Eur J Clin Pharmacol. 2012;68:1167–74.
Caldwell MD, Awad T, Johnson JA, et al. CYP4F2 genetic variant alters required warfarin dose. Blood 2008;111:4106–12.

35-YO Female, Post-DVT

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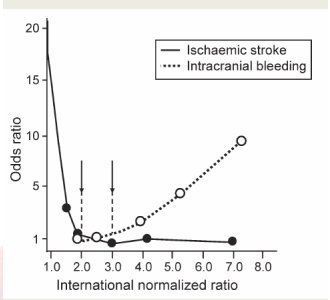
Coumadin Therapeutic Window



Turpie AGG. New oral anticoagulants in atrial fibrillation. Eur Heart J 2008;29:155–65

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