Decision Support

APSF Sept 6^{th} 2023

Kevin K. Tremper, PhD, MD
Professor
Department of Anesthesiology

COI

I have software patents granted (through the U of Michigan) regarding display technology.

I am the founder, President, investor and equity holder in AlertWatch, a University of Michigan Startup Company which has been acquired by BioIntelliSense for whom I am a consultant $$$$

Approximately 1 in 50 Surgical Patients (open procedures) will Die within One Month of Their Surgery

Postoperative Mortality in The Netherlands

Noordzij et al, *Anesthesiology* 2010; 1105-15

CDC: Leading Causes of Death

1. Heart Disease
2. Cancer
3. Chronic Respiratory Disease
4. Accidents
5. Stroke

Etc.

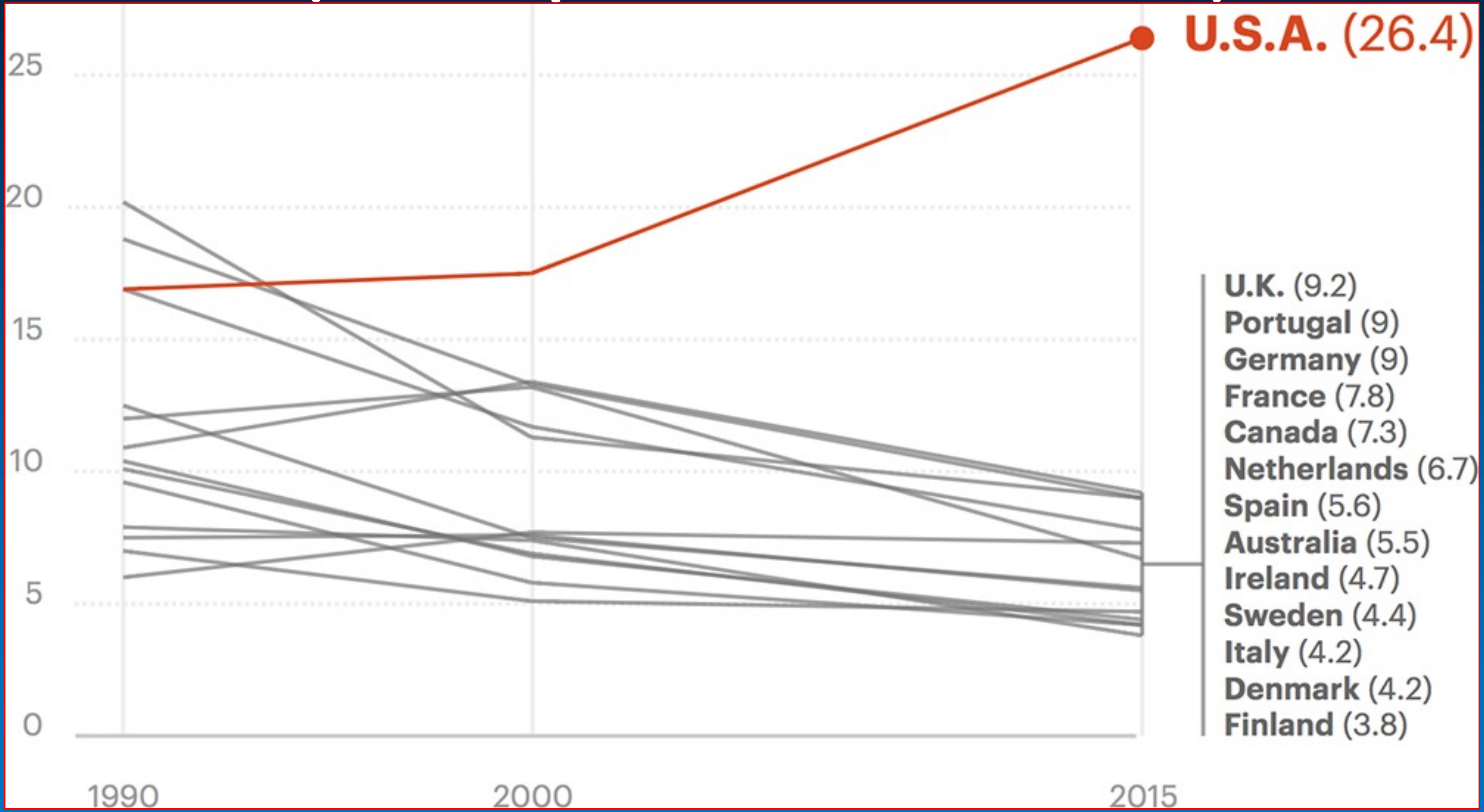
CDC: Leading Causes of Death

1. Heart Disease
2. Cancer
3. 30 Day Mortality after Surgery (190,000/yr)
4. Chronic Respiratory Disease
5. Accidents
6. Stroke

Etc.

Maternal Mortality is Rising in the U.S. As it Declines Elsewhere

(Deaths per 100,000 live births)



The Lancet, 2015

Automated Decision Support May Help

Types of DS

1. Automating Calculations/Alerts to improve standardization
   (live calculations)
2. Escalating alerts to help us follow out own protocols
   (following our own rules)
3. Providing alerts/recommendations we could not determine manually
   (Machine learning/AI driven)

"Life is like a box of chocolates"

My professional life in a nutshell

1975 to 1978 "If you would like to apply Eng to Med you should go to Med School and study continuous noninvasive O2 monitoring"

Irv Fatt UC Berkeley & John Severinghaus UCSF

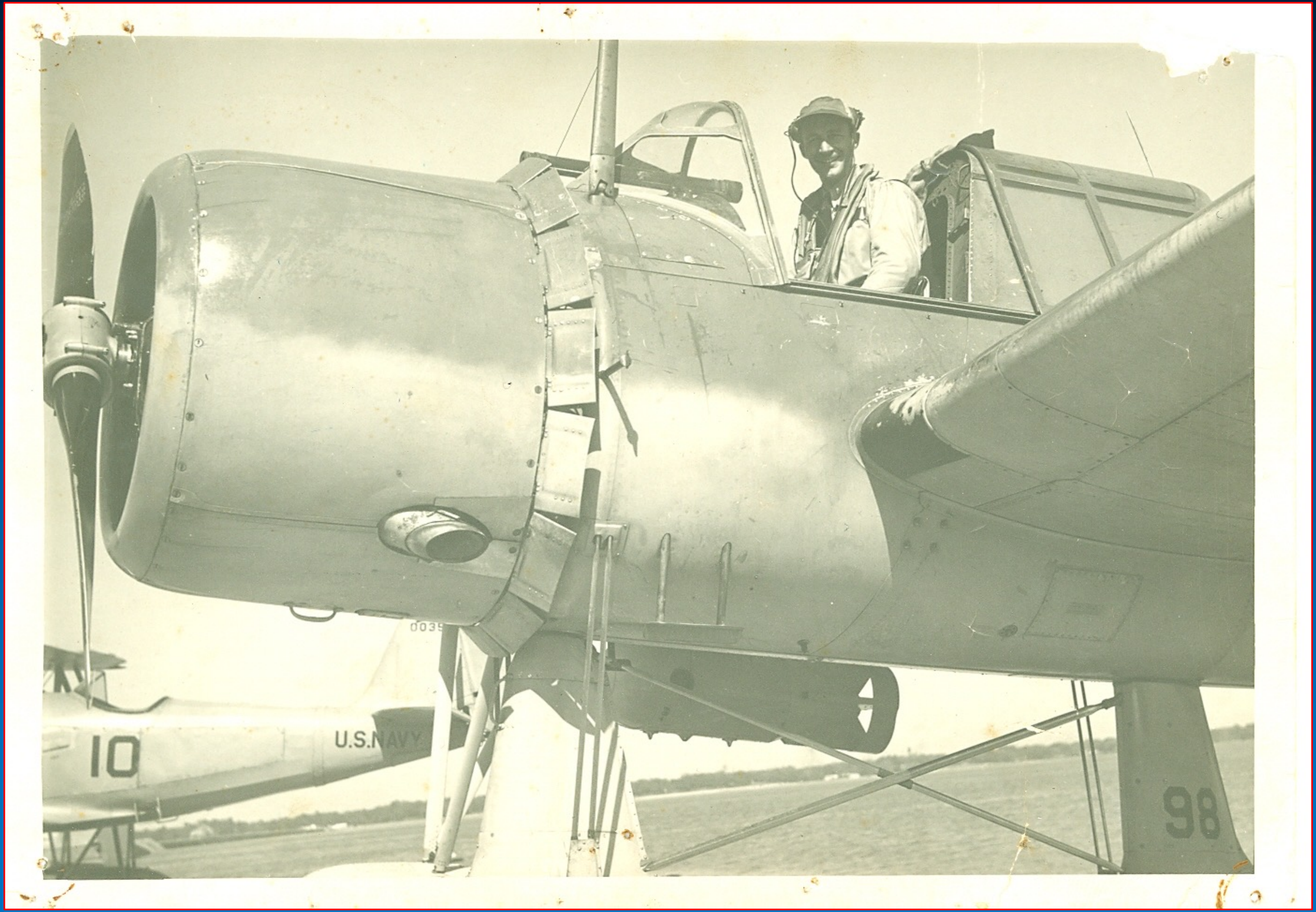
1978 to 1981 "If you would like to study monitoring & outcomes in sick people, come work in my SICU" Will Shoemaker

1990 to 2000 "If you want to collect lots of clinical data, make an electronic anesthesia record" Mike O'Reilly and I at U of M with SEC Inc (Vic & Sachin Kheterpal)

2008 to today "If you want to do large observational research to determine periop risk factors, add multiple institutions" Sachin Kheterpal , Nirav Shah ,Michael Mathis and the entire MPOG group

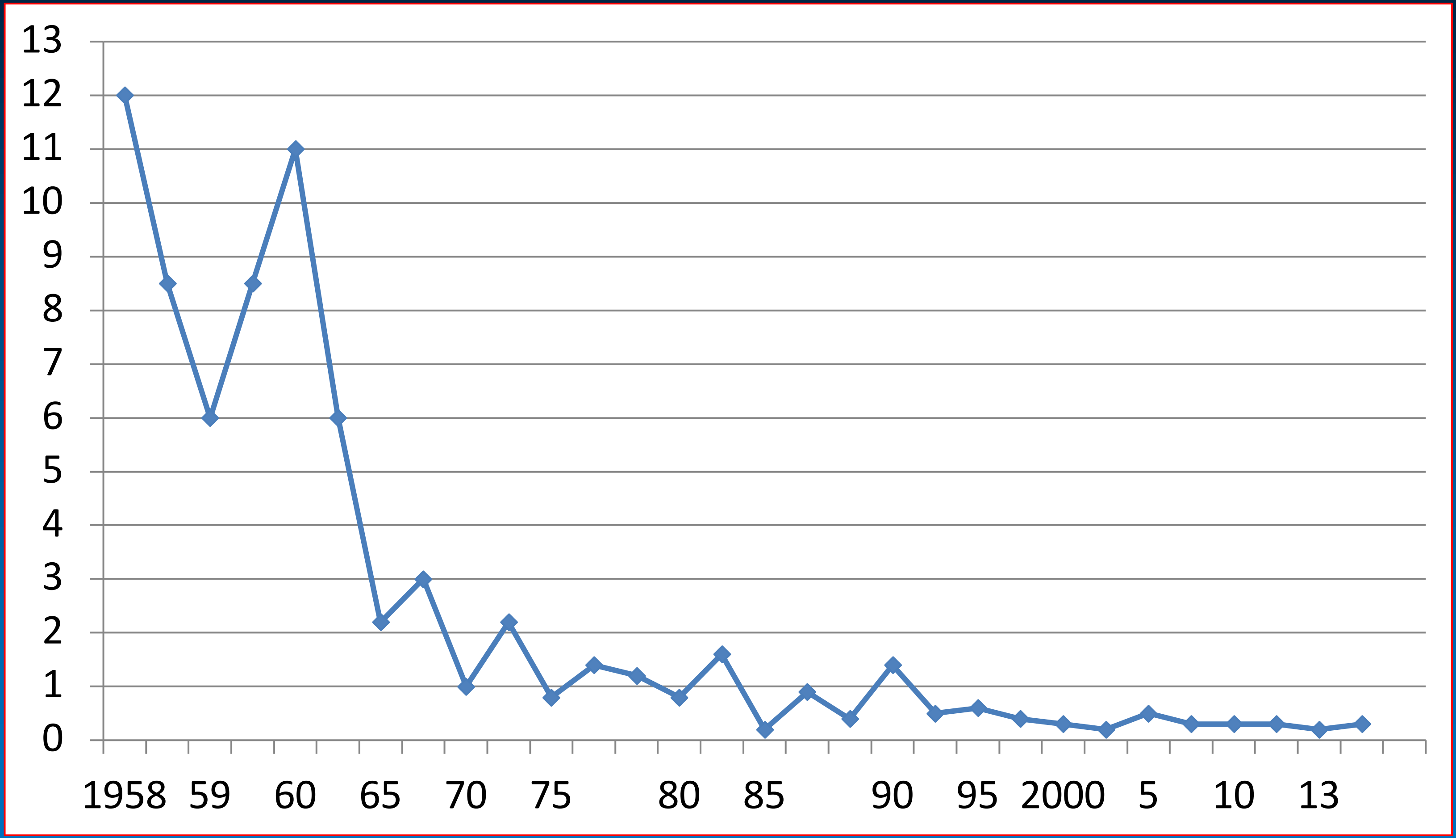
2008 to today "If you want clinicians to know who, where and when to apply this new knowledge, you need a decision support/alerting system. AlertWatch

etianCaptain Henry “Steve” Tremper WW2



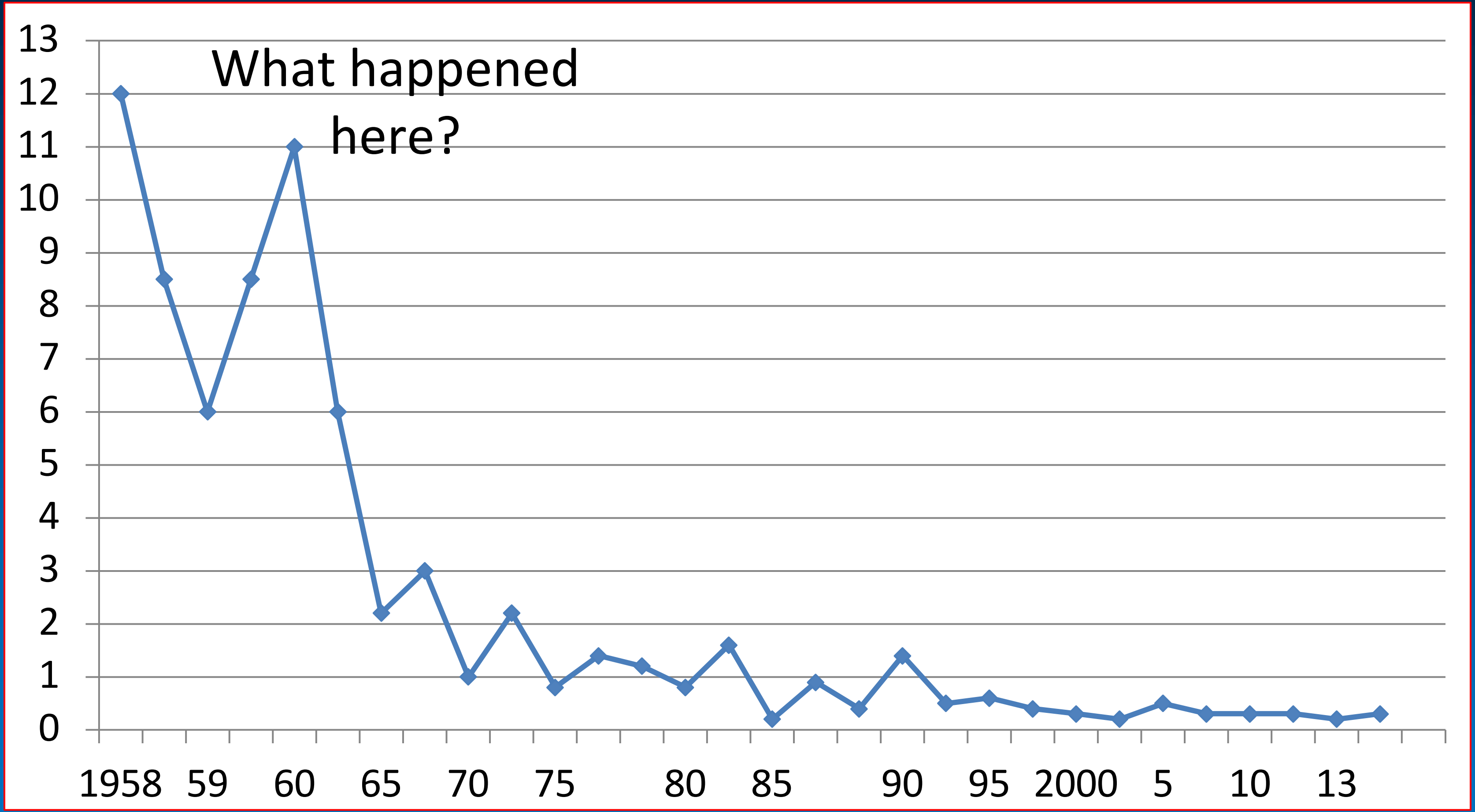
J-3 Cub, 1966:Downington PA
"Don't fly over anything you can't land on."

US Commercial Aviation Accident Rate/ Million Flights



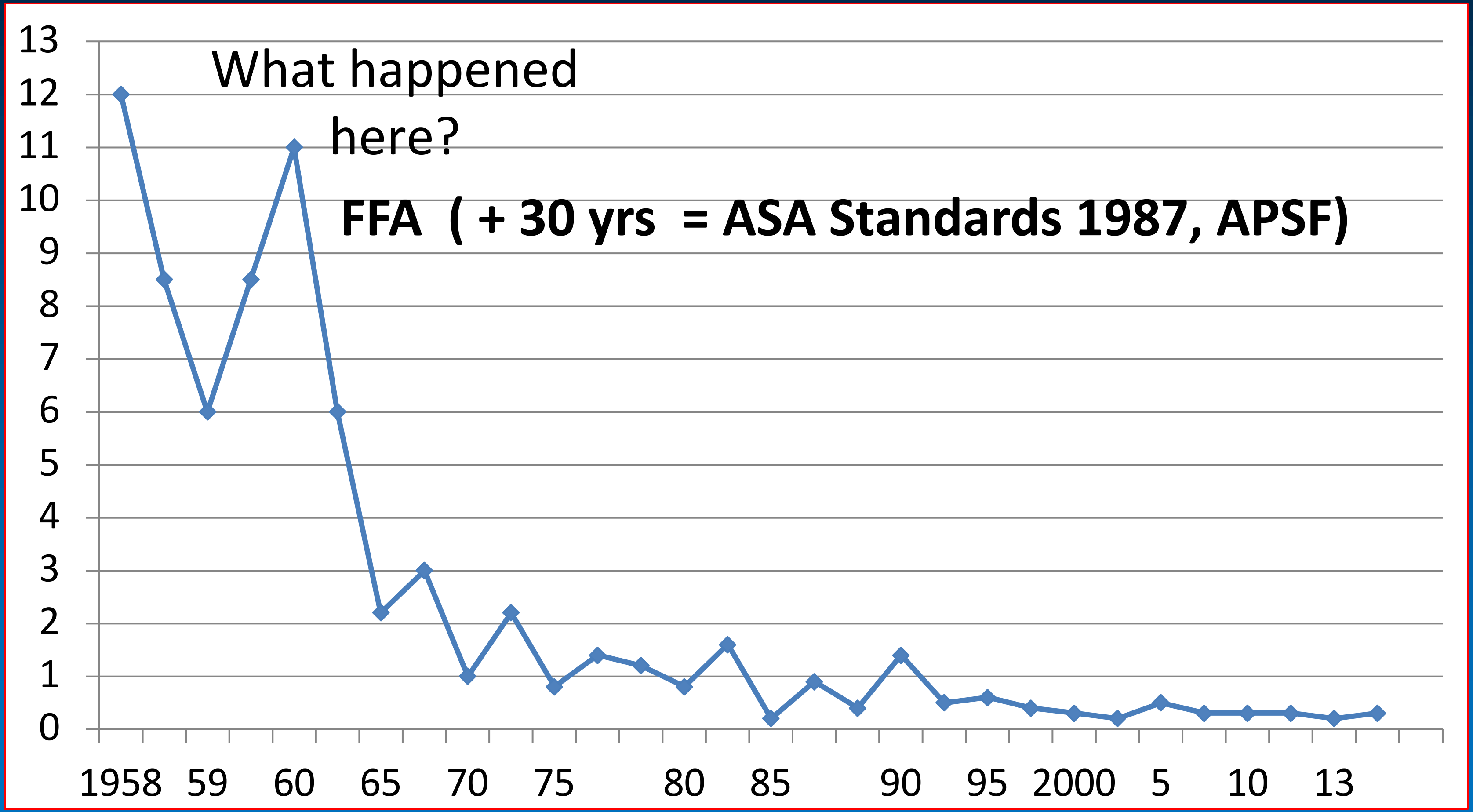
Commercial Aviation Accidents 1958-2013 A Statistical Analysis. [Online] Airbus_Aviation_Accidents-April2014[1]pdf. Accessed 2/3/2015.

US Commercial Aviation Accident Rate/ Million Flights



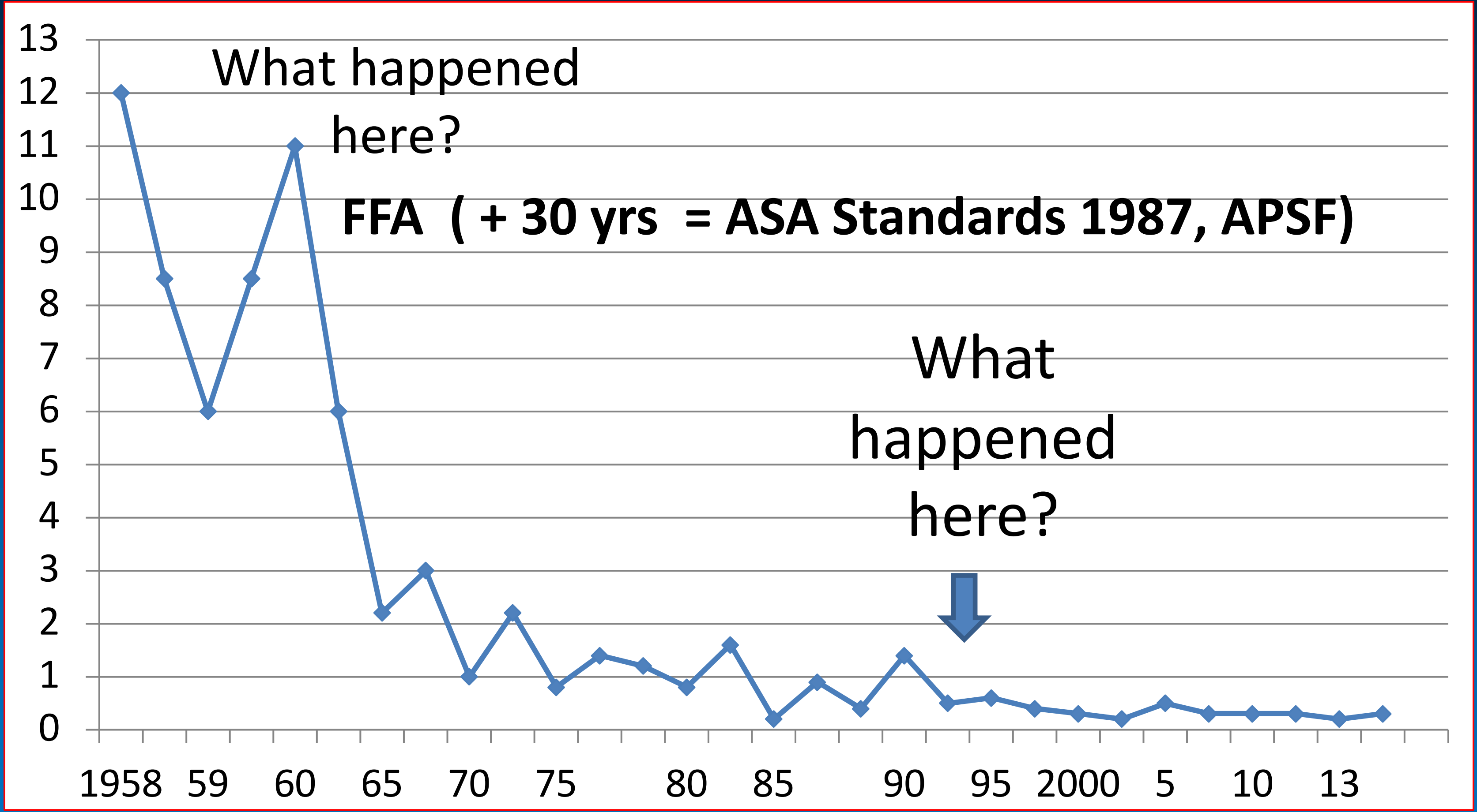
Commercial Aviation Accidents 1958-2013 A Statistical Analysis.
[Online] Airbus_Aviation_Accidents-April2014[1]pdf. Accessed 2/3/2015.

US Commercial Aviation Accident Rate/ Million Flights



Commercial Aviation Accidents 1958-2013 A Statistical Analysis.
[Online] Airbus_Aviation_Accidents-April2014[1]pdf. Accessed 2/3/2015.

US Commercial Aviation Accident Rate/ Million Flights



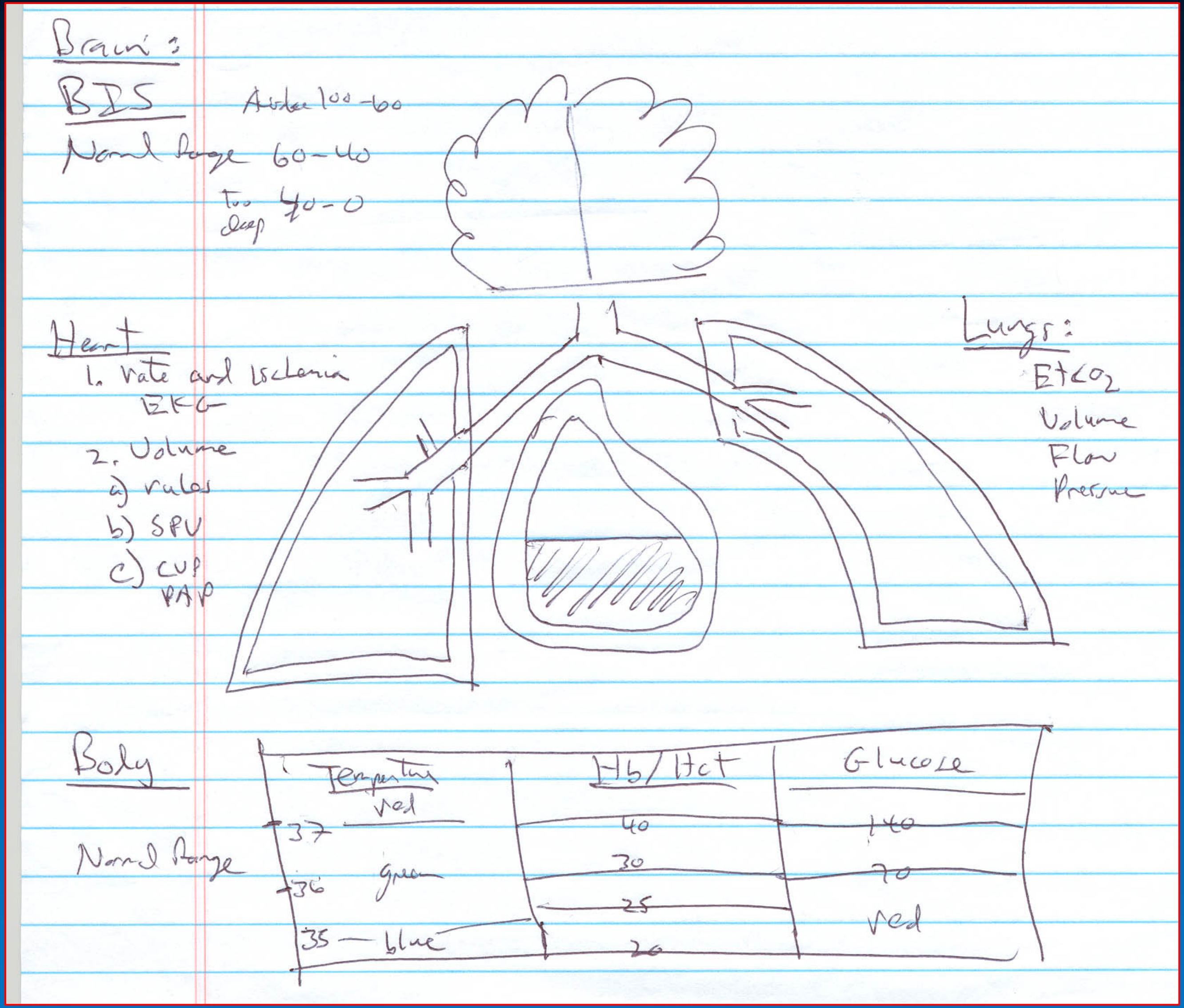
Commercial Aviation Accidents 1958-2013 A Statistical Analysis.
[Online] Airbus_Aviation_Accidents-April2014[1]pdf. Accessed 2/3/2015.

1960's - 1970's Cockpit, Crash 1:1,000,000

"Glass Cockpit," Crash 1:16,000,000

Integrated Avionics Screen

AlertWatch Draft 2007



Brain:

BIS

Awake 100-60

Normal Range 60-40

Too deep 40-0

Heart

1. rate and ischemia
   EKG
2. Volume
   a) rules
   b) SPV
   c) CVP
      PAP

Lungs:

$EtCO_2$

Volume

Flow

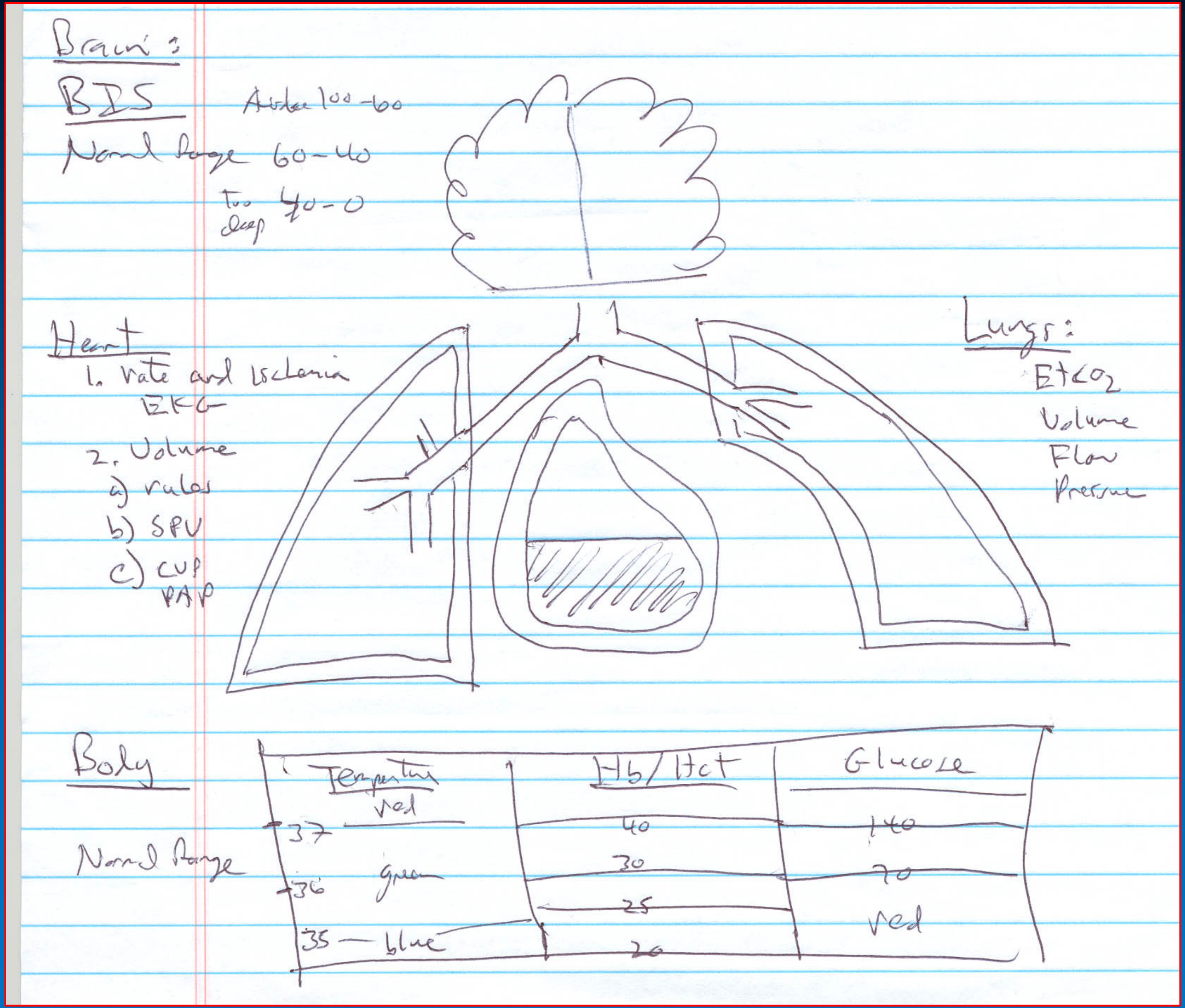
Pressure

Body

Normal Range

Temperature	Hb/Hct	Glucose
37 red	40	140
36 green	30	70
35 — blue	25	red
	20	

AlertWatch Draft 2007



Add Colors

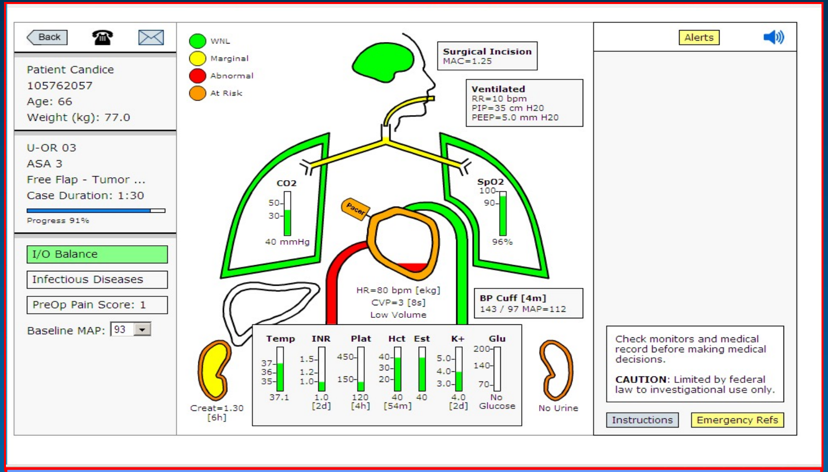
1. Automating Calculations/Alerts to improve standardization

(live calculations)

AW Multifunctional Monitor, 2011

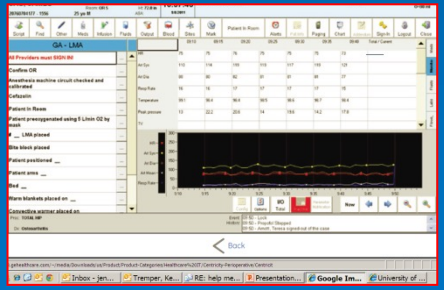
Monitors

LABS



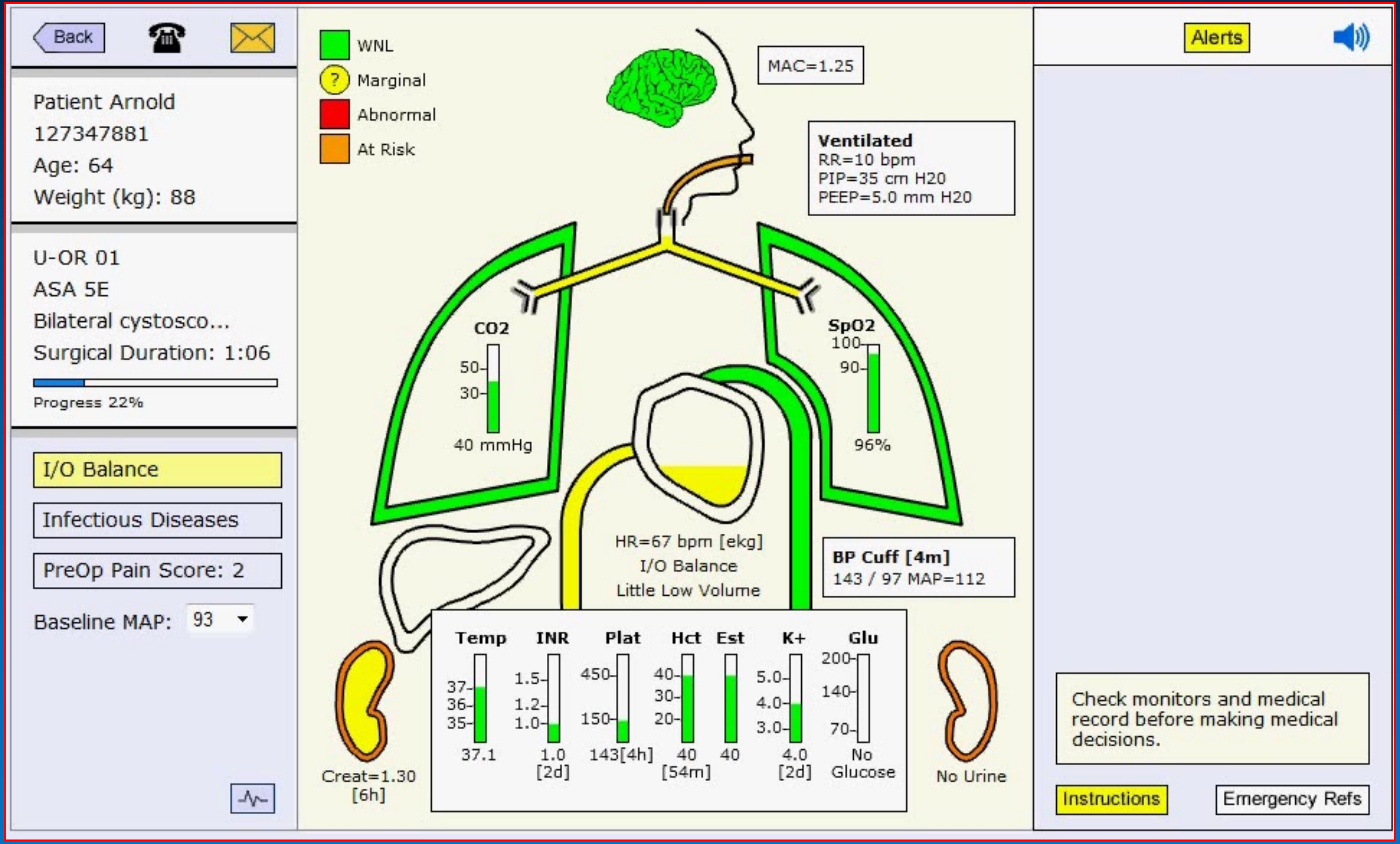
Decision Support Engine

H & P



AIMS

Working Prototype 2011
Lets do a study …..



IRB Questions:

Is it FDA Cleared ?   What ???

If it is turned on and off every two weeks ...
You need patient informed consent

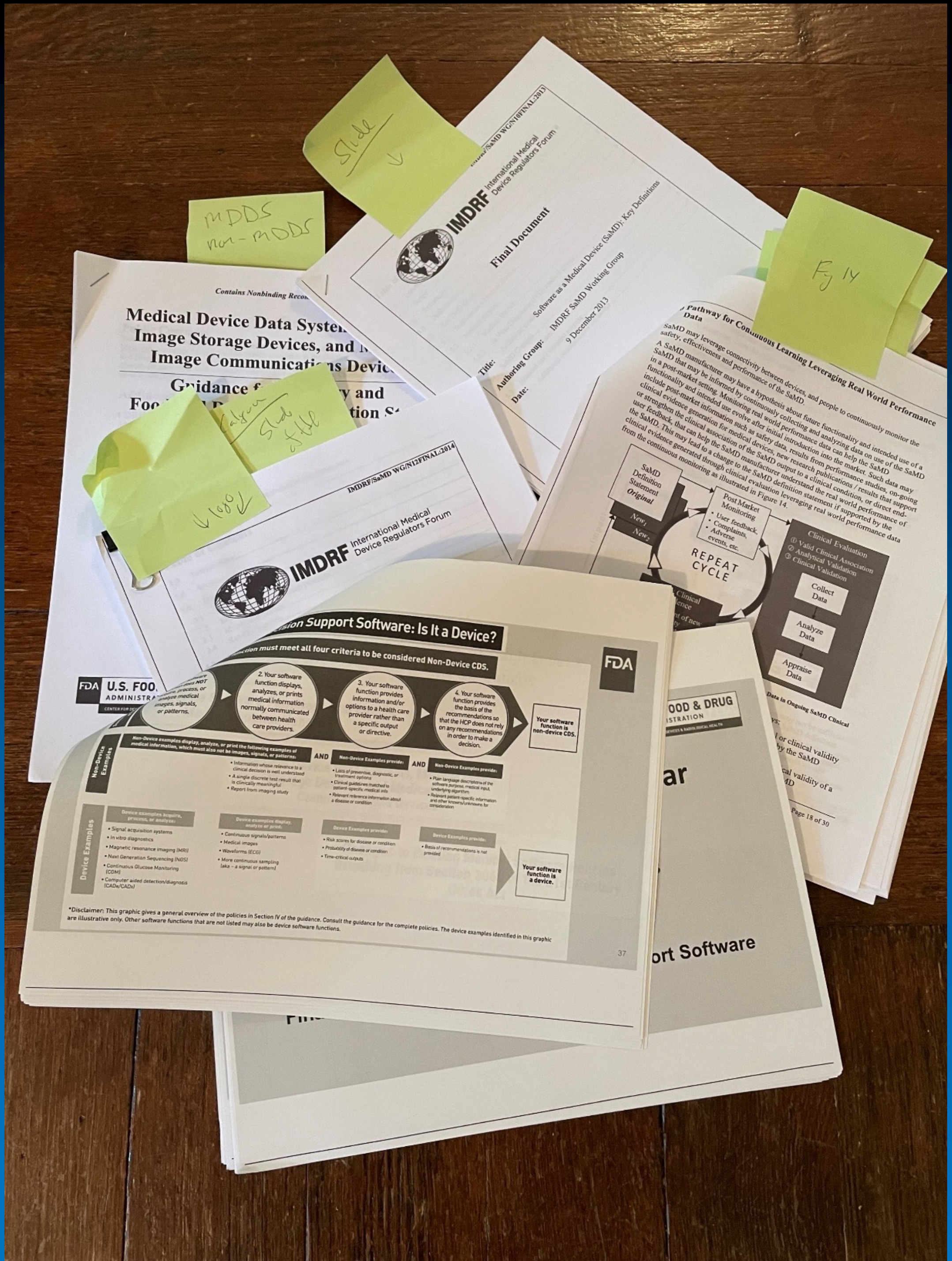
"We have developed a new software safety system, we don't know if it helps, is it OK if we turn if off for you?"

FDA MDDS 2011 (updated Sept 2022)

- Non-Regulated (MDDS): “Solely intended to transfer, store, convert format, display device data including waveforms”

- Regulated MDDS, 2011: “Software functions to **analyze or interpret** device data in addition to ….” (this is an MDDS Class II software device)

FDA Guidance Documents 2011-2022



Your Clinical Decision Support Software: Is it a Device?

Your Clinical Decision Support Software: Is It a Device?

FDA

The FDA issued a guidance, Clinical Decision Support Software, to describe the FDA's regulatory approach to Clinical Decision Support (CDS) software functions. This graphic gives a general and summary overview of the guidance and is for illustrative purposes only. Consult the guidance for the complete discussion and examples. Other software functions that are not listed may also be device software functions. *

Your software function must meet all four criteria to be Non-Device CDS.

Summary interpretation of CDS criteria

1. Your software function does **NOT** acquire, process, or analyze medical images, signals, or patterns.
2. Your software function displays, analyzes, or prints medical information normally communicated between health care professionals (HCPs).
3. Your software function provides recommendations (information/options) to a HCP rather than provide a specific output or directive.
4. Your software function provides the basis of the recommendations so that the HCP does not rely primarily on any recommendations to make a decision.

Your software function may be non-device CDS.

Non-Device Examples

Non-Device examples display, analyze, or print the following examples of medical information, which must also not be images, signals, or patterns:

- Information whose relevance to a clinical decision is well understood
- A single discrete test result that is clinically meaningful
- Report from imaging study

Device Examples

Device examples acquire, process, or analyze:

- Signal acquisition systems
- In vitro diagnostics
- Magnetic resonance imaging (MRI)
- Next Generation Sequencing (NGS)
- Continuous Glucose Monitoring (CGM)
- Computer aided detection/diagnosis (CADe/CADx)

OR

Device examples display, analyze or print:

- Continuous signals/patterns
- Medical images
- Waveforms (ECG)
- More continuous sampling (aka – a signal or pattern)

Device examples provide:

- Risk scores for disease or condition
- Probability of disease or condition
- Time-critical outputs

*Disclaimer: This graphic gives a general overview of Section IV of the guidance ("I

discussion. The device examples identified in this graphic are illustrative only and are not an exhaustive list. Other software functions that are not listed may also be device software functions.

Study on hold … FDA??

U of Michigan's Business Engagement Center's recommendations:

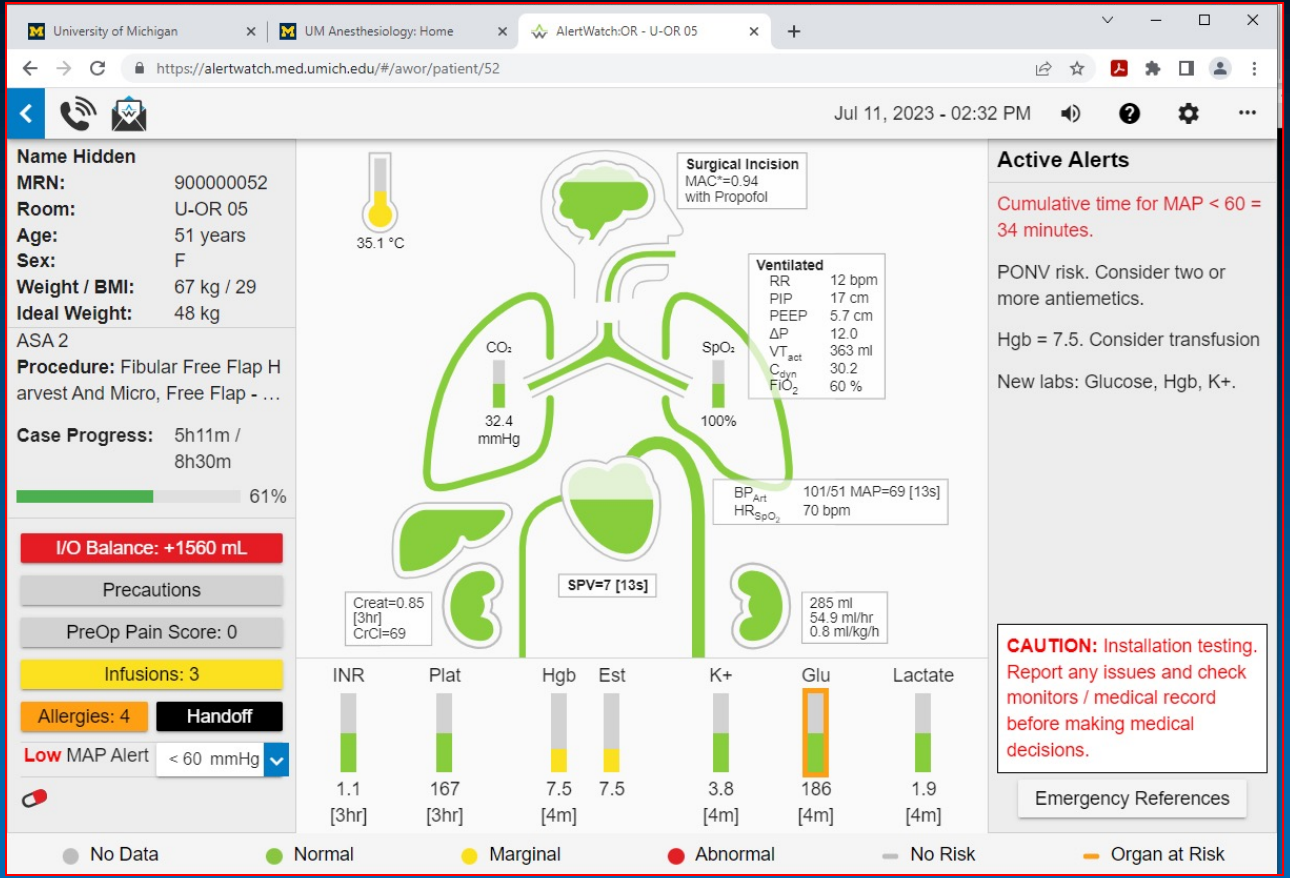
1. Get patents, we'll do that
2. Find a CEO, we'll help with that
3. Raise $$, you do that

5 years and $500K later we received FDA Clearance

AW decision support analysis/calculation

Examples:

1. I&O balance
2. Estimated Hb
3. Cumulative Hypotension
4. PPH Risk

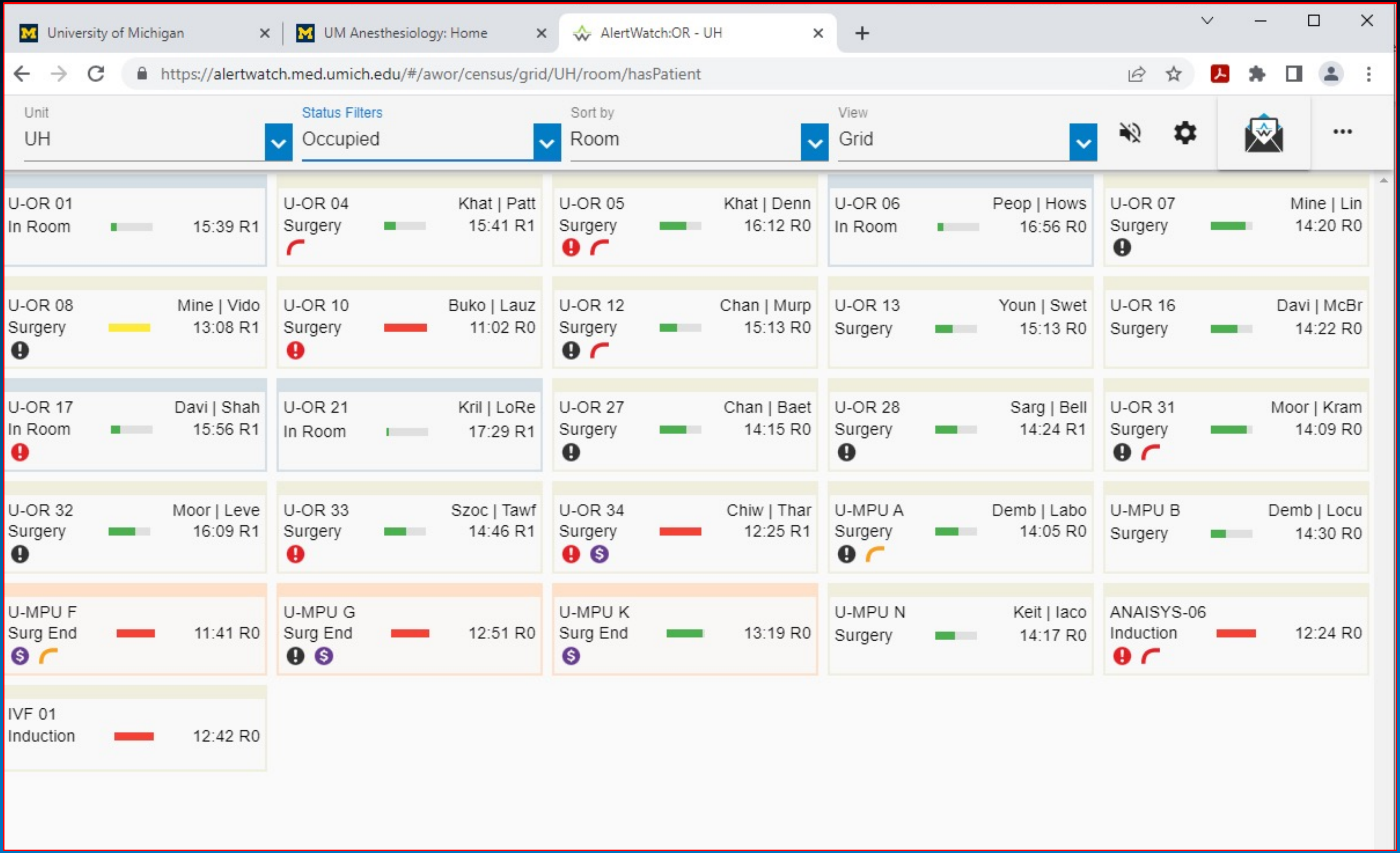


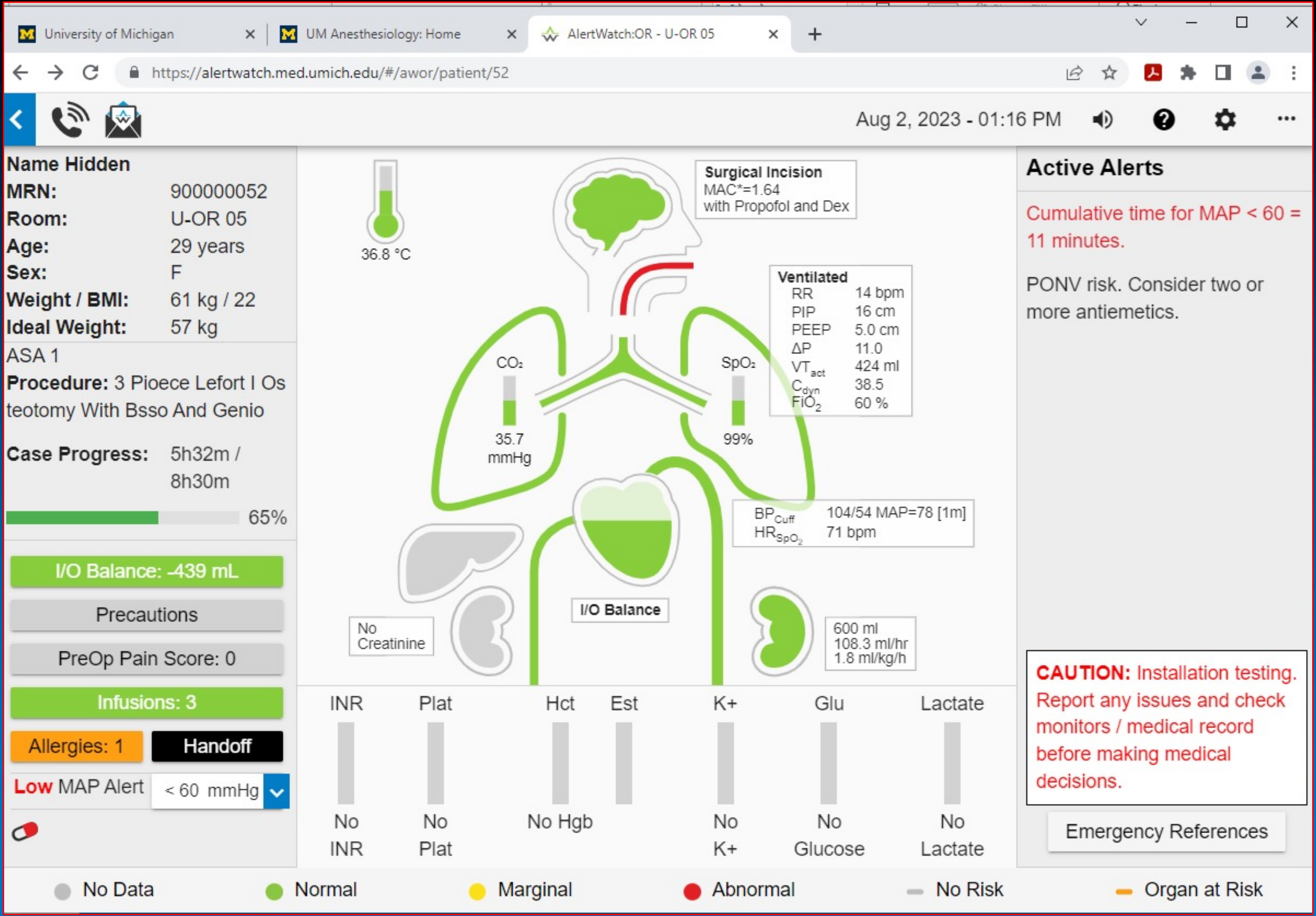
FDA?

What's with the yellow? Show us the published yellow ranges

Air Traffic Control

Flight Tower View : Wash U "ACTFAST"




University of Michigan
UM Anesthesiology: Home
AlertWatch:OR - U-OR 05
https://alertwatch.med.umich.edu/#/awor/patient/52
Aug 2, 2023 - 01:16 PM
Name Hidden
MRN: 900000052
Room: U-OR 05
Age: 29 years
Sex: F
Weight / BMI: 61 kg / 22
Ideal Weight: 57 kg
ASA 1
Procedure: 3 Pioece Lefort I Osteotomy With Bsso And Genio
Case Progress: 5h32m / 8h30m
65%
I/O Balance: -439 mL
Precautions
PreOp Pain Score: 0
Infusions: 3
Allergies: 1
Handoff
Low MAP Alert
< 60 mmHg
36.8 °C
Surgical Incision
MAC*=1.64
with Propofol and Dex
Ventilated
RR 14 bpm
PIP 16 cm
PEEP 5.0 cm
ΔP 11.0
VTact 424 ml
Cdyn 38.5
FiO2 60 %
CO2
35.7 mmHg
SpO2
99%
BPCuff 104/54 MAP=78 [1m]
HRSpO2 71 bpm
No Creatinine
I/O Balance
600 ml
108.3 ml/hr
1.8 ml/kg/h
INR
Plat
Hct
Est
K+
Glu
Lactate
No INR
No Plat
No Hgb
No K+
No Glucose
No Lactate
Active Alerts
Cumulative time for MAP < 60 = 11 minutes.
PONV risk. Consider two or more antiemetics.
CAUTION: Installation testing. Report any issues and check monitors / medical record before making medical decisions.
Emergency References
No Data
Normal
Marginal
Abnormal
No Risk
Organ at Risk

University of Michigan
UM Anesthesiology: Home
AlertWatch:OR - U-OR 05

https://alertwatch.med.umich.edu/#/awor/patient/52?popupName=ioBalance

Input / Output Balance

Estimated Blood Volume = 3810 mL

I/O Balance	= Added Fluid	- Insensible Loss	- EBL x 3	- Surgery Loss	- Urine Total	± Normalize
-451	+ 1500	- 1351	0	0	- 600	0

Added fluid = crystalloid (1500) + colloid (0) x 3 + albumin (0) x 1.5 + PRBC (0) x 3 + cellsaver (0) x 3

Insensible loss = [NPO until incision (8.7) + surgery hours (4.7)] x weight factor (101)

Weight factor =
- 40 + weight if weight > 20
- 20 + 2 x weight if weight > 10
- 4 x weight if weight ≤ 10

EBL (0)

Surgery loss = third space loss (0) x weight (61.2) x surgery hours (4.68)

Normalize = manual adjustment to total (0) via *Normalize* button.

I/O Settings

Normalize

NPO Time (hours):
9

3rd Space Loss:
None

I/O Balance References

- Crystalloids Versus Colloids: Exploring Differences in Fluid Requirements by Systematic Review and Meta-Regression **Summary**
  Cortés, Anesthesia & Analgesia, 2015
- Arterial Pressure Variation in Elective Noncardiac Surgery: Identifying Reference Distributions and Modifying Factors **Summary**
  Mathis, Anesthesiology, 2017
- Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery **Summary**

Prediction of blood volume in normal human adults

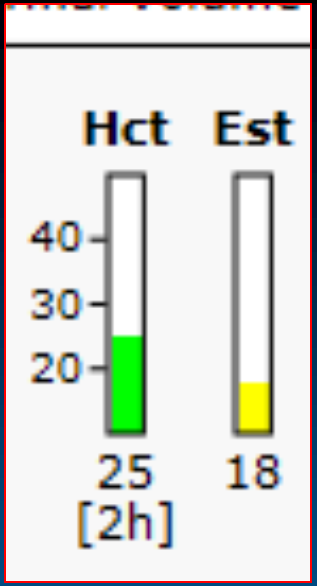
To fit the data, he used an "IBM electric digital computer" ... "a Herculean task by any other method"

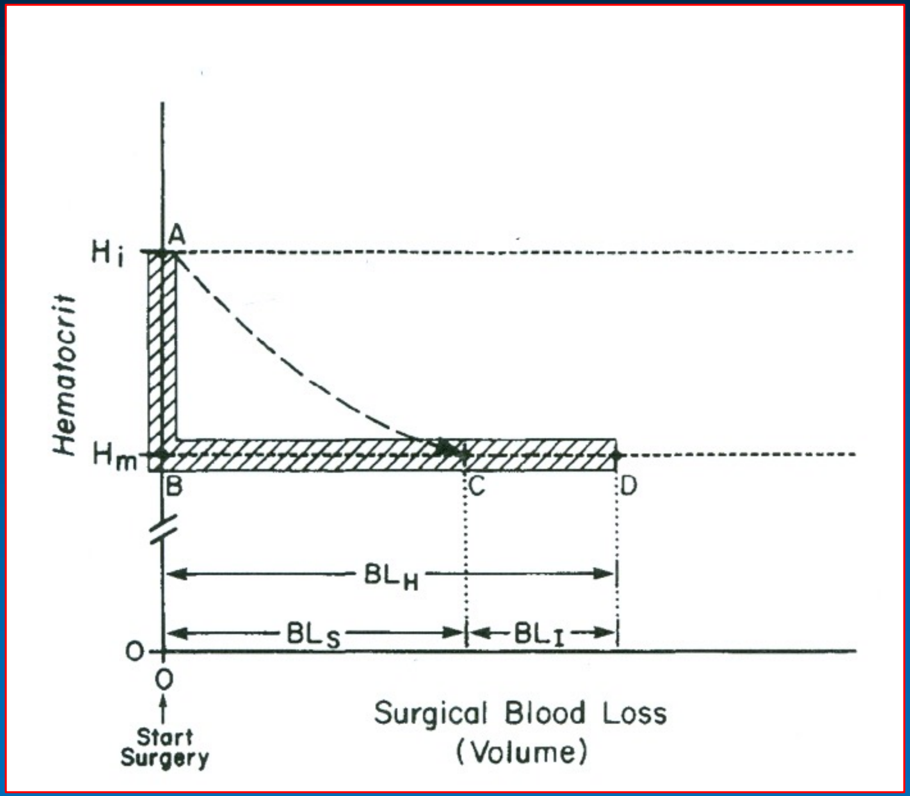
$$EBV = 0.3669 \times H^3 + 0.03219 \times W + 0.6041$$

(for men)

Nadler et al Surgery 1962

Estimated Hct





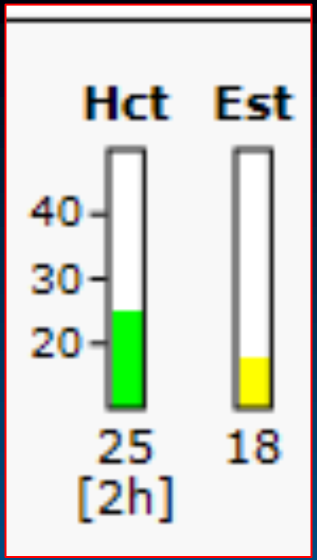
Maximum Blood Savings by Acute Normovolemic Hemodilution

Feldman et al Anesth & Analg 1995

Estimated Hct

$$EBL = EBV \ln Hct_i / Hct_m$$

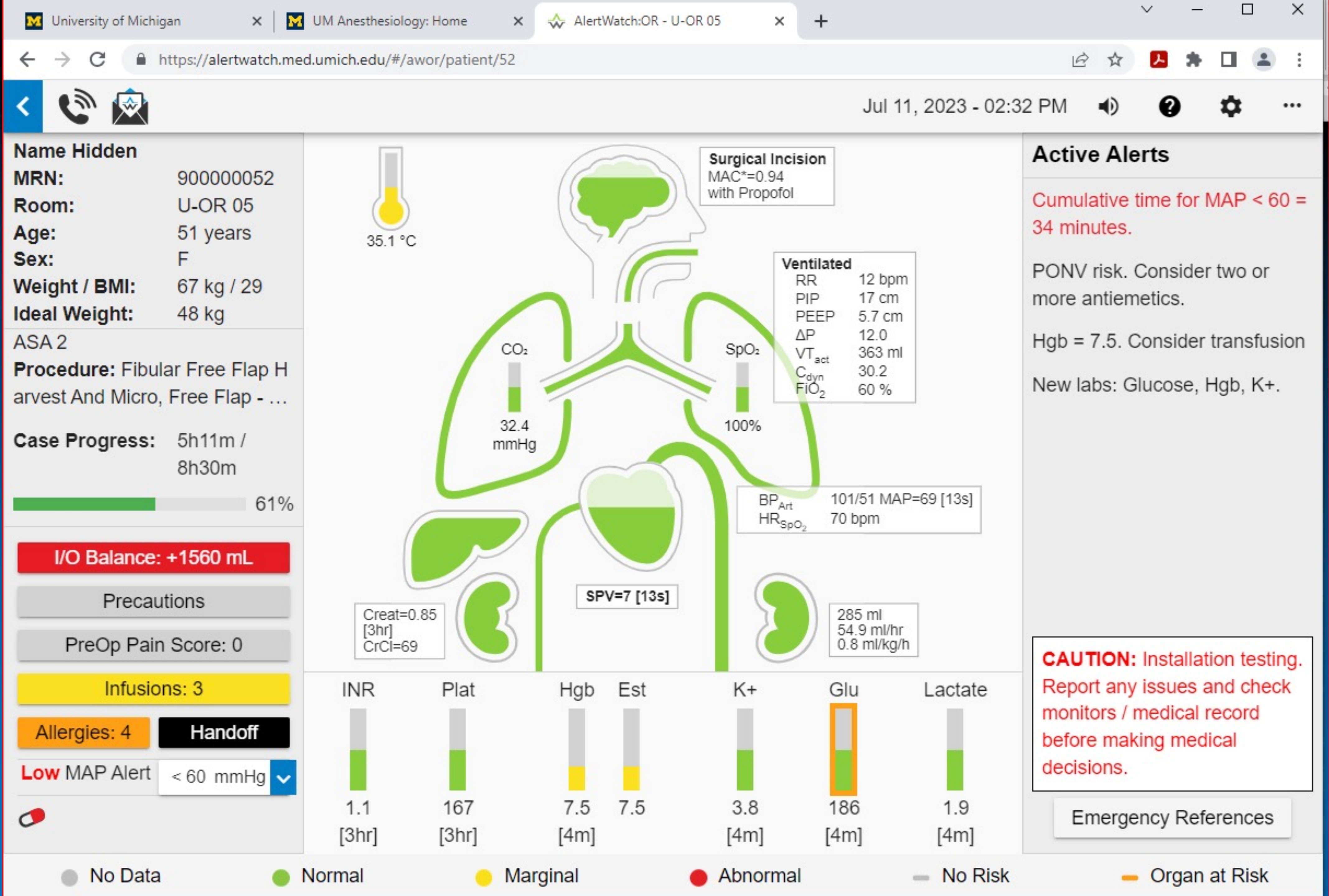
Solve for Hct_m



Estimated Hct = Hct / ($e^{EBL/EBV}$) + added blood

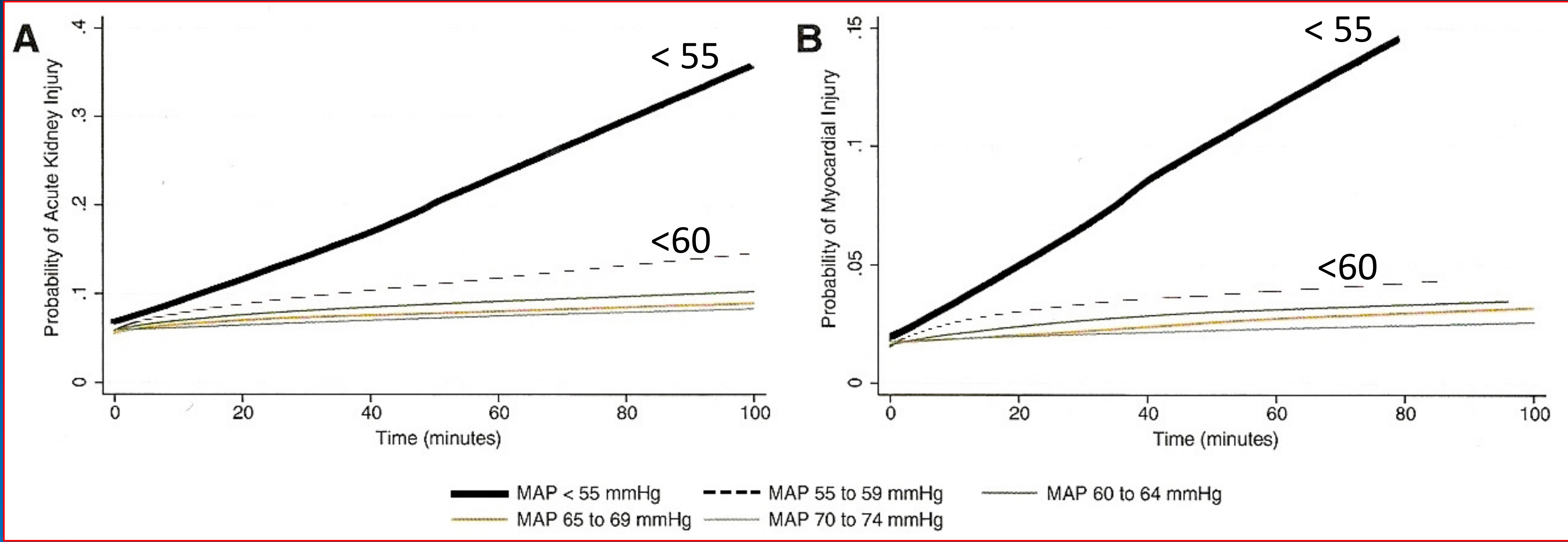
EBL = Estimated Blood Loss

EBV = Estimated Blood Volume


University of Michigan
UM Anesthesiology: Home
AlertWatch:OR - U-OR 05
https://alertwatch.med.umich.edu/#/awor/patient/52
Jul 11, 2023 - 02:32 PM
Name Hidden
MRN: 900000052
Room: U-OR 05
Age: 51 years
Sex: F
Weight / BMI: 67 kg / 29
Ideal Weight: 48 kg
ASA 2
Procedure: Fibular Free Flap Harvest And Micro, Free Flap - …
Case Progress: 5h11m / 8h30m
61%
I/O Balance: +1560 mL
Precautions
PreOp Pain Score: 0
Infusions: 3
Allergies: 4
Handoff
Low MAP Alert
< 60 mmHg
35.1 °C
Surgical Incision
MAC*=0.94
with Propofol
Ventilated
RR 12 bpm
PIP 17 cm
PEEP 5.7 cm
ΔP 12.0
VTact 363 ml
Cdyn 30.2
FiO2 60 %
CO2
32.4 mmHg
SpO2
100%
BPArt 101/51 MAP=69 [13s]
HRSpO2 70 bpm
SPV=7 [13s]
Creat=0.85 [3hr]
CrCl=69
285 ml
54.9 ml/hr
0.8 ml/kg/h
INR 1.1 [3hr]
Plat 167 [3hr]
Hgb 7.5 [4m]
Est 7.5
K+ 3.8 [4m]
Glu 186 [4m]
Lactate 1.9 [4m]
Active Alerts
Cumulative time for MAP < 60 = 34 minutes.
PONV risk. Consider two or more antiemetics.
Hgb = 7.5. Consider transfusion
New labs: Glucose, Hgb, K+.
CAUTION: Installation testing. Report any issues and check monitors / medical record before making medical decisions.
Emergency References
No Data
Normal
Marginal
Abnormal
No Risk
Organ at Risk

Keep MAP > 55 mmHg or 60 mmHg Cumulative BP

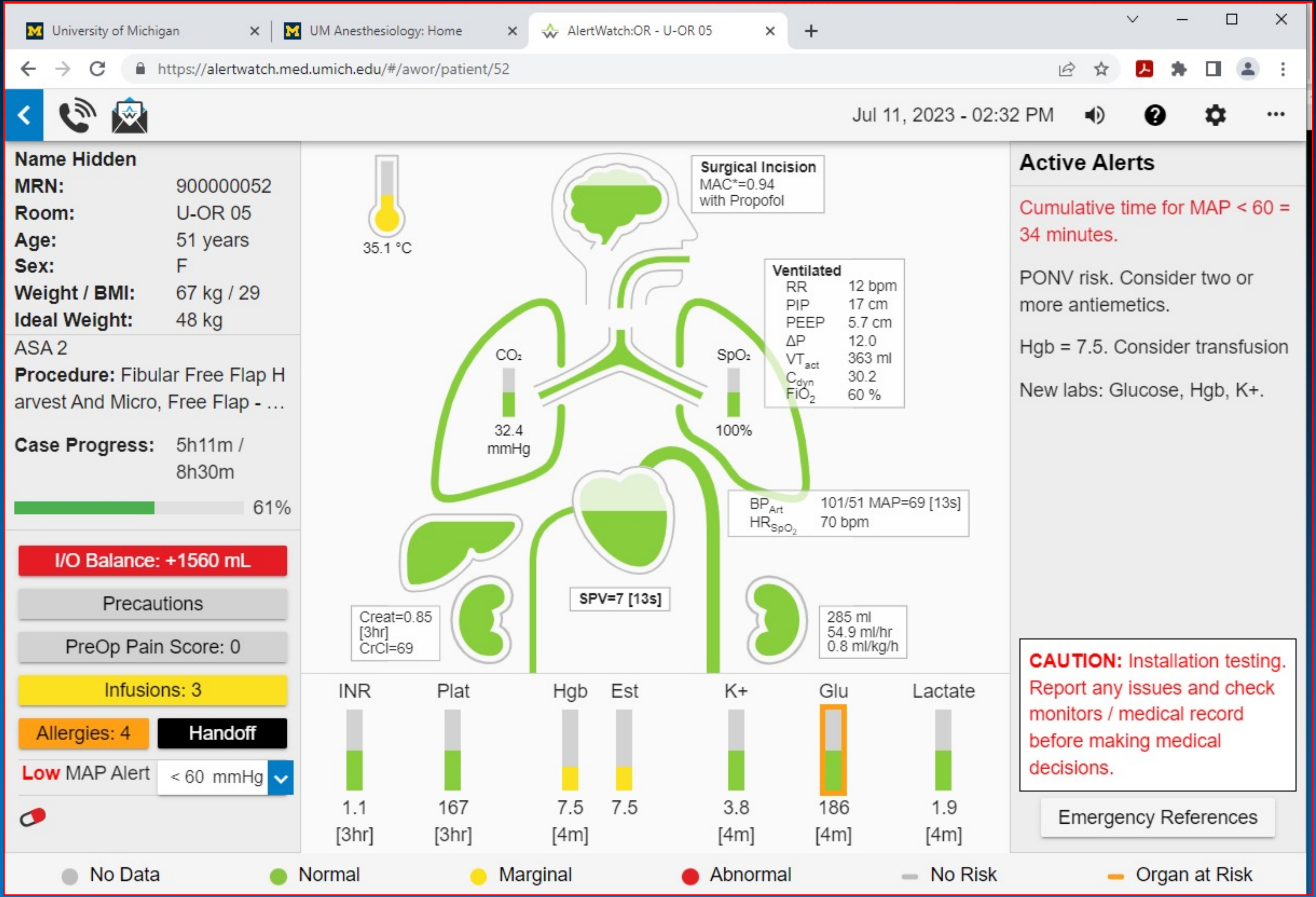
*A. Postop **Renal** Injury* *B. Postop **Myocardial** Injury*



Relationship between Intraoperative Mean Arterial Pressure and Clinical Outcomes after Noncardiac Surgery…

Walsh et. al., *Anesthesiology, V 119 No 3, 2013.*

AW Cumulative Hypotension

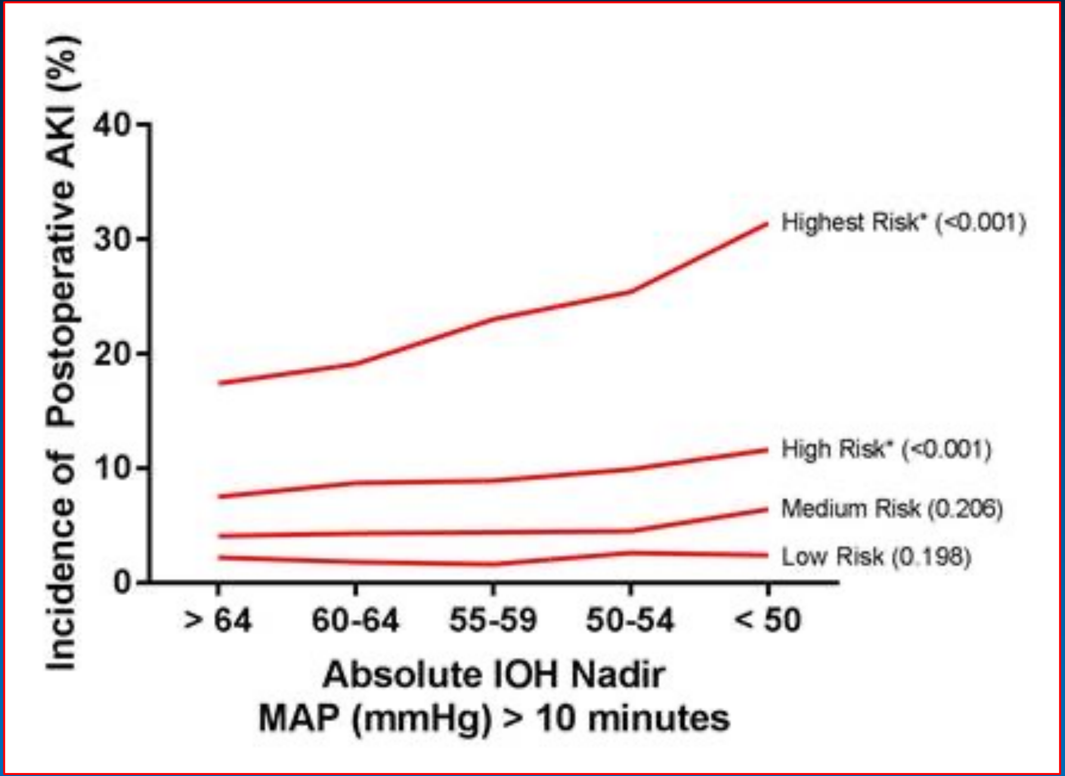


ANESTHESIOLOGY

Preoperative Risk and the Association between Hypotension and Postoperative Acute Kidney Injury

Michael R. Mathis, M.D., Bhiken I. Naik, M.B.B.Ch., Robert E. Freundlich, M.D., M.S., M.S.C.I., Amy M. Shanks, Ph.D., Michael Heung, M.D., Minjae Kim, M.D., Michael L. Burns, M.D., Ph.D., Douglas A. Colquhoun, M.B. Ch.B., M.Sc., M.P.H., Govind Rangrass, M.D., Allison Janda, M.D., Milo C. Engoren, M.D., Leif Saager, M.D., M.M.M., Kevin K. Tremper, M.D., Ph.D., Sachin Kheterpal, M.D., M.B.A., on behalf of the Multicenter Perioperative Outcomes Group Investigators*

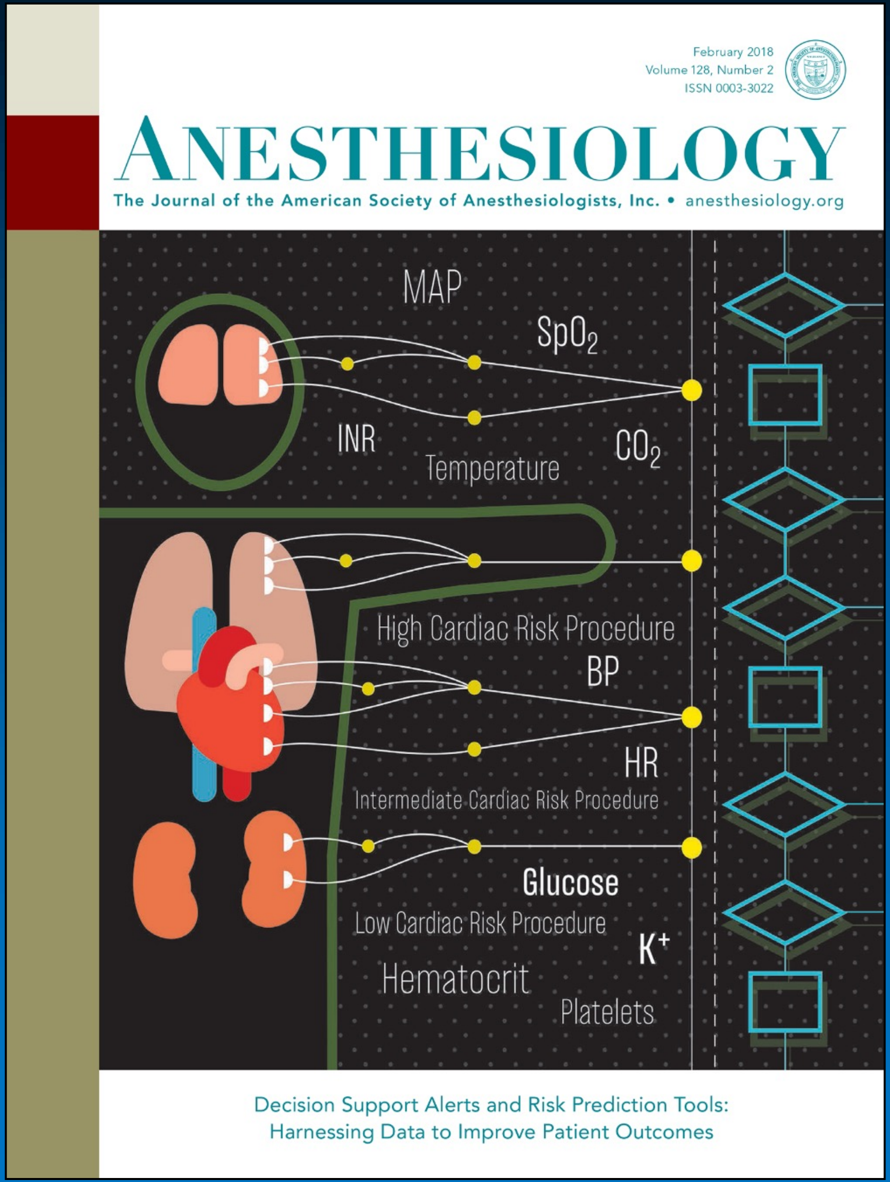
Anesthesiology 2020; XXX:00–00



Mathis et al Anesthesiology March 2020

6 Years of Observational Experience; Feb 2018

Kheterpal S, Shanks A and Tremper K



AlertWatch User vs Non-User
6 yrs and 26,769 cases

Process Measures:	P values
Hypotension < 55 mmHg *	<0.001
Crystalloid ml/kg/hr	<0.001
Tidal Volume 6-8 ml/Kg Ideal BW	<0.001

Clinical Outcomes (Historical vs Parallel):

MI 1.5% vs 2.6% vs 2.1% … Versus no difference

AKI ... No difference

Resource Differences:

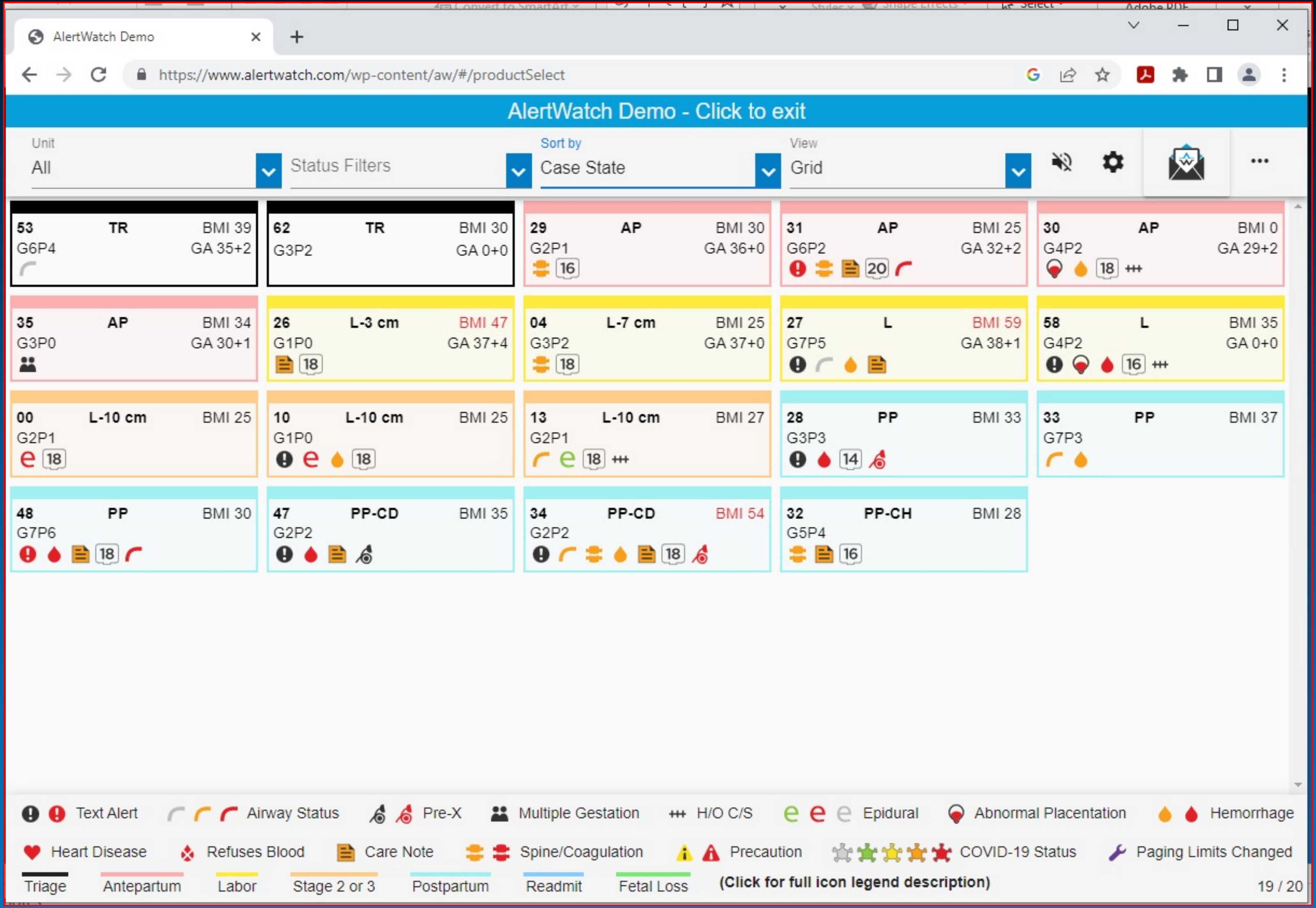
LOS 5 days vs 6 days	<0.001

Hospital Charges $3,603 less for AW patients

2. Escalating alerts to help us follow out own protocols

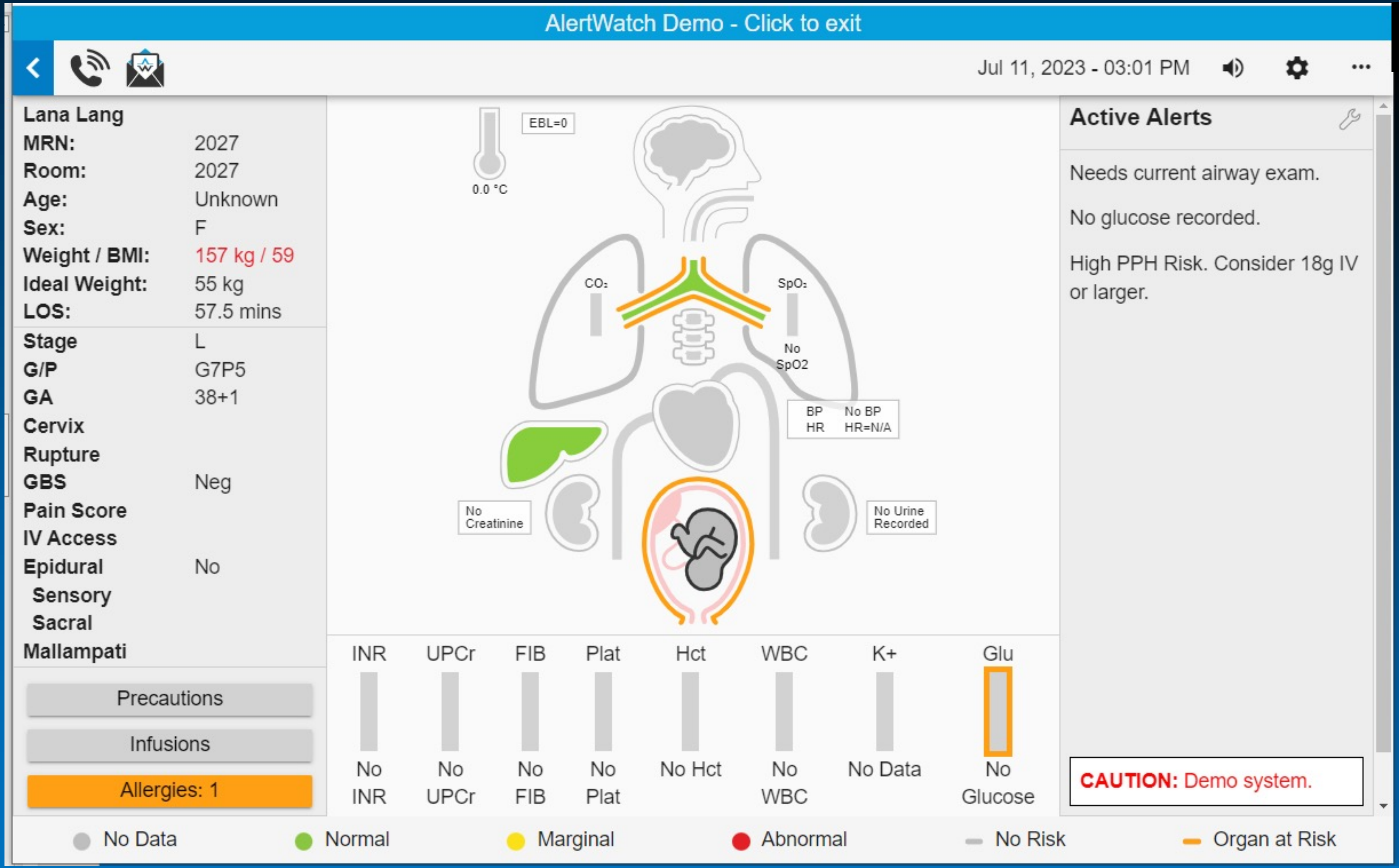
(following our own rules)

Maternal Decision Support for L&D



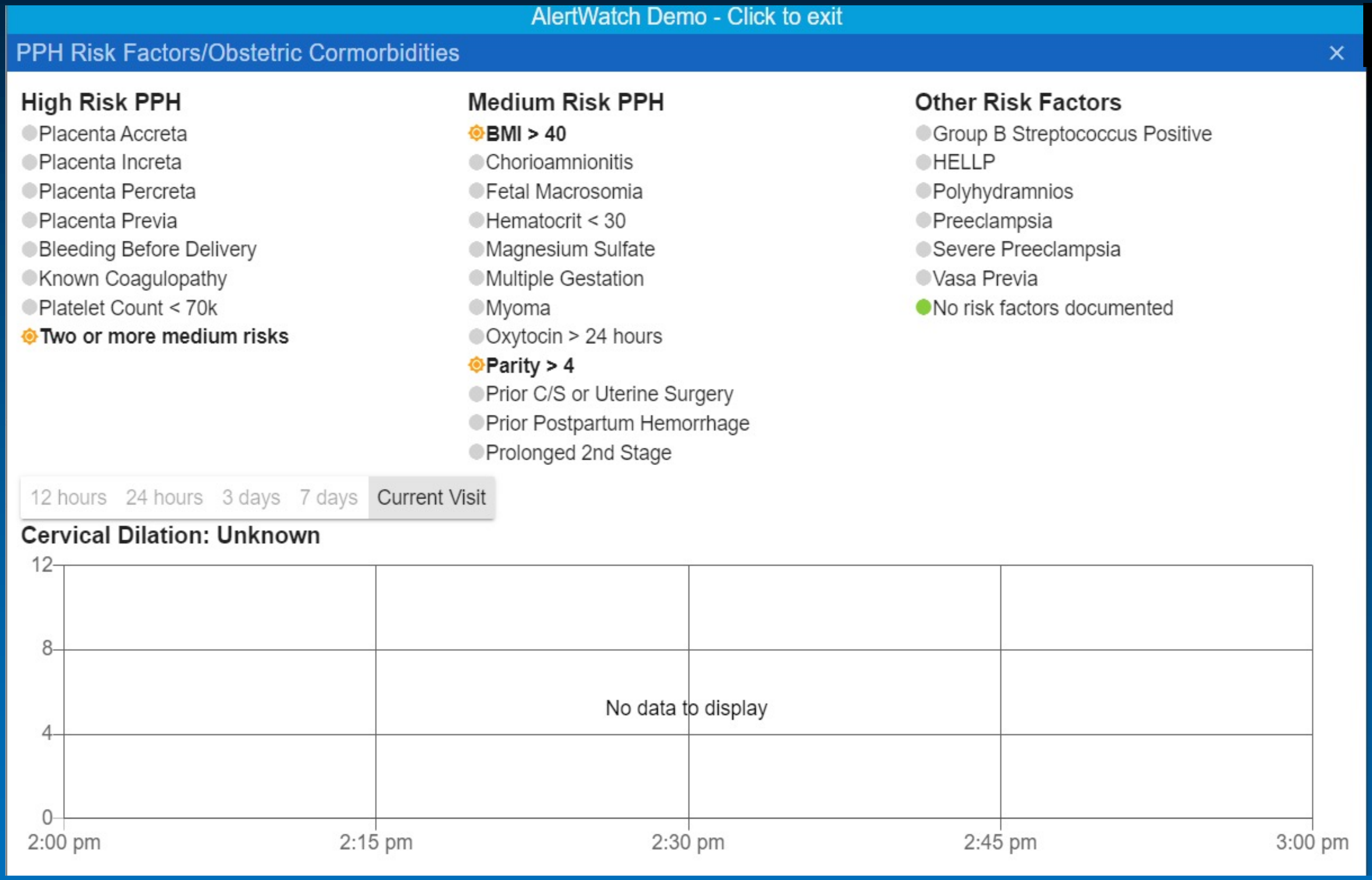
Tom Klumpner et al A&A Feb 2020

AWOB PPH Risk/PPH/Preecampsia

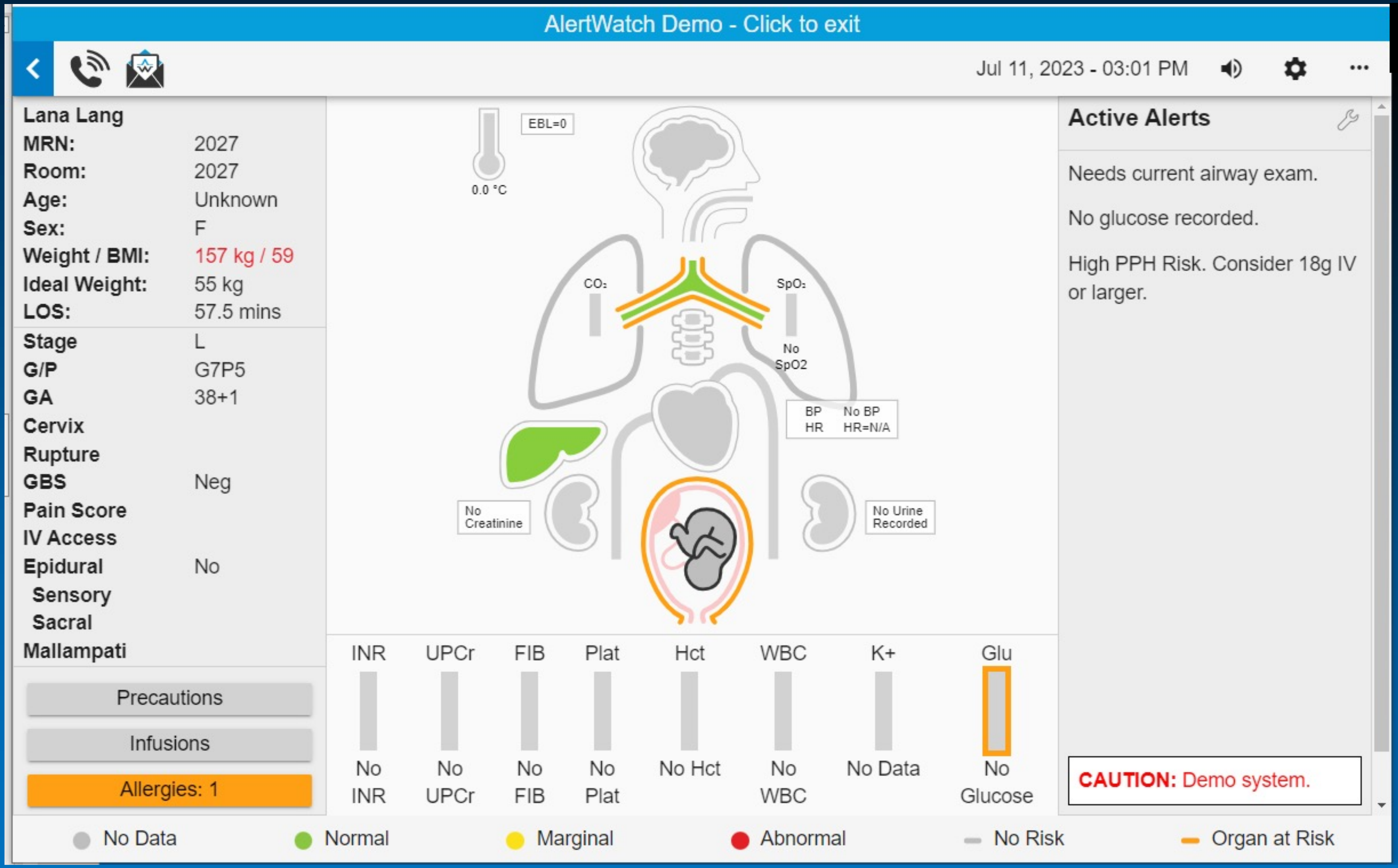


ACOG PPH Risk Factors

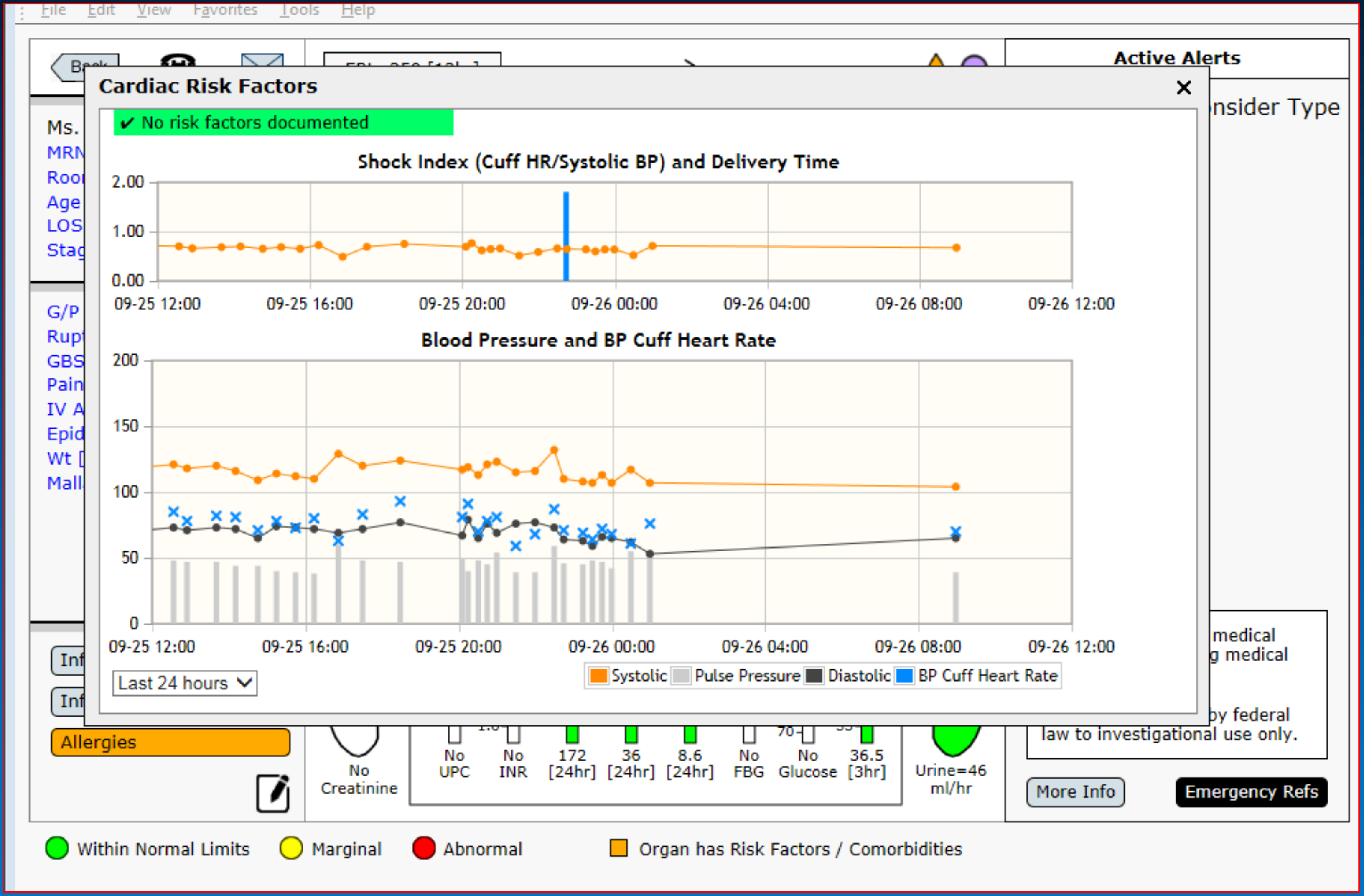
Checks IV size and Blood availability



AWOB PPH Risk/PPH/Preecampsia



HR, BP, Hb & Shock Index to Alert For Postpartum Hemorrhage



AWOB Paging Logic for: Hypotension * Hypertension Tachycardia Shock Index * Anemia *

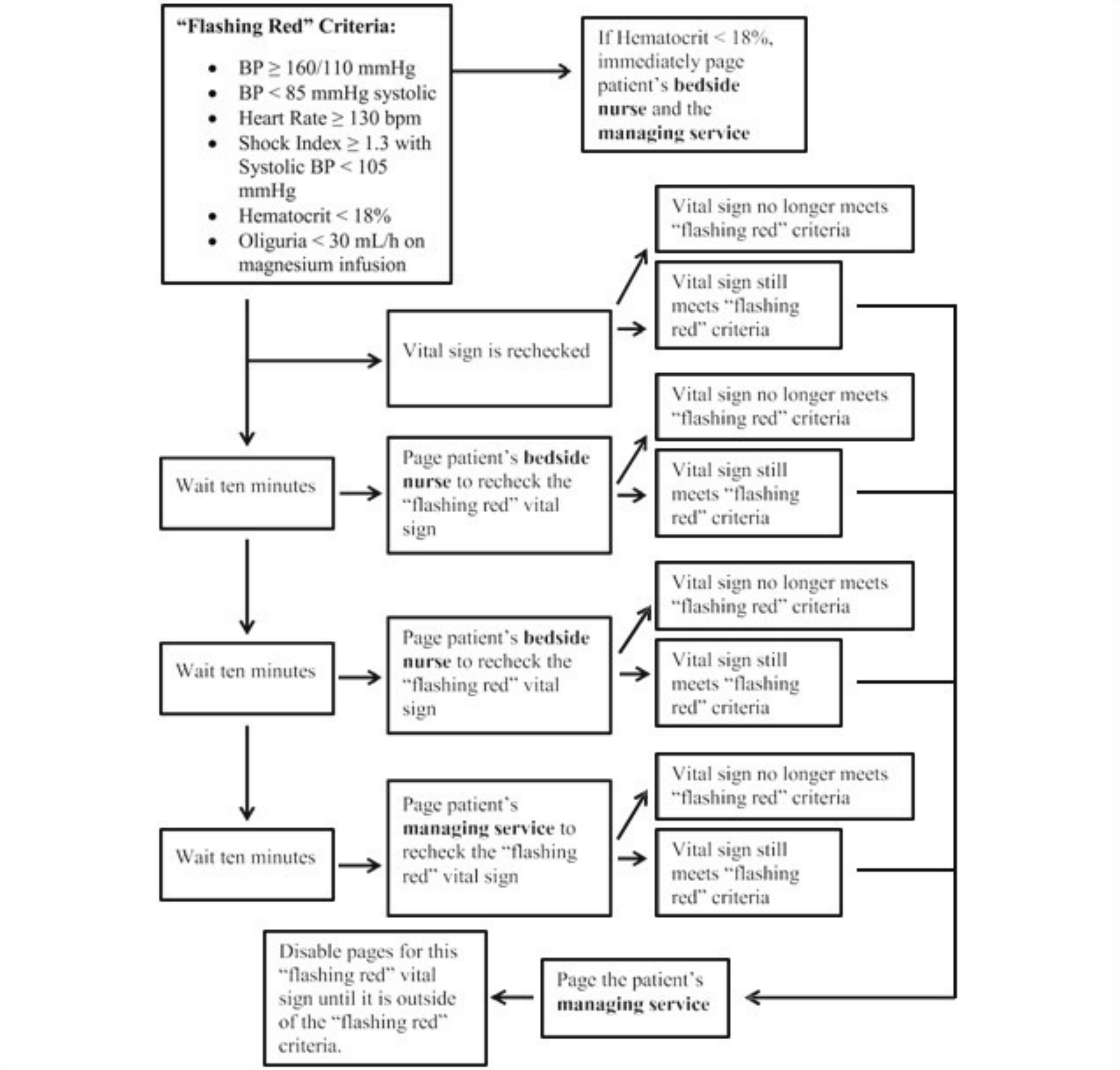


Fig. 4 Automated Paging Sequence. Automatic pages are sent to a patient's bedside nurse and managing service when defined "flashing red" criteria are met

“Algorithm” to Remove Artifacts

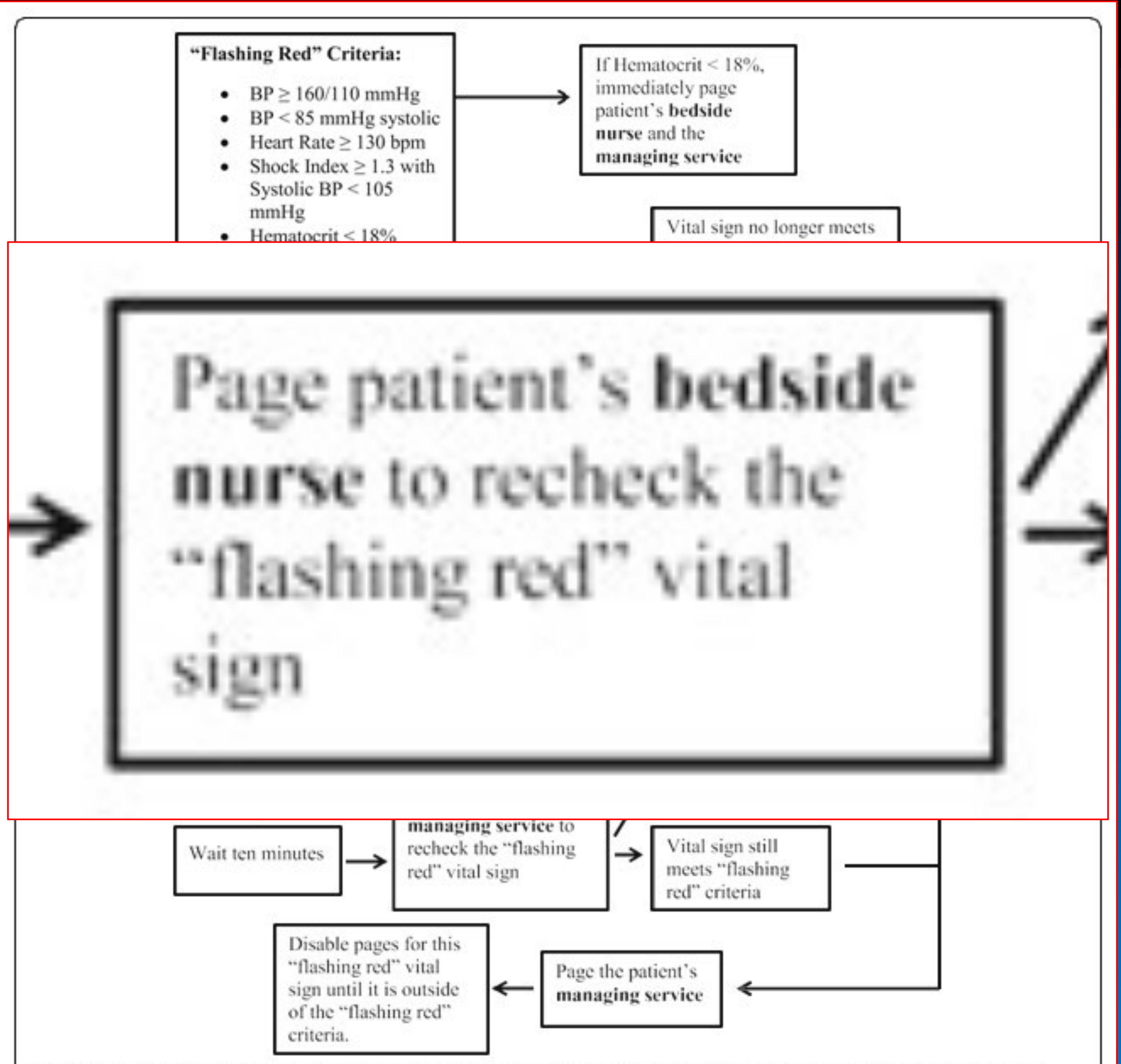


Fig. 4 Automated Paging Sequence. Automatic pages are sent to a patient’s bedside nurse and managing service when defined “flashing red” criteria are met

“PPH Risk Confirmed:
“Rm 18. Systolic BP 55 “

Frequency of Paging Alerts / 24 hrs. (50-bed L&D Unit)

	MEWC		AWOB: RN Pages	AWOB: MD Pages
BP < 90	12.8	BP < 85	6.4	0.96 (< once a day)
BP > 160	10		11	2.8
BPd > 100	14.5	BPd > 110	5.3	0.4
HR > 120	51	HR > 130	23.8	2.1
Total	150 (every 8 min)		47	6.3 (every 3.8 hrs)

Klumpner et al BMC Anesthesiology 2018

ORIGINAL CLINICAL RESEARCH REPORT

Use of a Novel Electronic Maternal Surveillance System and the Maternal Early Warning Criteria to Detect Severe Postpartum Hemorrhage

Thomas T. Klumpner, MD,*† Joanna A. Kountanis, MD,*† Sean R. Meyer, MBA,‡ Justin Ortwine, BS,* Melissa E. Bauer, DO,*† Alissa Carver, MD,† Anne Marie Piehl, MSN, RN, CNM,‡ Roger Smith, MD,† Graciela Mentz, PhD,* and Kevin K. Tremper, PhD, MD*

Comparing AWOB Paging Alerts to MEWC: Does it Work?

7,853 Deliveries (over 20 months)… 120 sPPH events (1.5%)

PPH = EBL > 1,000 ml

sPPH = > 4 units PRBCs
>2 PRBCs+ > units FFP
Return to OR
PP Hysterectomy
Uterine Artery Embolism
Admission to ICU

Klumpner et al A&A Feb 2020

AWOB vs MEWC*

Table 3. Test Characteristics of Automated Pages Versus Maternal Early Warning Criteria for Severely Morbid Postpartum Hemorrhage

	Automated Paging System Estimate (95% CI)	Maternal Early Warning Criteria[a] Estimate (95% CI)	*P* Value[b]
Sensitivity	60.8% (52.1–69.6)	75.0% (67.3–82.7)	.027
Specificity	82.5% (81.7–83.4)	66.3% (65.2–67.3)	<.001
Positive predictive value	5.1% (4.0–6.3)	3.3% (2.7–4.0)	.007
Negative predictive value	99.3% (99.1–99.5)	99.4% (99.2–99.6)	.358

***This assumes that there is 100% response rate of escalation of care when MEWC are met**

Klumpner et al A&A Feb 2020

AWOB vs MEWC*

Table 3. Test Characteristics of Automated Pages Versus Maternal Early Warning Criteria for Severely Morbid Postpartum Hemorrhage

	Automated Paging System Estimate (95% CI)	Maternal Early Warning Criteria[a] Estimate (95% CI)	*P* Value[b]
Se	60.8% (52.1–69.6)	75.0% (67.3–82.7)	7
Sp	82.5% (81.7–83.4)	66.3% (65.2–67.3)	1
Pos	5.1% (4.0–6.3)	3.3% (2.7–4.0)	7
Ne	99.3% (99.1–99.5)	99.4% (99.2–99.6)	8

of Automated Pages Versus Maternal Early Warning Criteria
e

Klumpner et al A&A Feb 2020

Conclusion

"The automated system identified 10 of 120 deliveries complicated by sPPH not identified by the MEWC. Using an automated alerting system in combination with a labor and delivery unit's existing nursing-driven early warning system may improve detection of sPPH."

Klumpner et al *Anesth & Analg*, Feb 2020

3. Providing alerts/recommendations we could not determine

(Machine learning/AI driven)

Epic's Sepsis Model (ESM) Issues … Controversial

- **38,455 admissions (Retrospective)**
- **2,552 (7%) had sepsis ESM =>6**
- **ESM identified 183 of these (7%) ROC = 0.63**
- **ESM missed 1,709 (67%) … despite generating 6,971 alters (18% of all pts)**
- **ie 109 alerts to identify one septic pt.**

- **Wong et al JAMA Int Med Aug 2021 181(8) 1065-1070**

Epic's Sepsis Model (ESM) Issues … Controversial

- 11,512 admissions (Before vs After study)
- 10.2% has sepsis, ESM => 5
- ROC = 0.83
- Mortality 11.9 % to 10.1 %

- Cull et al Crit Care Explor July 2023

Machine Learning/AI
How will the FDA handle this?

Clinical studies… and any revision will require a resubmission… unless you request and have it approved

A "Predetermined Change Control Plan"

My opinion…

- **Not an issue of insufficient analysis … Machine Learning/AI**
- **Its insufficient accurate high-resolution data…**

KEY POINTS

- **Question:** How well do automated pages generated by a novel maternal electronic surveillance system and the Maternal Early Warning Criteria (MEWC) detect severely morbid postpartum hemorrhage (sPPH)?
- **Findings:** While neither system was completely sensitive, the automated system was more specific and identified 10 of 120 deliveries complicated by sPPH that were not identified by the MEWC.
- **Meaning:** Using an automated alerting system in combination with a labor and delivery unit's existing nursing-driven early warning system may ultimately improve detection of sPPH.

Try Live Demo

Fundamental Claims for Translational Research

"Studies suggest that it takes an average of 17 years for research evidence to reach clinical practice."

Balas, E. A., & Boren, S. A. (2000). Yearbook of Medical Informatics: Managing Clinical Knowledge for Health Care Improvement. Stuttgart, Germany: Schattauer Verlagsgesellschaft mbH.

"It takes an estimated average of 17 years for only 14% of new scientific discoveries to enter day-to-day clinical practice."

Westfall, J. M., Mold, J., & Fagnan, L. (2007). Practice-based research - "Blue Highways" on the NIH roadmap. JAMA, 297(4), p. 403.