Laboratory Interpretive Services

TAKING YOUR LAB TO THE NEXT LEVEL IN MEETING MEDICAL NEEDS

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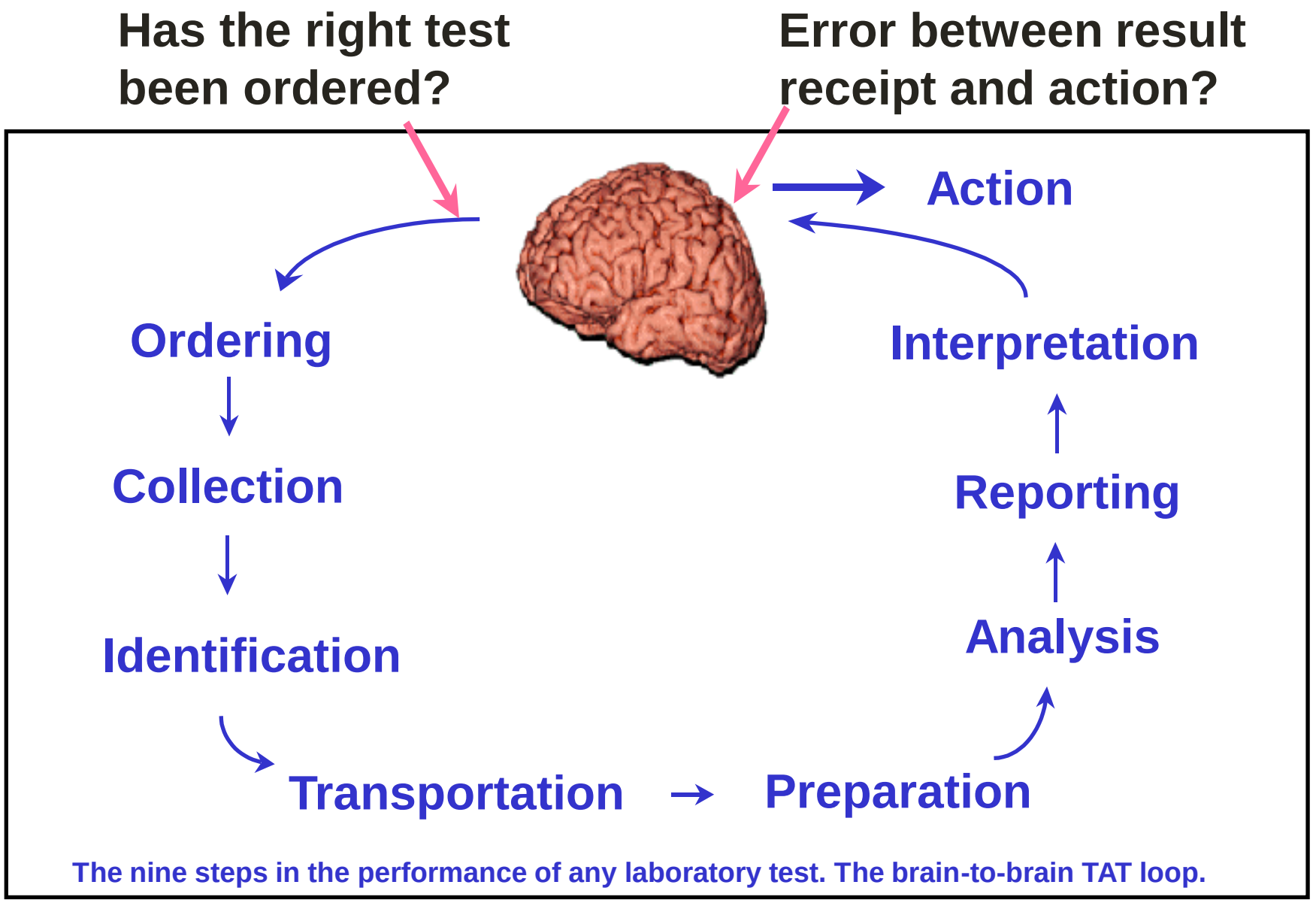
Learning Objectives

I. Recognize the complexity of physician ordering to select the right test for the patient

II. Identify how to provide an interpretive service

III. Describe the benefits of a Laboratory Formulary Committee

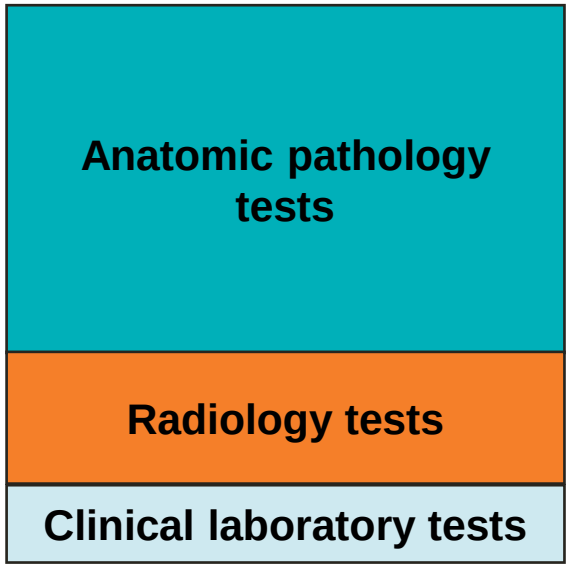


The nine steps in the performance of any laboratory test. The brain-to-brain TAT loop.

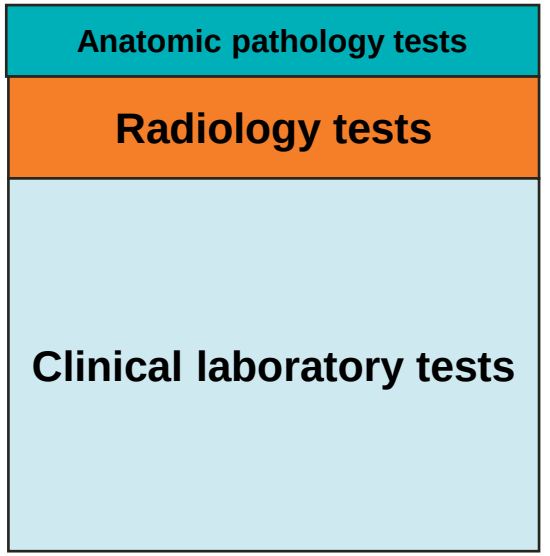
Lundberg, 1981 JAMA

Educational Mismatch with Medical Practice Competency

What medical students are taught about the diagnostic tests they will use in practice:



What diagnostic tests doctors order in practice and are required to interpret the test results by themselves:



NUMBER OF HOURS MEDICAL STUDENTS SPEND LEARNING AP: 60 – 300

NUMBER OF HOURS MEDICAL STUDENTS SPEND LEARNING LABORATORY MEDICINE: 9

Brian Smith and CLIHC group CDC preliminary data from survey US Medical Schools

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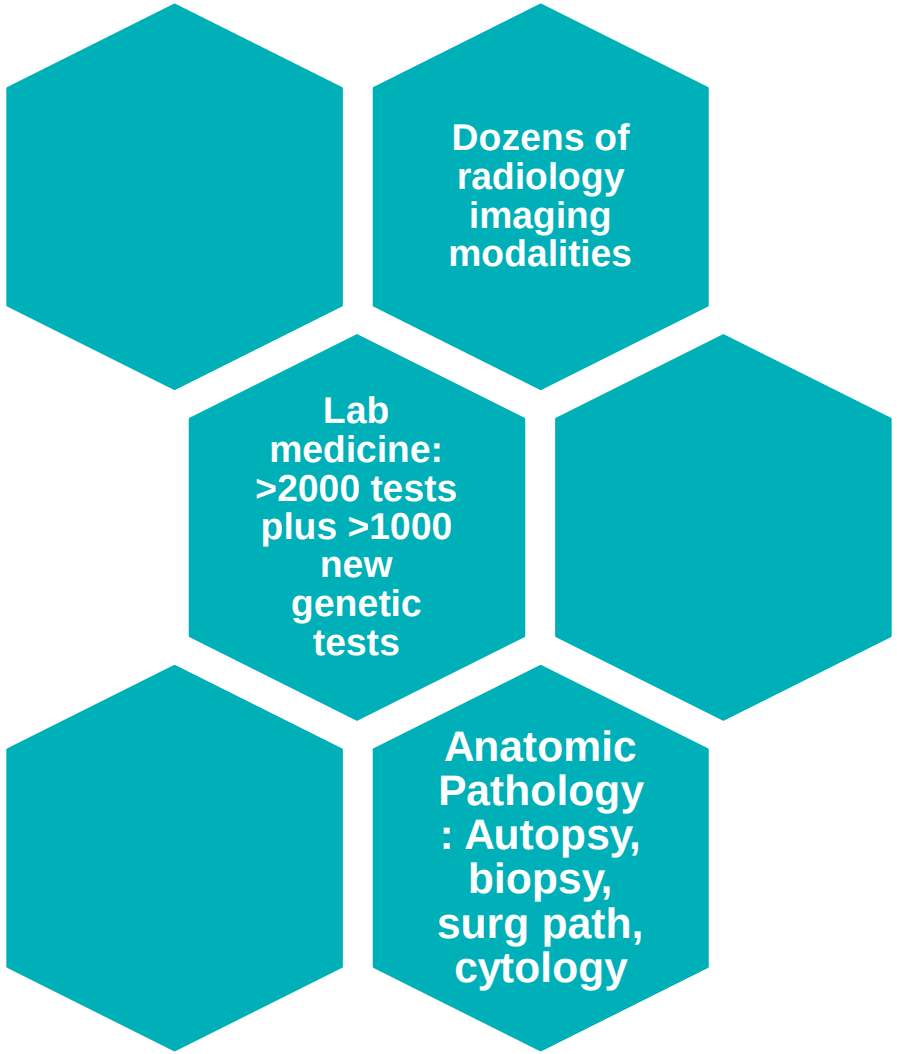
The Clinician's Diagnostic Challenge



- Radiologists do not give MRI images back to ordering physician without interpretation
- Anatomic pathologists do not give biopsies back to surgeons without interpretation

Why is it acceptable for clinical labs to give complex lab results back to physicians without interpretation?

Ordering Confusion

- Vitamin D
- Vitamin D2
- Vitamin D3

- 25 hydroxy vitamin D
- 25-OH vitamin D
- 25 hydroxy vitamin D2
- 25-OH vitamin D2
- 25 hydroxy vitamin D3
- 25-OH vitamin D3

- 1,25 dihydroxy vitamin D
- 1,25-diOH vitamin D
- 1,25 dihydroxy vitamin D2
- 1,25-diOH vitamin D2
- 1,25 dihydroxy vitamin D3
- 1,25-diOH vitamin D3

Multiple abbreviations and variations on naming

A doctor wants to know if a patient has vitamin D deficiency – which single test do they order?

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Consequences of Clinical Confusion

DOCTORS MISS THE NECESSARY TESTS

Laboratory testing is an integral part of clinical decision-making

- (29 – 98% of medical encounters order 1 or more laboratory tests, depending on the medical specialty – Outpatient 29%, ED 56%, inpatient 98%) *JALM 2017;01:410-14.*

Doctors order the wrong tests

- 25% of pathology tests are ordered unnecessarily. *Carter Review – Report of the Review of NHS Pathology Services in England 2006.*

Many approaches emerge to diagnose same condition

- 30% of care delivered in the US is inappropriate. *ASCP Choosing wisely campaign*

AREAS WHERE INTERPRETIVE ASSISTANCE NEEDED

- Hepatitis serologies
- Coagulation
- Drug testing
- Infectious disease

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Diagnostic Management Team (DMT)

- Physicians order tests by requesting DMT evaluation
  - Abnormal screening test
  - Clinical sign or symptom
- Expert team in the DMT synthesizes the clinical and laboratory data to provide a concise interpretive narrative based upon medical evidence

4 Pillars of a Diagnostic Management Team

Complex testing

- DMT clarifies unfamiliar test choices – through initial guidance or reflexive orders

Context-driven test selection

- Tests are chosen by group of laboratorians/clinicians in real-time based on clinical context (assists in best practice/guideline driven test selection)

Transparency

- DMT complements clinician's understanding of their patient's disease process

Interpretive reporting

- Interpretation ties the lab findings to clinical context to bring the findings together

Diagnosis and Treatment of Anemia

- Complex differential for anemia
  - Bleeding
  - Cancer/Leukemia
  - Age
  - Chronic disease
  - Iron deficiency
  - Hemoglobin variant

- Hematologists observe cell differential, but don't consider chemistry tests – chemists don't review heme results.
- Requires clinician to synthesize multiple results to develop a diagnosis

- A Heme DMT can review chemistry, hematology and other laboratory results to synthesize one combined interpretation that assist clinician in differential diagnosis of anemia and ongoing patient care

Heme DMT

Clinical components

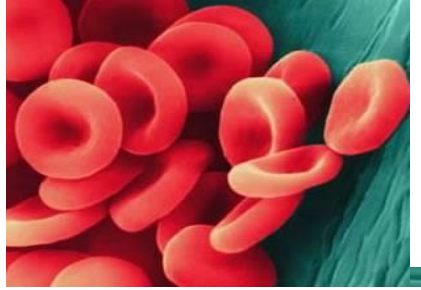
- Medical and family history
- Medications (hydroxyurea)
- Transfusion history

Analytical components

- HPLC (with reflex electrophoresis for hemoglobin variant)
- CBC (Hgb, RBC parameters, Mentzer's index, SickleDex)
- Iron studies (Iron, TIBC, % saturation, ferritin)
- Newborn screen results

Mentzer's Index

- If CBC shows microcytic anemia, ratio of MCV/RBC can distinguish iron deficiency from thalassemia.
- < 13 beta thalassemia more likely (thalassemia is a disorder of globin synthesis, normal amount of cells, but cells produced are smaller and more fragile, RBC normal, but MCV down, so ratio is low)
- >13 iron deficiency more likely (in iron deficiency bone marrow can't produce as many cells and cells are small, both MCV and RBC down)
- Not 100% reliable, iron deficiency and beta thalassemia can coexist, and ferritin more reliable measure of iron deficiency



High Performance Liquid Chromatography (HPLC)

BioRad Variant II β-Thal Short Program

Peak name	Retention time, min
F window	0.98–1.20
A_0 window	1.90–3.10
A_2 window	3.30–3.90
D window	3.90–4.30
S window	4.30–4.70
C window	4.90–5.30

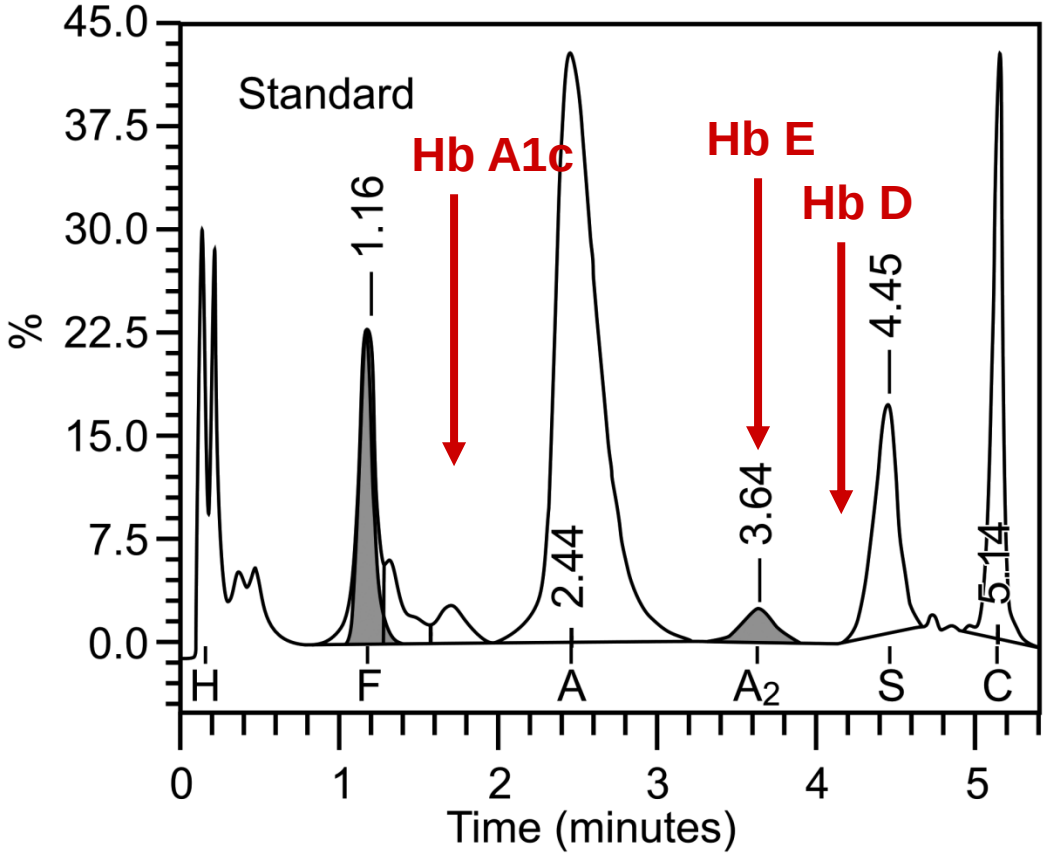
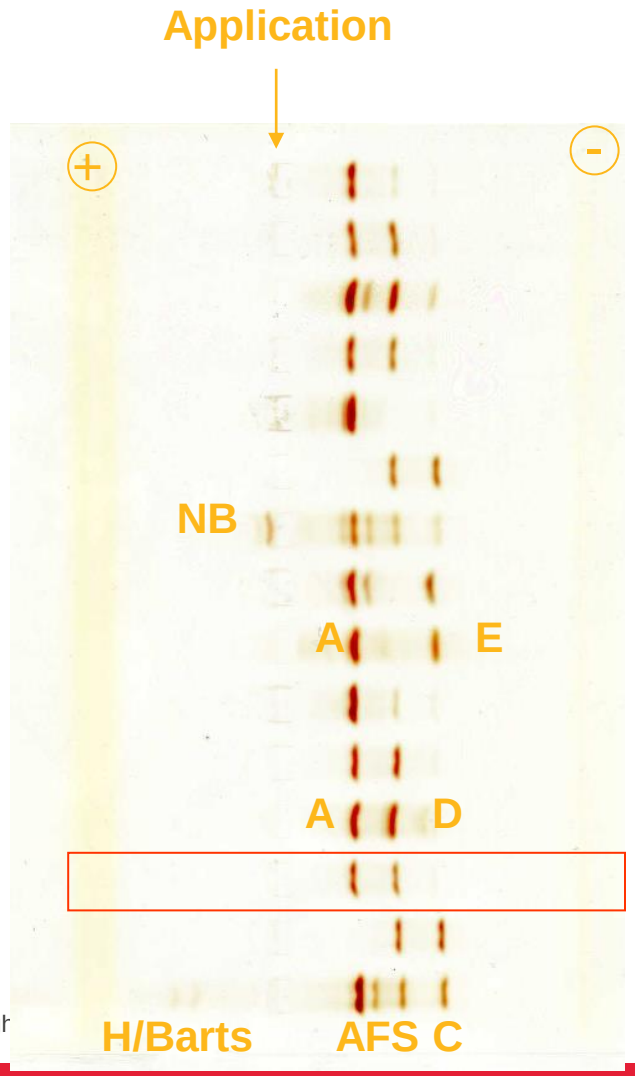


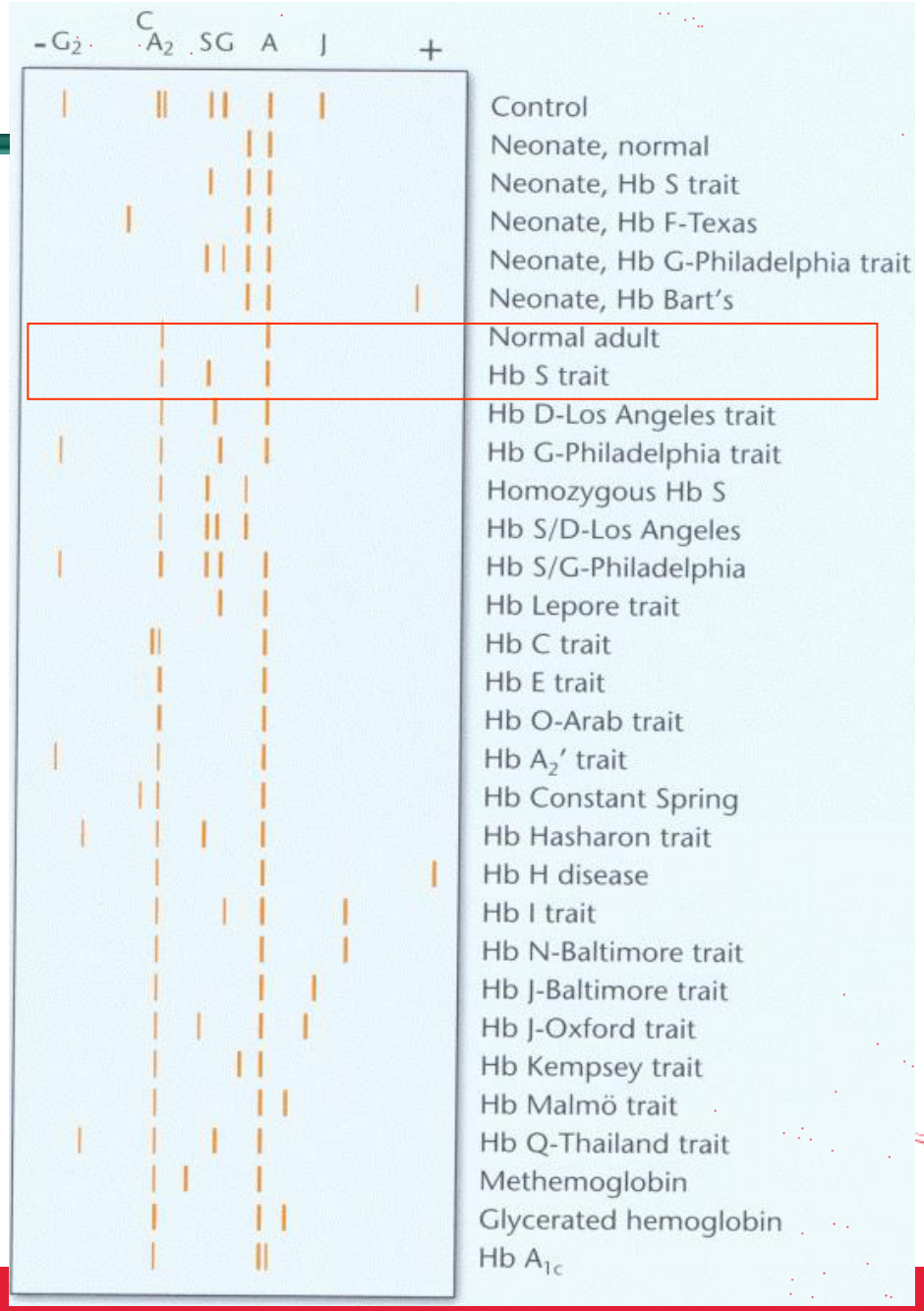
Table 2. Hemoglobins seen.

Variant name	n[a]	Retention time,[b] min	%Hb[c]	ΔTime,[d] months	Variant[e]
Hb Barts	ND[f]	0.2	ND	32	γ4
Hb H	12	0.2	12.5 (4.0)	32	β4
Hb F_1	ND	0.5	ND	32	–
Hb F	160[g]	1.10 (0.017)	1.0 (0.5)	32	–
Hb Hope	11	1.39 (0.007)	45.9 (2.2)	32	β 136Gly→Asp
Hb Camden	2	1.50; 1.48	52.4; 49.3	5	β 131Gln→Glu
Hb J-Oxford	1	1.60	24.7	–	α 15Gly→Asp
Hb Austin	3	1.68 (0.017)	47.1 (0.4)	12	β 40Arg→Ser
Hb N-Baltimore	6	1.70 (0.031)	47.8 (0.9)	21	β 95Lys→Glu
Hb Fukuyama	2	1.72; 1.73	–[h]	0	β 77His→Tyr
Hb Fannin-Lubbock	7	1.75 (0.024)	35.0 (3.0)	21	β 119Gly→Asp
Hb J-Anatolia	2	1.75; 1.75	19.9; 21.2	0.5	α 61Lys→Thr
Hb J-Mexico	2	1.74; 1.78	22.7; 22.3	10	α 54Gln→Glu
Hb J-Meerut	2	1.88; 1.88	25.4; 25.2	11	α 120Ala→Glu
Hb J-Toronto	1	1.94	–[i]	–	α 5Ala→Asp
Hb J-Bangkok	1	2.02	43.6	–	β 56Gly→Asp
Hb Ty Gard	1	2.20	34.1	–	β 124Pro→ Gln
Hb Köln[j]	2	2.26; 2.26 (4.93; 4.87)[j]	26.8; 23.5 (7.0; 7.3)[j]	24	β 98Val→Met
Hb A_0	160[g]	2.43 (0.041)	86.3 (1.5)	32	–
Hb New York	4[k]	2.43 (0.010)	Does not separate	12	β 113Val→Glu
Hb Twin Peaks	3	Appears as hump	Does not separate	11	α 113Leu→His
Hb Lepore	3	3.37 (0.019)	12.1 (1.5)	24	δβ-hybrid
Hb D-Iran	1	3.49	47.7	–	β 22Glu→Gln
Hb A_2	160[g]	3.63 (0.035)	2.7 (0.4)	32	–
Hb E	83[l]	3.69 (0.069)	30.3 (4.0)[m]	32	β 26Glu→Lys
Hb Osu-Christiansborg	1	3.77	44.0	–	β 52Asp→Asn
Hb G-Honolulu	1	3.86	27.4	–	α 30Glu→Gln
Hb Korle-Bu	8	3.92 (0.050)	46.5 (3.7)	16	β 73Asp→Asn
Hb D-Punjab	7	4.18 (0.007)	33.1 (1.8)	24	β 121Glu→Gln
Hb G-Philadelphia	8	4.22 (0.037)	26.4 (6.6)	29	α 68Asn→Lys
Hb E-Saskatoon	2	4.34; 4.32	39.3; 40.4	2	β 22Glu→Lys
Hb S	3587[n]	4.51 (0.030)	34.9 (4.1)[m]	32	β 6Glu→Val
Hb Manitoba	1	4.58	16.5	–	α 102Ser→Arg
Hb Montgomery	7	4.58 (0.020)	15.7 (2.2)	32	α 48Leu→Arg
Hb A_2'	81[o]	4.59 (0.030)	1.2 (0.1)	2	δ 16Gly→Arg
Hb Q-Thailand	1	4.67	29.3	–	α 74Asp→His
Hb Hasharon	7	4.83 (0.016)	17.9 (1.5)	32	α 47Asp→His
Hb O-Arab	6	4.91 (0.008)	35.9 (3.0)	24	β 121Glu→Lys
Hb G-Siriraj	1	5.08	24.2	–	β 7Glu→Lys
Hb C	962[p]	5.18 (0.013)	35.6 (4.0)[m]	32	β 6Glu→Lys

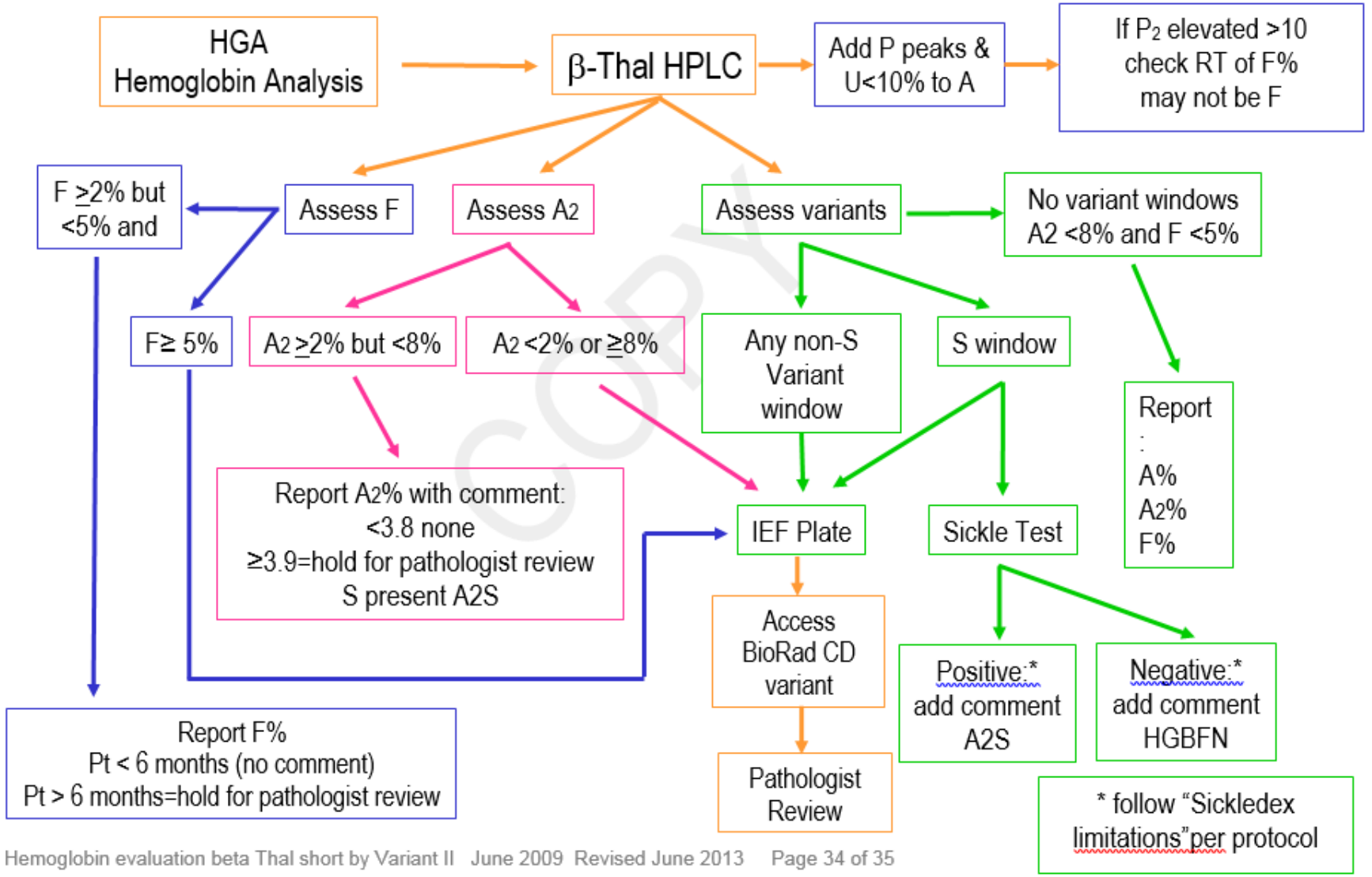
[a] Number of observations.
[b] Mean (SD) relative retention time except when n was <3, for which the individual retention times are given.
[c] Mean (SD) percentage of the hemoglobin variant as a fraction of the total hemoglobin.

Isoelectric Focusing (IEF)





APPENDIX 4 Flow Diagram for Hemoglobin Evaluation (Test HGA)



Case

- 33 mo male, unknown ethnicity with anemia (9.7 Hgb), microcytosis (small cells), anisocytosis (unequal size). Mentzer's index = 13.4 (indeterminate - > 13 Fe deficiency < 13 Thalassemia)

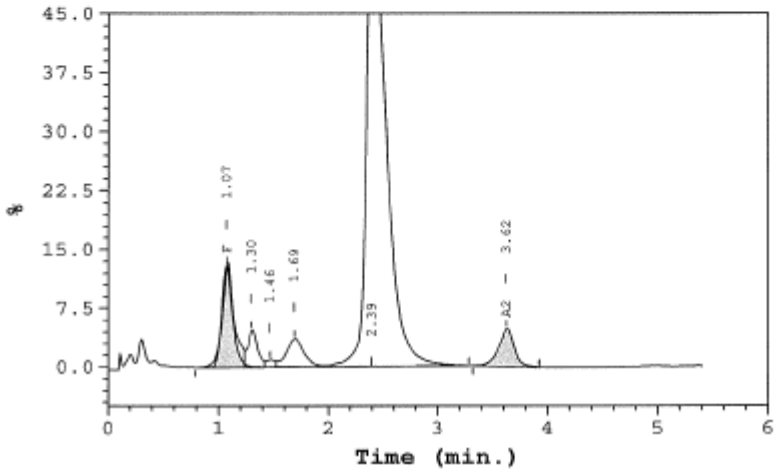
Peak Name	Calibrated Area %	Area %	Retention Time (min)	Peak Area
F	9.6*	---	1.07	171503
P2	---	3.0	1.30	54609
Unknown	---	0.6	1.46	10855
P3	---	4.3	1.69	77112
Ao	---	77.3	2.39	1386411
A2	4.9*	---	3.62	92199

Total Area: 1,792,689

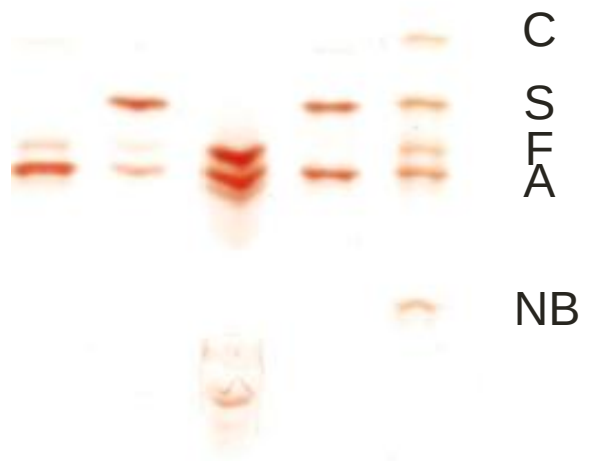
F Concentration = 9.6* %
A2 Concentration = 4.9* %

*Values outside of expected ranges

Analysis comments: Held for IEF



HbF = 9.6%* (<2%)
HbA = 85.5%* (>90%)
HbA2 = 4.9%* (2.5 – 3.9%)



HEMOGLOBIN VARIANT EVALUATION :

note: The hemoglobin profile shows an elevated hemoglobin F and A2. Given the elevated hemoglobin A2 and the patient's peripheral smear findings (microcytosis and mild anisocytosis), these findings are suggestive of beta-thalassemia trait in the appropriate clinical context.

Electronically signed out by:
Aaron C. Shaver, M.D., Ph.D.

The sample was analyzed by High Performance Liquid Chromatography (HPLC) and the relative mobility of the patient's sample was compared with that of hemoglobins A, F, S, C, D and E.

HEMOGLOBIN A	85.5	%
HEMOGLOBIN A2	4.9	%
HEMOGLOBIN F	9.6	%
HGB EVAL INTERPRETATION	An Isoelectric Focusing (IEF) plate was performed and evaluated	

- Microcytosis – small red blood cells
- Anisocytosis – RBCs of varying size

Reasons for Requesting Hemoglobin Variant Analysis

- Anemia of unknown origin in ethnic patient
- Follow-up to abnormal newborn screen
- Adoption
- Athletic exam for competitive sports
- Prenatal screening – patients of ethnic origin

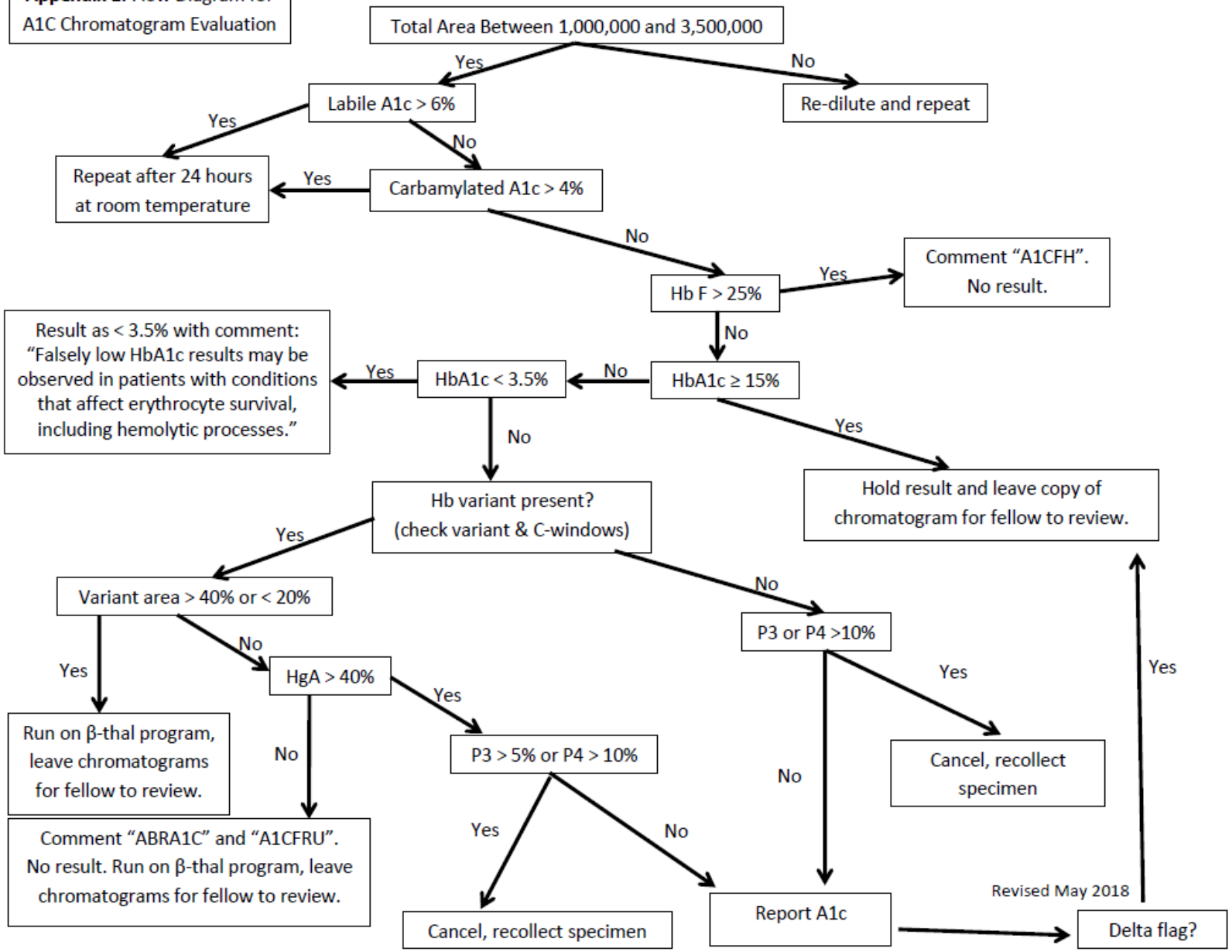
Endocrine HbA1c DMT

HPLC ANALYSIS THAT FAILS A DELTA CHECK OR >15% FLAG

Clinical/Analytical components:

- Medical history
- Diagnosis of diabetes
- Prior HbA1c result
- Drugs/medications
- Recent transfusions
- Hemoglobin variant

Appendix 1: Flow Diagram for A1C Chromatogram Evaluation



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Inappropriately Low HbA1c	Inappropriately High HbA1c	Variable Effect on HbA1c+
• Hemolysis • Certain hemoglobinopathies • Recent blood transfusion • Acute blood loss • Hypertriglyceridemia • Drugs* • Chronic liver disease	• Iron deficiency • Vitamin B12 deficiency • Alcoholism • Uremia • Hyperbilirubinemia • Drugs*	• Fetal hemoglobin • Methemoglobin • Certain hemoglobinopathies

*Refer text and Table 2 + method-dependent

Postulated Mechanism	Falsely Low HbA1c	Falsely High HbA1c
Increased erythrocyte destruction	Dapsone[11-16] Ribavirin[17] Antiretrovirals[18] Trimethoprim-Sulfamethoxazole[14]	
Altered hemoglobin	Hydroxyurea[19]	
Altered glycation	Vitamin C[10] Vitamin E[10] Aspirin (small doses)[10]	
Interference with assays		Aspirin (large doses)[20] Chronic opiate use[21]

Indian J Endocrinol Metab. 2012 Jul-Aug; 16(4): 528–531.
Drugs affecting HbA1c levels
Ranjit Unnikrishnan, Ranjit Mohan Anjana, and Viswanathan Mohan

DOB:

19-148-002413B

Comments: A1C

2.00mL Lavender ES

Report Generated: 05/28/2019 13:15:02

Operator ID: NR

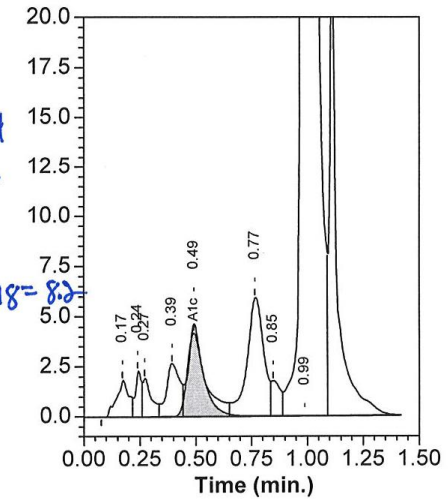
Peak Name	NGSP %	Area %	Retention Time (min)	Peak Area
A1a	---	1.0	0.171	17117
A1b	---	0.6	0.239	10276
F	---	0.7	0.270	12514
LA1c	---	1.4	0.393	23977
A1c	4.2	---	0.490	52526
P3	---	4.5	0.766	74885
P4	---	0.7	0.846	11636
Ao	---	87.9	0.987	1467591

Total Area: 1,670,521

HbA1c (NGSP) = 4.2 %

eAG = 74

26 y/o male white cystic fibrosis lung tx 7/14 poorly controlled diabetes prior 5/3/2019 = 8.4 on DAPSONE 12/3/2018 = 8.2 transfused on 5/9



DO NOT Report

- Recent transfusion
  - "Hemoglobin A1c is not accurate due to recent transfusion"
- Dapsone
  - unable to report HbA1c result due to interference from the medication Dapsone"

JW 5/28/2019

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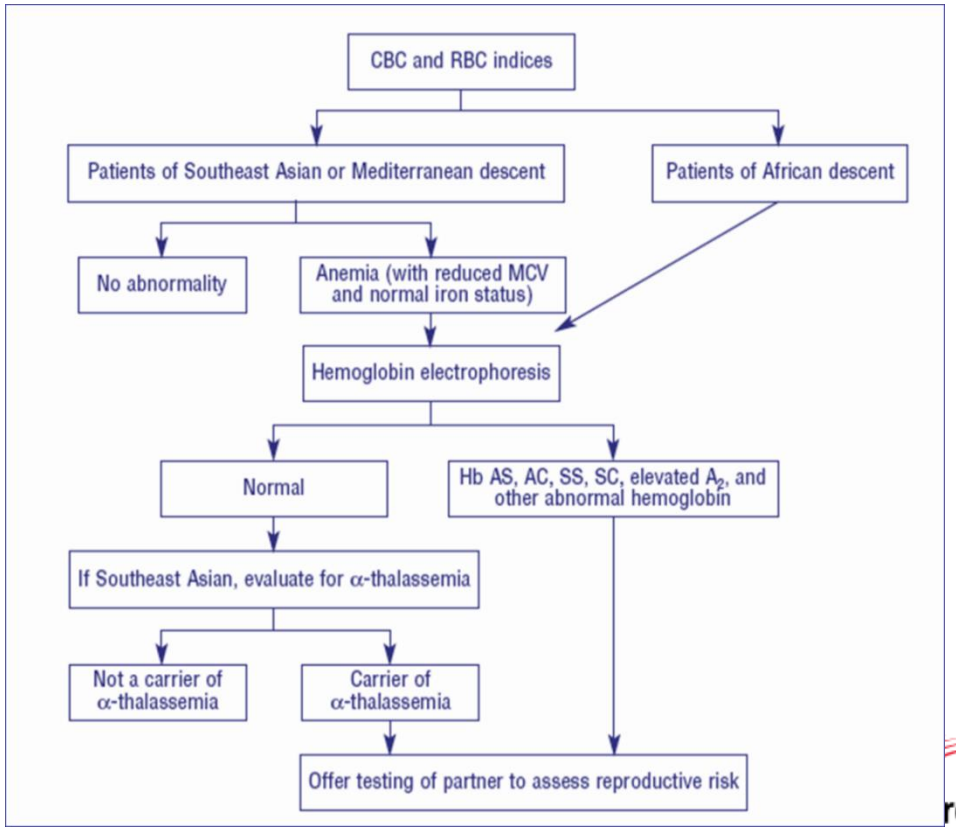
Prenatal Laboratory Testing

- American College of Obstetricians and Gynecologists (ACOG) recommend hemoglobin variant screening on high-risk populations, including individuals of African, Southeast Asian and Mediterranean ancestry
- Testing is not recommended in low-risk ethnic groups such as Caucasians, Japanese, Native Americans, Inuit and Koreans

	ALL PREGNANT WOMEN	SPECIFIC HIGH-RISK POPULATIONS
Blood type and screen	✓	
CBC with platelet count	✓	
Urine culture and sensitivity	✓	
Hepatitis B surface antigen	✓	
Rubella screening	✓	
HIV testing	✓	
Syphilis screening	✓	
Chlamydia screening	✓	
Cystic fibrosis carrier screening	✓	
Gonorrhea screening		✓
Gestational diabetes screening		✓
Hemoglobinopathy screening		✓



Prenatal Hemoglobin Variant Orders

- We noted an unusual number of hemoglobin variant test orders on prenatal patients from low-risk ethnicities – contrary to ACOG guidelines, primarily from 4 OB/GYN clinics
- In these clinics, orders were directed by electronic order set – automatically orders hemoglobin variant screening on all patients, regardless of ethnicity, at their first prenatal visit
- This workflow requires physician to remove the hemoglobin variant test from low risk patients – an added step that is often missed
- We updated physician order sets to better align to ACOG guidelines – removed hemoglobin variant test as part of order set
- Physician education for changed workflow to remember to add the hemoglobin variant test for high risk ethnic groups

Impact of Improved Utilization

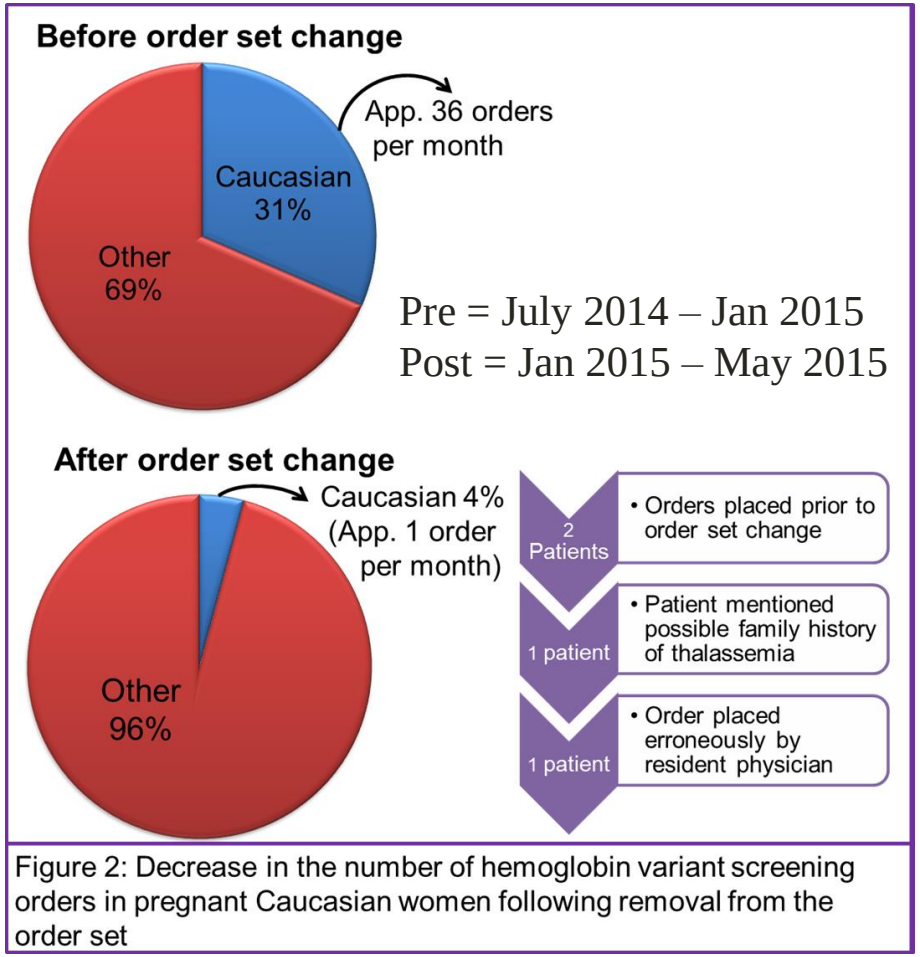


Figure 2: Decrease in the number of hemoglobin variant screening orders in pregnant Caucasian women following removal from the order set

	OB/GYN HEMOGLOBIN VARIANT SCREENING TEST VOLUME/MONTH	ASSOCIATED COST *
Before order set change	36	Patient cost/test $120 ($120 X 36 = $4,320) Reagent cost/test $12.15 ($12.15 X 36 = $437.40) **Total monthly cost = $4,757.40**
After order set change	1	Patient cost/test $120 ($120 X 1 = $120) Reagent cost/test $12.15 ($12.15 X 1 = $12.15) **Total monthly cost = $132.15**
* Additional costs associated with this test include labor costs for technologist to run and report the test, as well as resident/fellow and medical director time to review results **Estimated annual savings of $55, 503**		

Reasons for Ordering Toxicology DMT

- Pain management compliance
- Screening for drugs-of-abuse
- Outpatient ADHD medication compliance
- Cancer and transplantation use of cannabis
- Interpretation of DAU test results

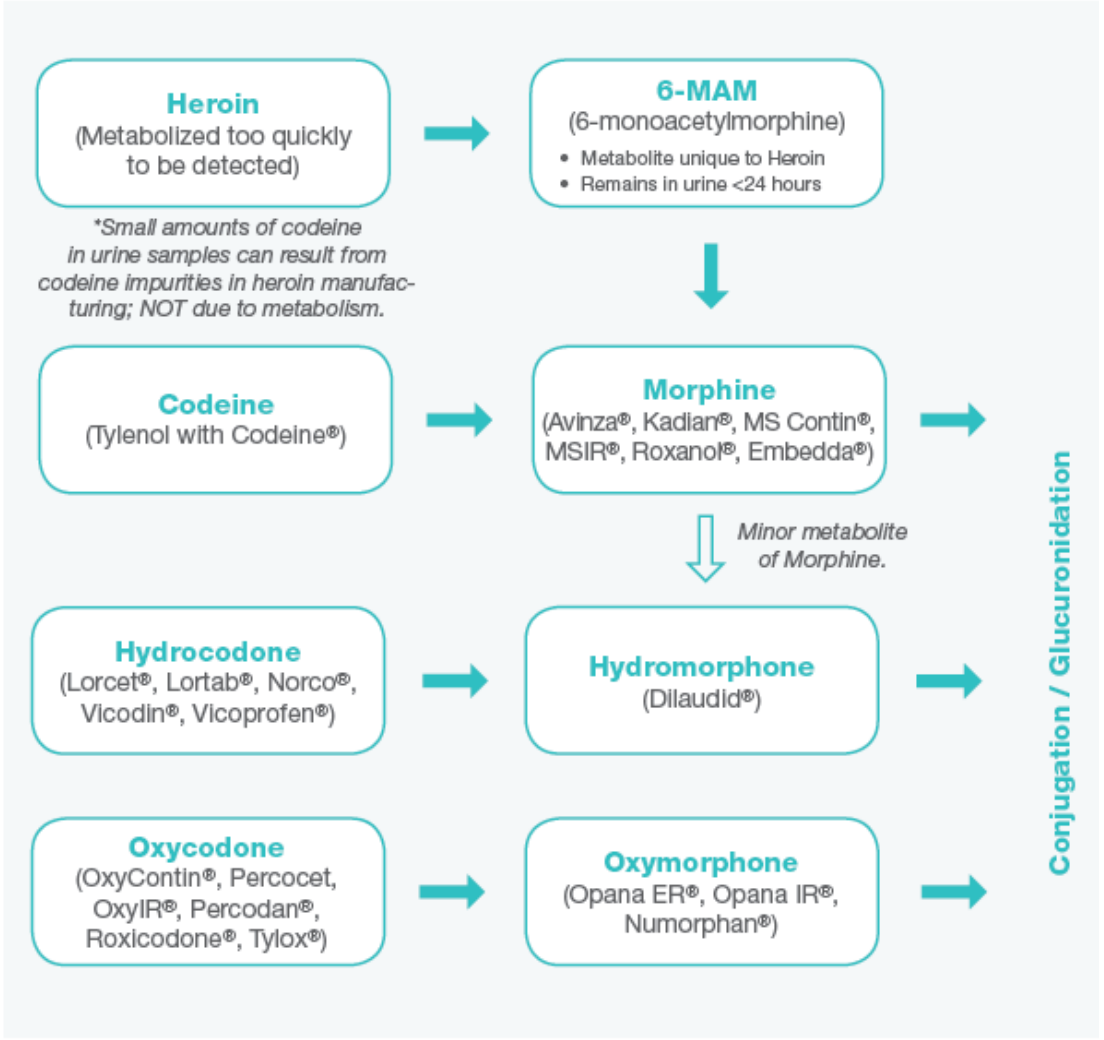
Toxicology DMT

Clinical components

- Clinical question being asked!
- Medical history
- Medication history

Analytical components

- Immunoassay screen results (raw data)
- Mass spectrometry results (quantitative)
- Urine creatinine/osmolality or signs of adulteration
- Urinalysis if available (specific gravity)



After Oxycodone use, urine may be positive for:

- Oxycodone only
- Oxycodone and Oxymorphone
- Oxymorphone only

Hydrocodone can be present at very high Oxycodone concentrations because Hydrocodone can be an impurity in the manufacturing process.

After Oxymorphone use, urine should be positive for Oxymorphone.

Hydrocodone is a trace metabolite of Codeine. Although rarely detected, it may be present if Codeine concentrations are very high.

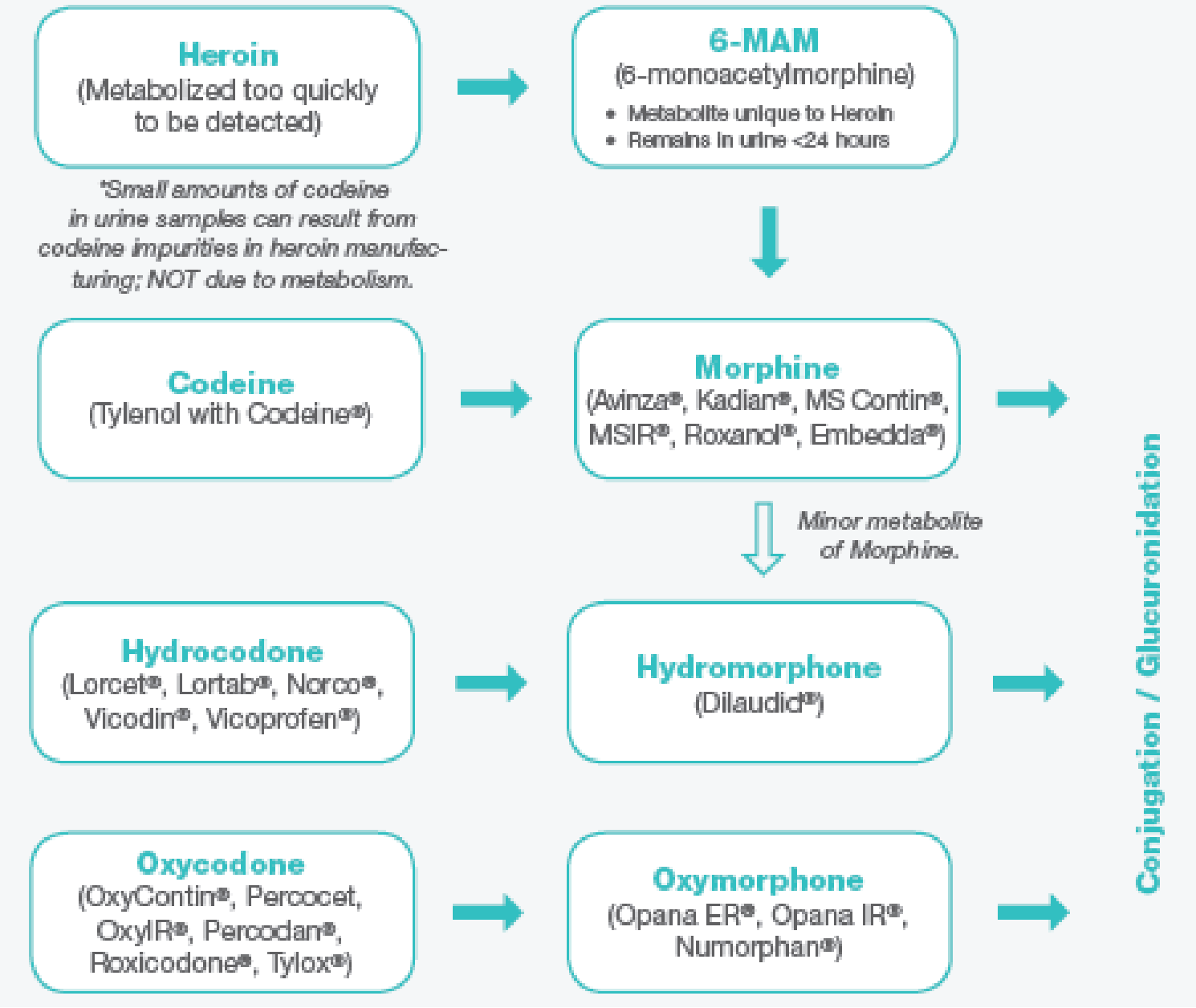
After Morphine use, urine may be positive for Morphine. Hydromorphone is a trace metabolite of Morphine found only when very high levels of Morphine are present.

Drugs Not Prescribed in Patient's Sample

- The laboratory was asked to provide an interpretation of the presence of hydrocodone and dihydrocodeine in this patient's specimen.
- The patient is prescribed oxycodone.
- Semi-quantitative results by mass spectrometry were 3030 ng/mL for oxycodone, 854 ng/mL for oxymorphone, 213 ng/mL for hydrocodone, and 23 ng/mL for dihydrocodeine.
- Hydrocodone can be seen in small amounts in prescription oxycodone.
- Dihydrocodeine is a metabolite of hydrocodone.
- The relative concentrations of the analytes are consistent with use of oxycodone.

Case

- Physician calls regarding interpretation of DAU test results
- Patient is on OxyIR (oxycodone intermediate release), #180/mo.
- **Drug test screen results**:
  - Opiate screen positive (>30,000 ng/mL reactivity),
  - Oxycodone screen negative (<300 ng/mL)
- **Drug MS confirmation results**:
  - Morphine (50,000 ng/mL)
  - Hydromorphone (120 ng/mL).



Laboratory Interpretation

- On review of results, screening immunoassay was positive (>30,000 ng/mL reactivity) to opiate class and negative for oxycodone reactivity.
- Confirmation by GC/MS demonstrated the presence of morphine (50,000 ng/mL) and hydromorphone (120 ng/mL).
- These results are more consistent with the use of morphine than oxycodone, as trace amounts of hydromorphone can be seen with higher concentrations of morphine.
- Please contact lab if further questions.

Amino Acid Metabolism

- Humans are unable to synthesize all twenty AA needed for protein synthesis.
- AA which cannot be synthesized must then be acquired via the diet (essential AA).
- Dietary intake of AA is typically not balanced to exactly match the body's demands. Dietary AA must be chemically modified and rearranged to provide adequate levels of all the AA needed.
- Large number of pathways in the body for balancing the pool of AA, both for synthesis and for degradation. The number of enzymes involved creates a great potential for genetic diseases. Disruption (by mutation of just one enzyme) in the metabolism of only one AA can have profound consequences for growth and development; some of the genetic diseases are fatal.

Amino Acids

Essential amino acids

- Essential amino acids cannot be made by the body. As a result, they must come from food
- The nine essential amino acids are: histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine

Nonessential amino acids

- "Nonessential" means that our bodies produce an amino acid, even if we don't get it from the food, we eat
- They include: alanine, asparagine, aspartic acid, and glutamic acid

Conditional amino acids

- Conditional amino acids are usually not essential, except in times of illness and stress
- They include: arginine, cysteine, glutamine, tyrosine, glycine, ornithine, proline, and serine

Reasons for Requesting Inborn Errors of Metabolism DMT

Newborn

- Failure to thrive
- Family history
- Abnormal newborn screen

Child/adolescent

- Developmental delay
- Vomiting, seizure disorders
- Autism spectrum and behavioral disorders

Nutritional support

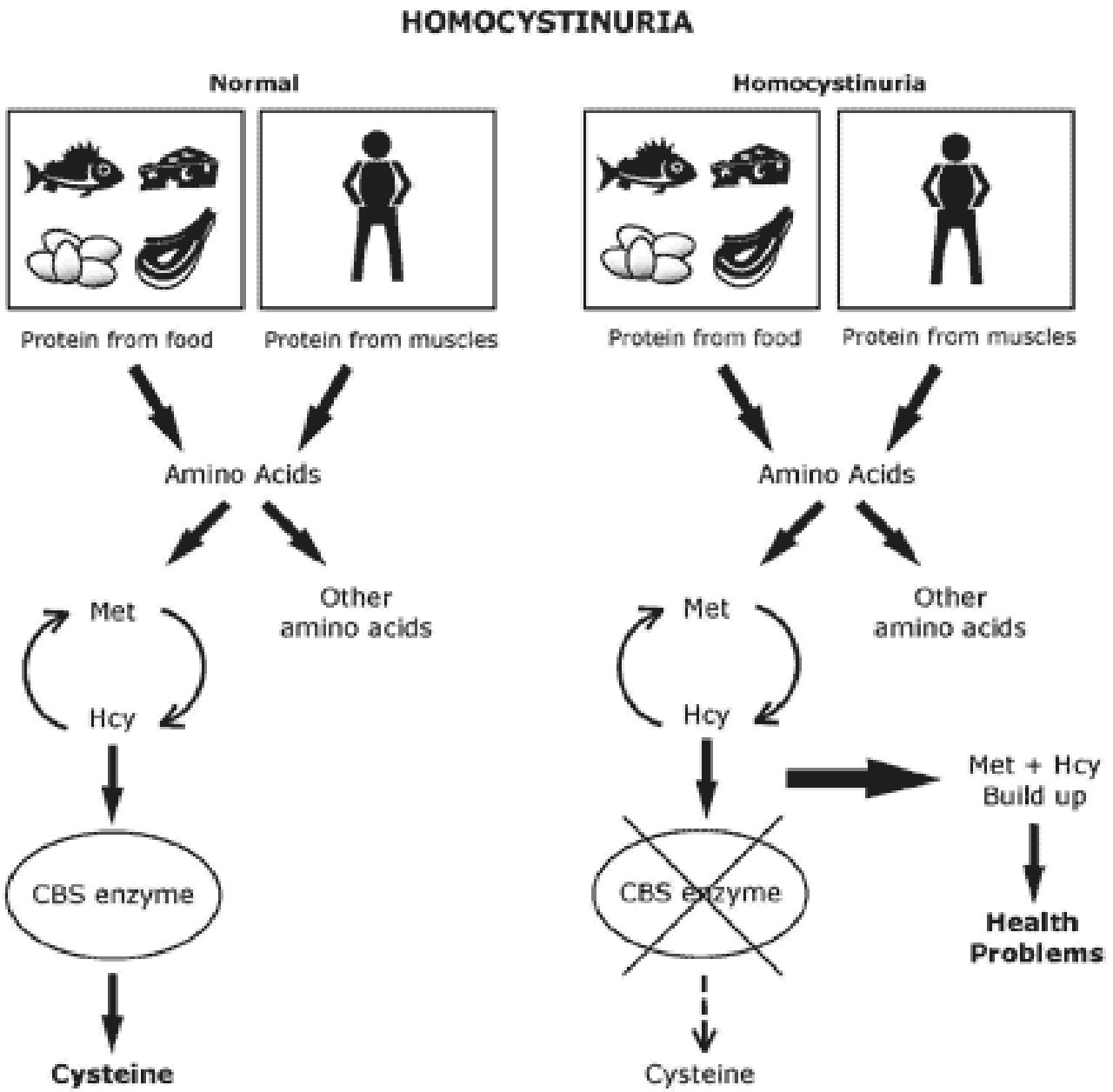
Inborn Errors of Metabolism DMT

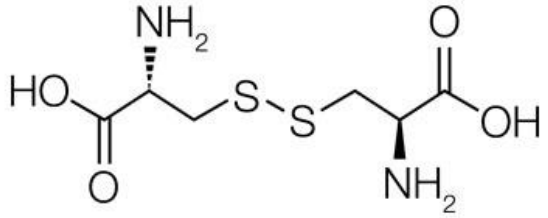
Clinical components

- Medical and family history
- Medications
- Nutrition and diet

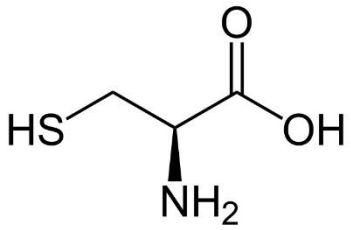
Analytical components

- Newborn screen
- Past AA, organic acids, acylcarnitine or genetic test results
- Plasma, Urine or CSF amino acid analysis

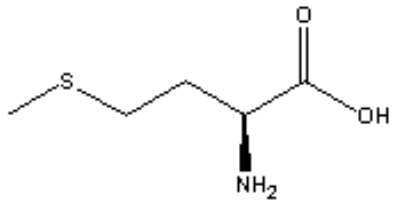




Cystine = oxidized dimer of cysteine



Cysteine



Methionine

Interpretation: Bailey is a 6 year old female with homocystinuria, on treatment. The plasma amino acid profile shows a minor elevation in methionine. Free homocystine was not detected on this profile

Plasma Amino Acids:
Alanine: 443 mcmol/L (Ref: 152-547)
Aminobutyric Acid: 8 mcmol/L (Ref: 4-31)
Arginine: 66 mcmol/L (Ref: 10-140)
Asparagine: 50 mcmol/L (Ref: 23-112)
Aspartic Acid: 5 mcmol/L (Ref: 1-24)
Citrulline: 34 mcmol/L (Ref: 1-46)
Cystine: 19 mcmol/L (Ref: 5-45)
Glutamic Acid: 15 mcmol/L (Ref: 10-133)
Glutamine: 730 mcmol/L (Ref: 254-823)
Glycine: 285 mcmol/L (Ref: 127-341)
Histidine: 73 mcmol/L (Ref: 41-125)
Hydroxyproline: 21 mcmol/L (Ref: 3-45)
Iso-Leucine: 49 mcmol/L (Ref: 22-107)
Leucine: 80 mcmol/L (Ref: 49-216)
Lysine: 67 mcmol/L (Ref: 48-284)
Methionine: ***51*** mcmol/L (Ref: 7-47)
Ornithine: 54 mcmol/L (Ref: 10-163)
Phenylalanine: 49 mcmol/L (Ref: 26-91)
Proline: 204 mcmol/L (Ref: 59-369)
Serine: 131 mcmol/L (Ref: 69-187)
Taurine: 55 mcmol/L (Ref: 10-170)
Threonine: 71 mcmol/L (Ref: 35-226)
Tryptophan: 47 mcmol/L (Ref: 31-79)
Tyrosine: 56 mcmol/L (Ref: 24-115)
Valine: 149 mcmol/L (Ref: 74-321)

Other Amino Acid: free homocystine = 0 mcmol/L

Interpretation: Brandon is an 11 year old male with homocystinuria, on treatment. The plasma amino acid profile shows an elevated methionine. Free homocystine was not detected on this profile.

Plasma Amino Acids:
Alanine: 268 mcmol/L (Ref: 152-547)
Aminobutyric Acid: 13 mcmol/L (Ref: 4-31)
Arginine: 74 mcmol/L (Ref: 10-140)
Asparagine: 37 mcmol/L (Ref: 23-112)
Aspartic Acid: 6 mcmol/L (Ref: 1-24)
Citrulline: 36 mcmol/L (Ref: 1-46)
Cystine: 28 mcmol/L (Ref: 5-45)
Glutamic Acid: 28 mcmol/L (Ref: 10-133)
Glutamine: 591 mcmol/L (Ref: 254-823)
Glycine: 155 mcmol/L (Ref: 127-341)
Histidine: 74 mcmol/L (Ref: 41-125)
Hydroxyproline: 22 mcmol/L (Ref: 3-45)
Iso-Leucine: 58 mcmol/L (Ref: 22-107)
Leucine: 104 mcmol/L (Ref: 49-216)
Lysine: 129 mcmol/L (Ref: 48-284)
Methionine: ***74*** mcmol/L (Ref: 7-47)
Ornithine: 51 mcmol/L (Ref: 10-163)
Phenylalanine: 48 mcmol/L (Ref: 26-91)
Proline: 127 mcmol/L (Ref: 59-369)
Serine: 79 mcmol/L (Ref: 69-187)
Taurine: 55 mcmol/L (Ref: 10-170)
Threonine: 77 mcmol/L (Ref: 35-226)
Tryptophan: 48 mcmol/L (Ref: 31-79)
Tyrosine: 46 mcmol/L (Ref: 24-115)
Valine: 189 mcmol/L (Ref: 74-321)

Other Amino Acid: free homocystine = 0 mcmol/L

Interpretation: Timothy is an 18 month old male being seen to evaluate signs of failure to thrive. The urine amino acid concentrations are normalized to creatinine. The patient's low creatinine of 29 mg/dL (RI 40-200) may have falsely elevated several amino acids. Interpret results with caution.

URINE AMINO ACIDS:

U 1 Methylhistidine: 614 mcmol/gm_Cr (Ref: 1-980)
U 3 Methylhistidine: 528 mcmol/gm_Cr (Ref: 20-610)
U Alanine: ***1266*** mcmol/gm_Cr (Ref: 292-1151)
U alpha Aminobutyric Acid: ***124*** mcmol/gm_Cr (Ref: 1-80)
U Aminoadipic Acid: ***0*** mcmol/gm_Cr (Ref: 1-80)
U Arginine: ***128*** mcmol/gm_Cr (Ref: 1-80)
U Asparagine: ***507*** mcmol/gm_Cr (Ref: 1-283)
U Aspartic Acid: 55 mcmol/gm_Cr (Ref: 18-89)
U Citrulline: 34 mcmol/gm_Cr (Ref: 1-62)
U Cystine: ***214*** mcmol/gm_Cr (Ref: 53-186)
U gamma Aminobutyric Acid: 38 mcmol/gm_Cr (Ref: 24-262)
U Glutamic Acid: ***252*** mcmol/gm_Cr (Ref: 1-97)
U Glutamine: ***2852*** mcmol/gm_Cr (Ref: 398-2089)
U Glycine: ***6348*** mcmol/gm_Cr (Ref: 974-3151)
U Histidine: ***4052*** mcmol/gm_Cr (Ref: 602-2540)
U Homocystine: 0 mcmol/gm_Cr (Ref: <=1)
U Hydroxypro: ***138*** mcmol/gm_Cr (Ref: 1-115)
U Isoleucine: 52 mcmol/gm_Cr (Ref: 1-53)
U Leucine: 124 mcmol/gm_Cr (Ref: 27-159)
U Lysine: ***624*** mcmol/gm_Cr (Ref: 89-611)
U Methionine: 66 mcmol/gm_Cr (Ref: 44-257)
U Ornithine: ***72*** mcmol/gm_Cr (Ref: 1-71)
U Phenylalanine: 231 mcmol/gm_Cr (Ref: 62-274)
U Proline: ***100*** mcmol/gm_Cr (Ref: 1-80)
U Serine: ***2224*** mcmol/gm_Cr (Ref: 283-1097)
U Taurine: ***1803*** mcmol/gm_Cr (Ref: 106-1770)
U Threonine: ***1369*** mcmol/gm_Cr (Ref: 89-549)
U Tyrosine: ***510*** mcmol/gm_Cr (Ref: 89-425)
U Valine: ***214*** mcmol/gm_Cr (Ref: 1-71)

Ur Creatinine: ***29*** mg/dL (Ref: 40-200)

Identifying Information/Interval History/Parent Concerns:
Timothy presents to the clinic today with mother and father for a well visit. Chart reviewed and history obtained from parents. He is currently under treatment with multiple specialists for severe failure to thrive, rickets and developmental delay. He has had initial outpatient follow up visits with endocrine, GI, nutrition, feeding therapy, ortho, pulmonary, PT and OT. Initial neuro and ophtho consults scheduled. He has TEIS eval and therapy in the works. We are attempting to schedule genetics follow up. His urine amino acids were abnormal but possible invalidated by a low urine creatinine. He has sweat chloride testing scheduled. Parents report he will now scoot on his bottom and he is starting to pull to a standing position. He does not get to a sitting position from lying nor crawl yet. His vocabulary is increasing and he knows > 10 words. He has responded well to VitD and his daily vit D was stopped at his endo visit and calcium decreased. He is due for repeat 2 wk f/u endo labs today. At nutrition visit last week parents were instructed to add 2 bolus feeds during the day but mom has not started these yet. He recently took Clinda for cervical lymphadenitis, this is much improved.

Other Chemistry DMTs

- Inborn errors of metabolism
  - Plasma AA, organic acids, acylcarnitine, genetic analysis
- Volatile ingestion
  - Osmolality, GC/HS, urinalysis/crystals, lytes, pH, osmolal gap
- Miscellaneous tox (Poison control center/ED)
  - Pain management
  - Acid/base MS with additional reflexive testing as needed for unknown ingestions
  - Newer designer drugs of abuse
- Endocrine
  - Aldosterone/renin ratio for refractory hypertension- screen for adrenal adenoma
  - CAH panel – testosterone, androstenedione, cortisol, 17-OH pregnenalone, progesterone, 17-OH progesterone, testosterone

The Dilemma of Advancing Science

- Rapidly advancing laboratory technologies offer opportunity to deliver on promise of personalized medicine to provide tailored care for each individual across the lifespan
- Evidence demonstrating improved patient outcomes from these technologies often lags behind adoption
- Escalating costs of innovative tests (up to 14% increase) is outpacing rising health-care costs (4-5% per year) with some genetic tests exceeding $10,000 for a patient
- VUMC chartered a Laboratory Formulary Committee to control laboratory costs patterned after the Pharmacy Formulary Committee that controls cost of medication

The Laboratory Formulary Committee

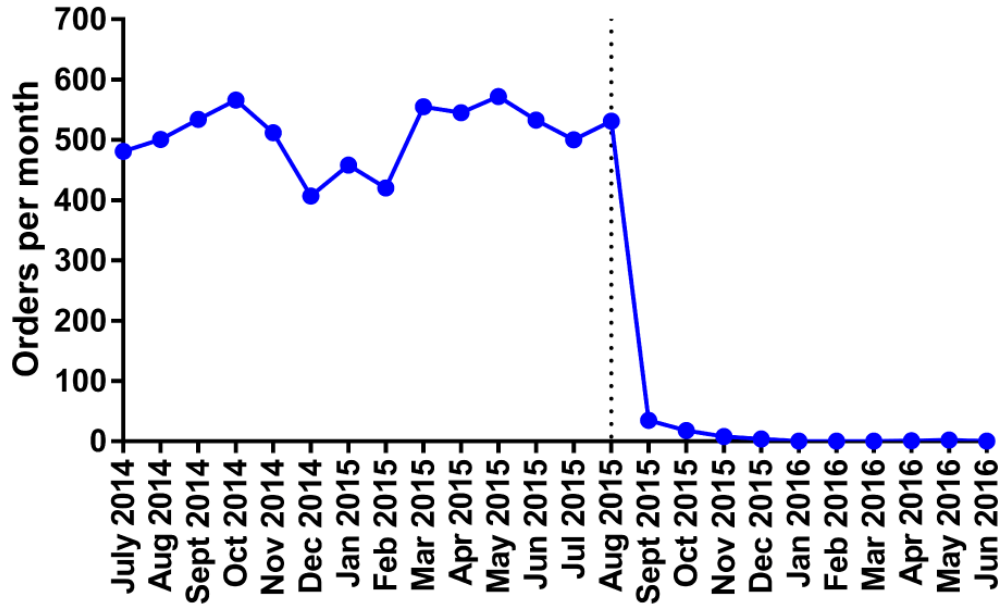
- Responsible for all inpatient and outpatient lab ordering
- Reviews evidence, consults with content experts and develops guidelines, substitutions, or restrictions to promote appropriate utilization of laboratory testing
- Subcommittee of Pharmacy, Therapeutics and Diagnostics Committee – exists outside any department and comprises voting members from diverse clinical departments and specialties with only a single pathologist
- Assisted by lab medical directors, administrators, finance representatives, LIS specialists, IT developers, data analysts, genetic counselors and project managers

Laboratory Formulary Examples

- Lab formulary focused on eliminating tests that were no longer gold standard or were of limited clinical utility
- Fractionated 25-OH vitamin D, only recommended when total vitamin D levels do not align with clinical presentation, but was often being ordered together with total Vitamin D = cost savings $102,842.

Fractionated 25-Hydroxyvitamin-D Orders Before and After Orderable Elimination

The ability to generate new orders for fractionated 25-hydroxyvitamin D was removed from the electronic ordering system in August 2015 (dotted line). The blue line represents total orders per month before and after the orderable removal.



Source: Authors

NEJM Catalyst (catalyst.nejm.org) © Massachusetts Medical Society

Laboratory Formulary Examples

- TAT for esoteric test results often exceed length of stay.
- Lab formulary required tests with median TAT > 7 days to be approved by on-call medical director before inpatient ordering – restriction decreased orders by 48% = **cost savings $257,745**
- Expert review of genetic tests to evaluate appropriateness of orders given clinical presentation, price variations among labs, optimal reflex testing and best TATs.
- LIS system implemented to facilitate holding samples for review and quickly redirecting to new labs without need for new blood draws. Genetic test review = **$394, 625 cost savings**

Summary

- ✓Medical knowledge is growing exponentially
- ✓Challenge for physicians to stay abreast of latest laboratory testing and algorithms
- ✓DMTs assist physicians by providing expert interpretative guidance towards best practice and support in answering diagnostic questions
- ✓Opportunity for the laboratory to actively participate on the healthcare team

Thanks to Dr. Michael Laposata for use of some introductory slides for this presentation

Thank You!