Microbiology and Coagulation Testing: LIS

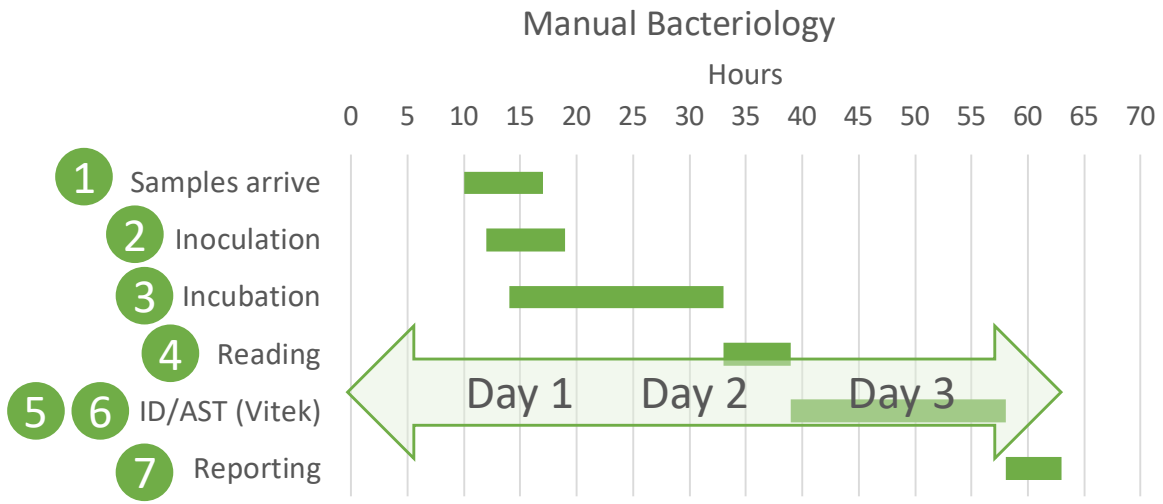
Pathology Informatics Summit 2018

May 21, 2018

Dr. JiYeon Kim

Goals of talk

1. Review what makes for distinctive microbiology LIS features, and what data drives decision-making in clinical infectious diseases
2. Be familiar with trends in microbiology automation, new diagnostic technologies
3. Understand how new anticoagulation drugs are affecting coagulation test results
4. Consider future LIS data needs, including the need for “talking” interfaces with other clinical information systems outside the lab



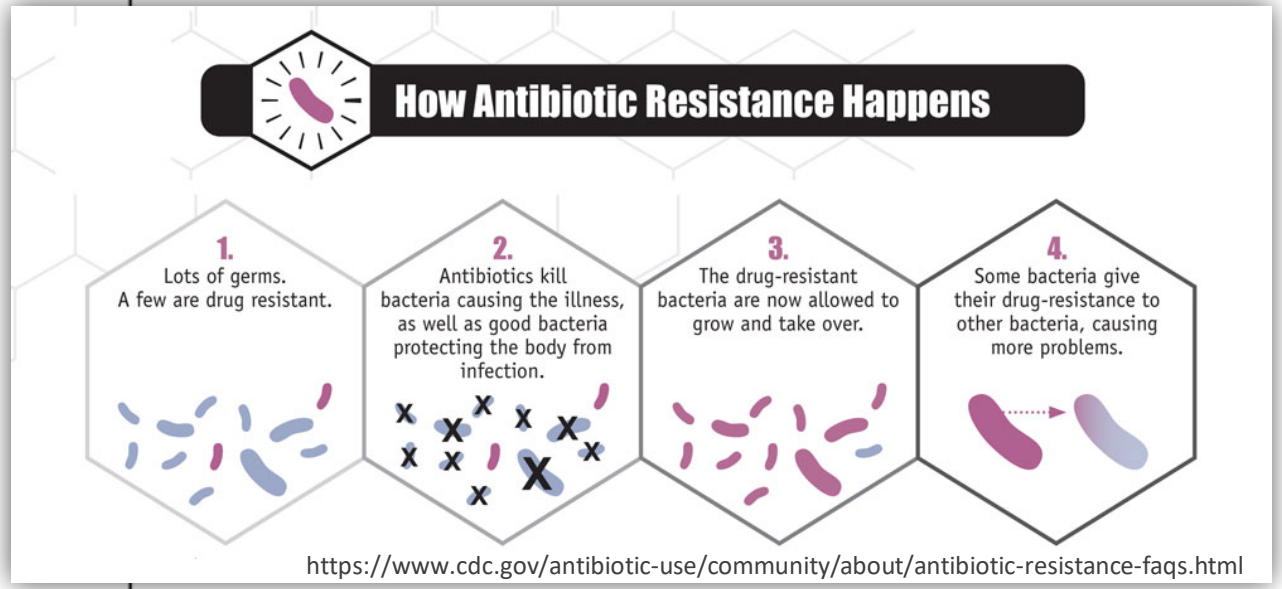
Role of Microbiologist: Cartoon by Czichos

Provider questions for clinical microbiology lab:

1. Is my patient's illness caused by a microbe?
2. If yes, what is it?
3. What is the antibiotic susceptibility profile of that organism so that therapy can be targeted?

Uncertainty drives use of broad-spectrum antibiotics.

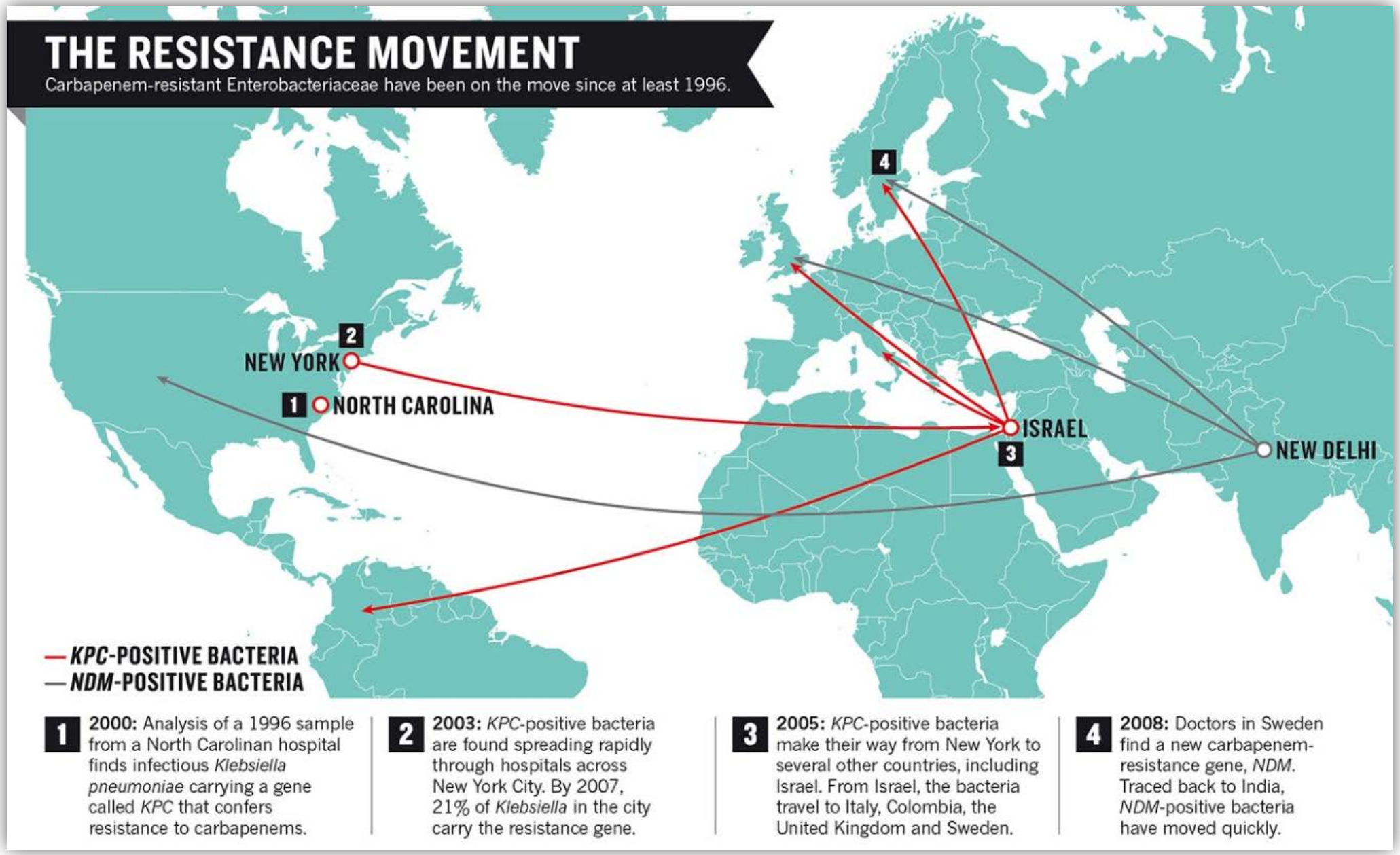
Global rise in antibiotic consumption



https://www.cdc.gov/antibiotic-use/community/about/antibiotic-resistance-faqs.html

Uncertainty drives use of broad-spectrum antibiotics.

Lancet Infect Dis. 2013 Dec;13(12):1057-98. doi: 10.1016/S1473-3099(13)70318-9.



McKenna M. Nature 2013;499:394-6

Mortality from Infectious Diseases

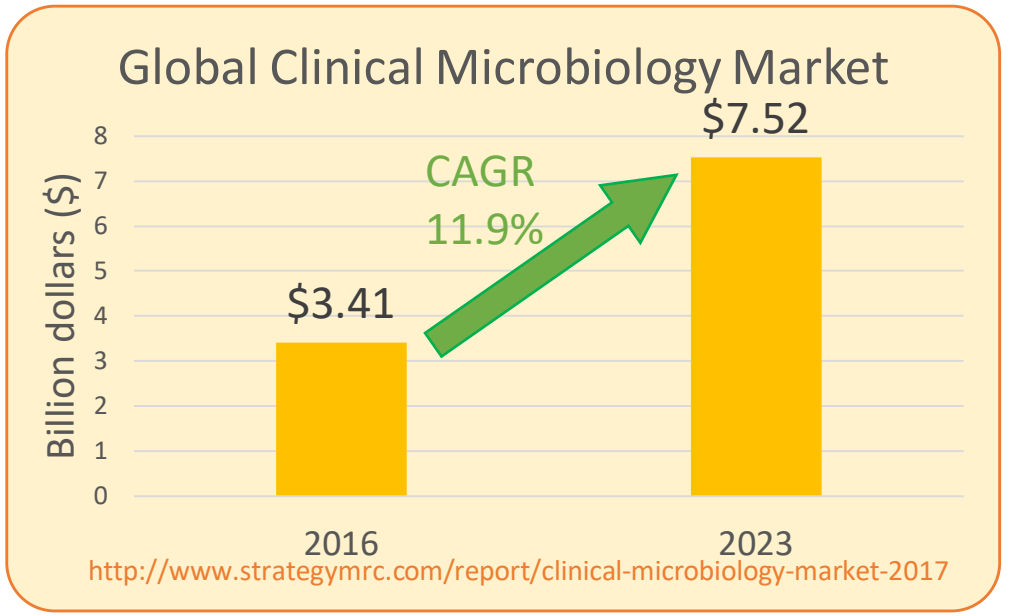
Deaths due to infectious diseases in the United States:

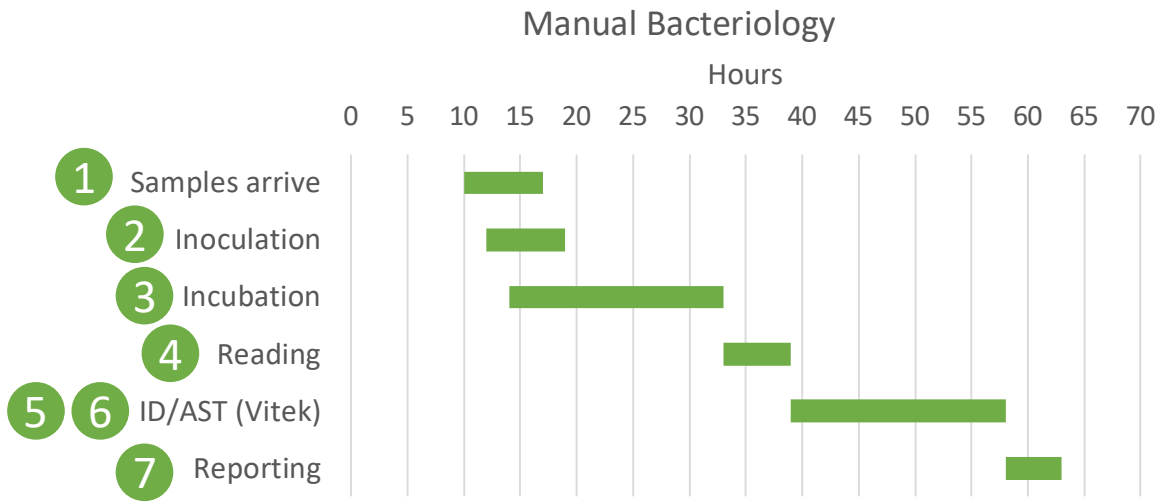
1. Heart disease: 633,842
2. Cancer: 595,930
3. Chronic lower respiratory diseases: 155,041
4. Accidents (unintentional injuries): 146,571
5. Stroke (cerebrovascular diseases): 140,323
6. Alzheimer's disease: 110,561
7. Diabetes: 79,535
8. Influenza and Pneumonia: 57,062
9. Nephritis, nephrotic syndrome and nephrosis: 49,959
10. Intentional self-harm (suicide): 44,19
11. Septicemia: 40,685

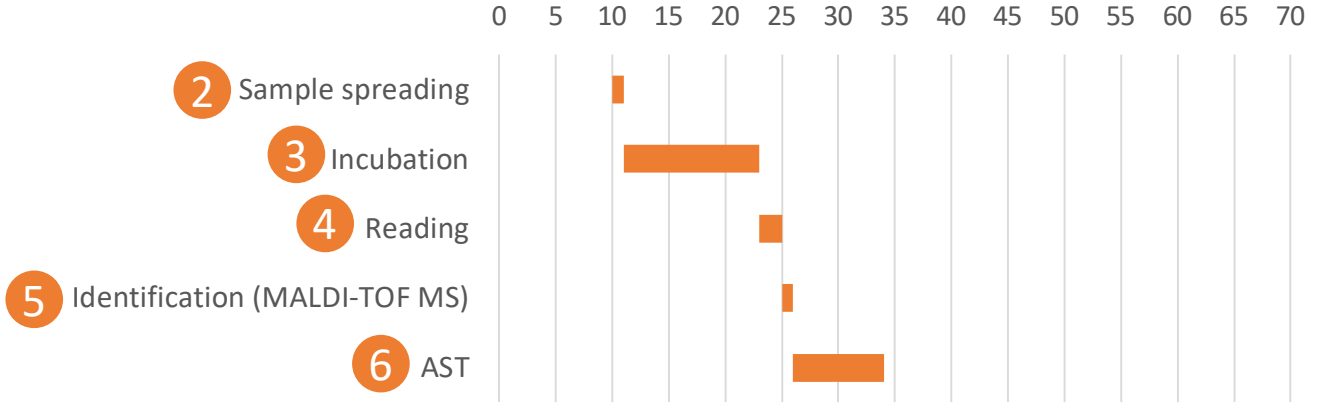
CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™
National Center for Health Statistics

DRIVING INCREASES:

- Aging population
- Drug-resistance microorganisms
- Global warming, spread of tropical disease carriers into new areas

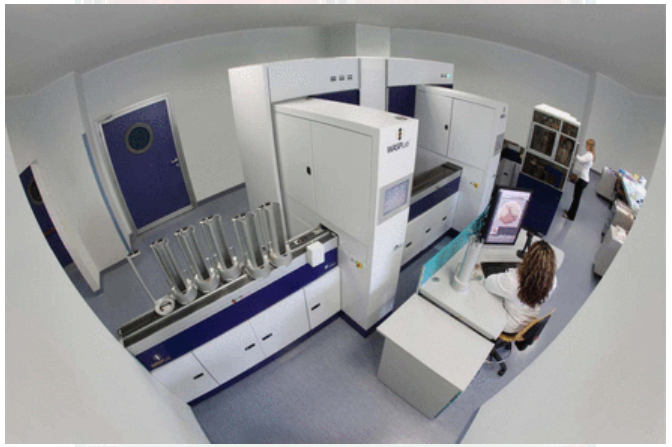






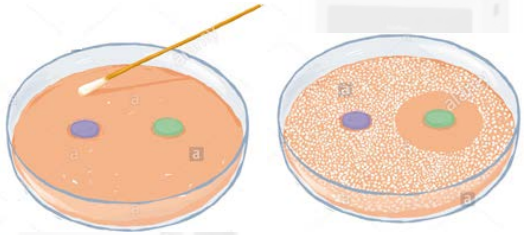
Microbiology LIS **Interfaces**

Role of Microbiologist: Cartoon by Czichos



Microbiology LIS **Interfaces**

2. Programmable plate inoculators/streakers
3. Automated incubators; automated growth and detection systems
    - Ex: Bactec, BacT/ALERT, MGIT, TREK, etc.
4. Automated plate readers



Xpert SA Nasal Complete G3 — Assay 4

Test Result: MRSA POSITIVE; SA POSITIVE

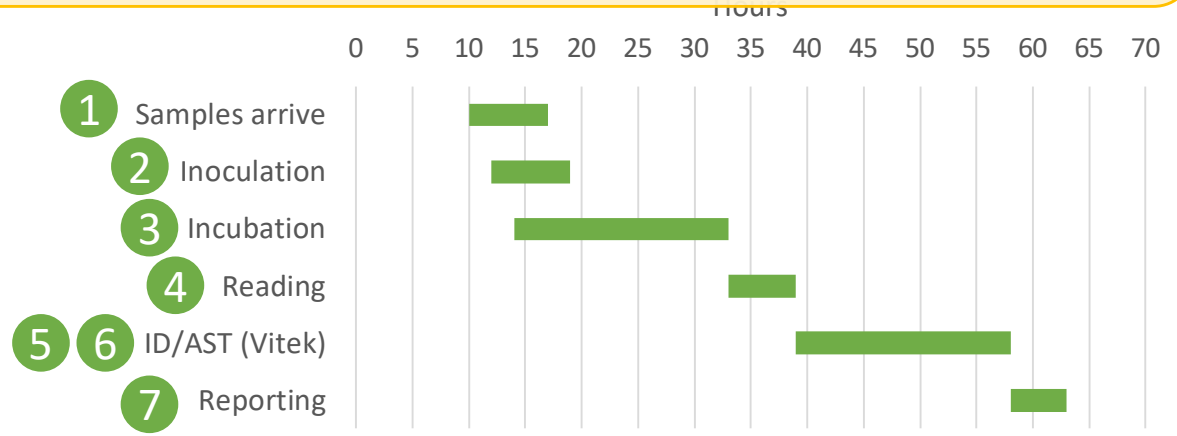
Test and Analyte Result

Analyte Name	Ct	EndPt	Analyte Result	Probe Check Result
SPC	36.9	23.0	NA	PASS
SPA	23.9	428.0	POS	PASS
mec	24.4	349.0	POS	PASS
SCC	25.5	440.0	POS	PASS

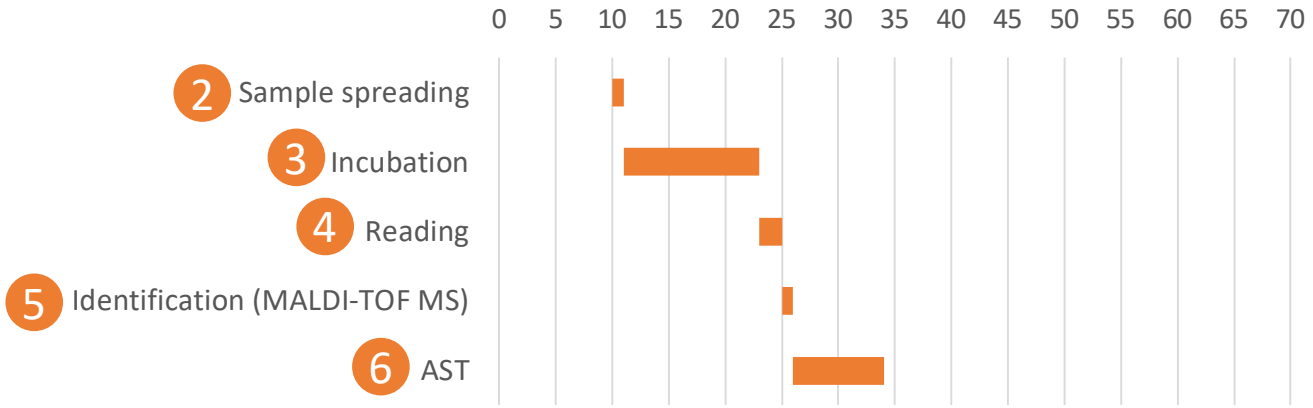
Microbiology LIS Interfaces

- 2 Programmable plate inoculators/streakers
- 3 Automated incubators; automated growth and detection systems
  - Ex: Bactec, BacT/ALERT, MGIT, TREK, etc.
- 4 Automated plate readers
- 5 5 Identification of organisms
  - 5 Biochemical-based microbial identification
  - 5 MALDI-ToF mass spectrometry
  - 5 Genetic markers and sequencing
- 6 6 Susceptibility testing
  - 6 Traditional phenotypic tests
  - 6 Genetic markers

Specimen types, and related preparation and sequences for testing, are varied and difficult to completely automate. Results take time (hours to days).



Automation and New Tech



Microbiology LIS **Best Practices**

- ✓ Intelligent decision support business rules for routine common tasks (efficiency) as well as sentinel events
- ✓ Preliminary versus final status messages.

Microbiology LIS **Best Practices**

Data is relational and needs traceability:

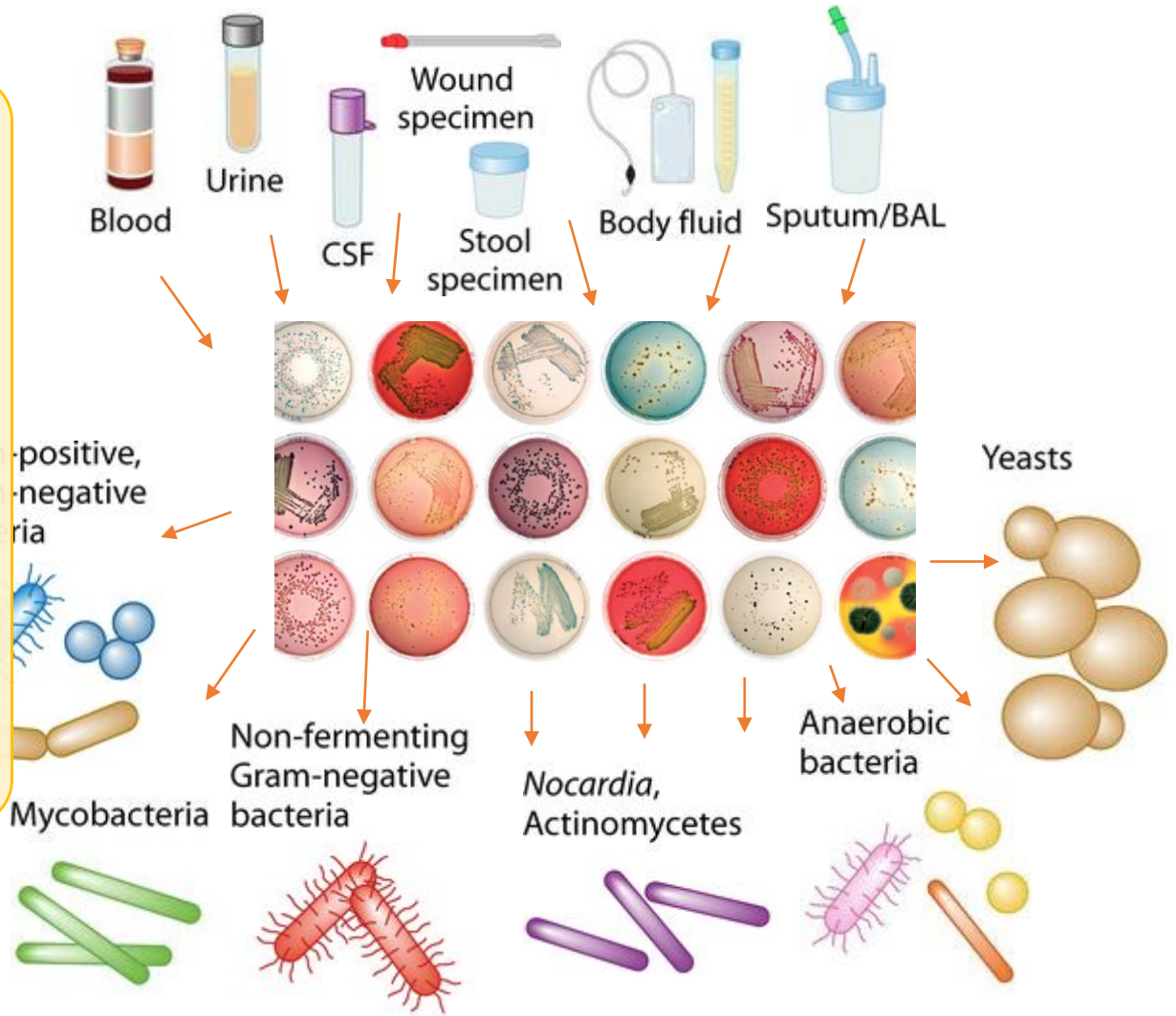
Order (e.g., respiratory culture)

→multiple **specimens** (e.g., induced sputum #1, #2, #3)

→→ multiple **culture** media (e.g., aerobic, anaerobic, fungal)

→→→ multiple **isolates** (e.g., Staph. aureus, H. influenzae)

→→→→ multiple **observations** per isolate (e.g., gram stain, colony count, identification, antibiotic **susceptibility** panels), separated as "preliminary" versus "final"



Generic Microbiology HL7 Result Message		Example of sputum culture
MSH	Message header	
PID	Patient identification	
[PV1]	Patient visit information	
{	--- Order begins	
[ORC]	Order control	
OBR	Observation request	OBR|1| = sputum culture OBX|1| = Microorganism|1| = S. aureus OBX|2| = Colony ct|1| = 10,000-90,000 OBX|3| = Microorganism|2| = Beta-hemolytic Streptococcus OBX|4| = Colony ct|2| = <1,000 OBX|5| = Microorganism|3| = Haemophilus influenzae OBX|6| = Colony ct|3| = 10,000-90,000
[{ NTE }]	Notes and comments	
[OBX]	Observation *OBX-4-observation sub-ID sequential numbering to link observations to isolates*	
[{ NTE }]	Notes and comments	
}	--- Observation end	
}	--- Order end	

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PID	Patient identification	
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}	--- Order end	

```
MSH|^~\&|LabOneApp|LabOne^45D0470381^CLIA|NEDSS^1644^WA-
   DOH||20011001183345||ORU^R01^ORU_R01|113661|P|2.3.1<cr>

PID|||999-3^^^GoodDr^MR||Able^Michael^D^^^^L<cr>

ORC|RE|0889436^GoodDr|ABC012345^LabOne||||||20011001182914|
   L0234^Roberts^Steve^^^^^LabOne^L^^^EI
   ||^Good^Robert^^^^MD^^L<cr>

OBR|1|0889436^GoodDr|ABC012345^LabOne|6460-0^Spt Routine
   Cult^LN|||20011001091234|||||||200110010823|SPT&
   Sputum&HL70070|^Good^Robert^^^^MD^^L||||||20011002072359
   ||MB|P<cr>

OBX|1|CE|11475-1^MICROORGANISM IDENTIFIED:^LN|1| L-
   24801^Staphylococcus aureus^SNM<cr>

OBX|2|CE|564-5^Colony count^LN |1|10,000-90,000<cr>

OBX|3|CE|11475-1^MICROORGANISM IDENTIFIED:^LN|2|L-
   25128^Beta hemolytic Streptococcus A^SNM<cr>

OBX|4|CE|564-5^Colony count^LN |2|<1,000<cr>

OBX|5|CE|11475-1^MICROORGANISM IDENTIFIED:^LN|3|L-13401 ^
   Haemophilus influenzae^SNM<cr>

OBX|6|CE|564-5^Colony count^LN|3|10,000-90,000<cr>

OBR|2||ABC012346^LabOne|29576-6^Bacterial Susc Panel
   Islt^LN|||||||||||||||||11475-1&MICROORGANISM
   IDENTIFIED:&LN^1^Staphylococcus
   aureus|||0889436&GoodDr^ABC012345&LabOne<cr>

OBX|1|CE|28-1^Ampicillin MIC^LN|1|32|µg/mL||R<cr>

OBX|2|CE|32-3^Amoxicillin+Clav MIC^LN |1|2|µg/mL||S<cr>

OBX|3|CE|76-0^Cefazolin MIC^LN |1|8|µg/mL||S<cr>

OBR|3||ABC012347^LabOne|29576-6^Bacterial Susc Panel
   Islt^LN|||||||||||||||||||||11475-1&MICROORGANISM
   IDENTIFIED:&LN^3^Haemophilus
   influenzae|||0889436&GoodDr^ABC012345&LabOne<cr>

OBX|1|CE|29-9^Ampicillin KB^LN|3|||S<cr>

OBX|2|CE|21-6^Amoxicillin+Clav KB^LN|3|||S<cr>

OBX|3|CE|77-8^Cefazolin KB^LN|3|||S<cr>
```

Unlike chemistry tests (close-ended, from 1 order to 1 result), microbiology data requires flexibility to accommodate many **open-ended parent-child relationships** (1 to many).

Specimen types, and related preparation and sequences for testing, are varied and difficult to completely automate. Results take time (hours to days)

Data is relational and n

Order (e.g., respiratory cult
→multiple **specimens** (e.g.,
→→ multiple **culture** medi
→→→ multiple **isolates** (e
→→→→ multiple **observa
identification, antibiotic sus
"final"

URINE CULTURE Order:

Status: Final result Visible to patient: No (Not Released) Next appt: None Dx:

Notes Recorded by

	4/11/18 12:00 PM	Flag
FINAL RESULT	(A)	A
	>100,000 cfu/ml Escherichia coli Organism is a possible multi-drug resistant bacteria. In serious infections cefepime may not be as effective as other agents. Please consult Infectious Diseases regarding its use. <10,000 CFU/mL of Insignificant Growth	
ORGANISM	Escherichia coli	A

Susceptibility

	Escherichia coli ANTIMICROBIAL SUSCEPTIBILITY	
Ampicillin	>=32	RESISTANT
Cefazolin urine	>=64	RESISTANT
Cefepime	4	INTERMEDIATE
Ceftazidime	16	RESISTANT
Ceftriaxone	>=64	RESISTANT
Ciprofloxacin	>=4	RESISTANT
Ertapenem	<=0.5	SUSCEPTIBLE
Gentamicin	<=1	SUSCEPTIBLE
Meropenem	<=0.25	SUSCEPTIBLE
Nitrofurantoin	<=16	SUSCEPTIBLE
Piperacillin+Tazobactam	<=4	SUSCEPTIBLE
Trimethoprim+Sulfamethoxazole	<=20	SUSCEPTIBLE

Narrative

Specimen Collected: 04/11/18 12:00 PM Last Resulted: 04/14/18 2:22 AM

Lab Flowsheet Order Details View Encounter Lab and Collection Details Routing Result History

Wyoming Department of Health

ctices

usiness rules for routine well as sentinel events

s messages.

, OBX-4-observation sub-ID observations to isolates

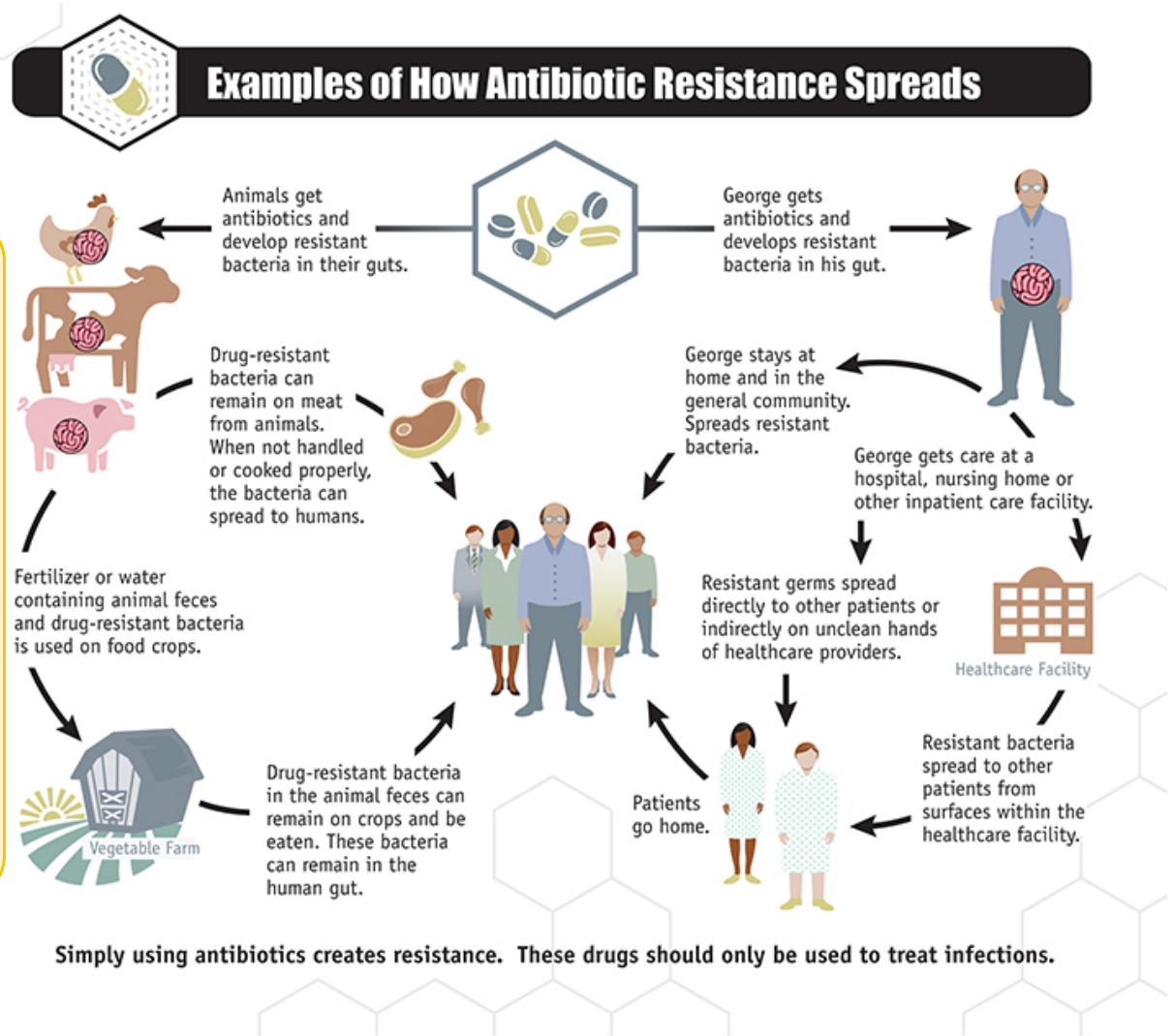
g sent to EHR (if it can

Outbreaks: Hospitals, Communities

Data needs aggregation, mandatory reports to public health authorities

- from multiple specimens to one patient (e.g., same pathogen isolated from multiple sources)
- from multiple antibiotic susceptibility patterns from the same and/or different organisms to the appropriate treatment plan
- from multiple patients to the same hospital floor or unit
- … to the same institution/city/state (e.g., antibiogram)

https://www.cdc.gov



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automate. Results take tim

Data is relational:

Order (e.g., respiratory culture
→multiple **specimens** (e.g., inc
→→ multiple **culture** media (e
→→→ multiple **isolates** (e.g.,
→→→→ multiple **observation**
identification, antibiotic suscep
"final"

Data needs aggregation, r
health authorities

- from multiple specimens to c
  from multiple sources)
- from multiple antibiotic susc
  different organisms to the ap
- from multiple patients to the
- … to the same institution/city

AEROBIC BACTERIAL CULTURE, STERILE SITE Order:

Status: **Final result** Visible to patient: **No (Not Released)** Next appt: **05/18/2018 at 10:20 AM in Internal Medicine**

Newer results are available. Click to view them now.

	8/12/17 10:46 AM	Flag
FINAL RESULT	! (A)	A

```
Moderate growth of: Enterobacter cloacae Complex

Moderate growth of: Klebsiella oxytoca
Organism is a possible multi-drug resistant bacteria.
In serious infections cefepime may not be as
effective as other agents. Please consult
Infectious Diseases regarding its use.

Moderate growth of: Enterococcus faecalis
```

ORGANISM	Enterobacter cloacae complex !	A
ORGANISM	Klebsiella oxytoca !	A
ORGANISM	Enterococcus faecalis !	A

Susceptibility

	Enterobacter cloacae complex ANTIMICROBIAL SUSCEPTIBILITY	Klebsiella oxytoca ANTIMICROBIAL SUSCEPTIBILITY
Ampicillin	>=32 RESISTANT	>=32 RESISTANT
Ampicillin+Sulbactam		>=32 RESISTANT
Cefazolin	>=64 RESISTANT	>=64 RESISTANT
Cefepime		2 SUSCEPTIBLE
Ceftazidime		16 RESISTANT
Ceftriaxone	<=1 SUSCEPTIBLE	>=64 RESISTANT
Ciprofloxacin	<=0.25 SUSCEPTIBLE	<=0.25 SUSCEPTIBLE
Ertapenem		<=0.5 SUSCEPTIBLE
Gentamicin	<=1 SUSCEPTIBLE	<=1 SUSCEPTIBLE
Meropenem		<=0.25 SUSCEPTIBLE
Piperacillin+Tazobactam	<=4 SUSCEPTIBLE	8 SUSCEPTIBLE
Trimethoprim+Sulfamethoxazole	<=20 SUSCEPTIBLE	>=320 RESISTANT

Susceptibility

	Enterococcus faecalis ANTIMICROBIAL SUSCEPTIBILITY
Ampicillin	<=2 SUSCEPTIBLE
Gentamicin Synergy	SUSCEPTIBLE [1]
Streptomycin Synergy	SUSCEPTIBLE [1]
Vancomycin	1 SUSCEPTIBLE

Practices

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as well as sentinel events

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eing sent to EHR (if it can
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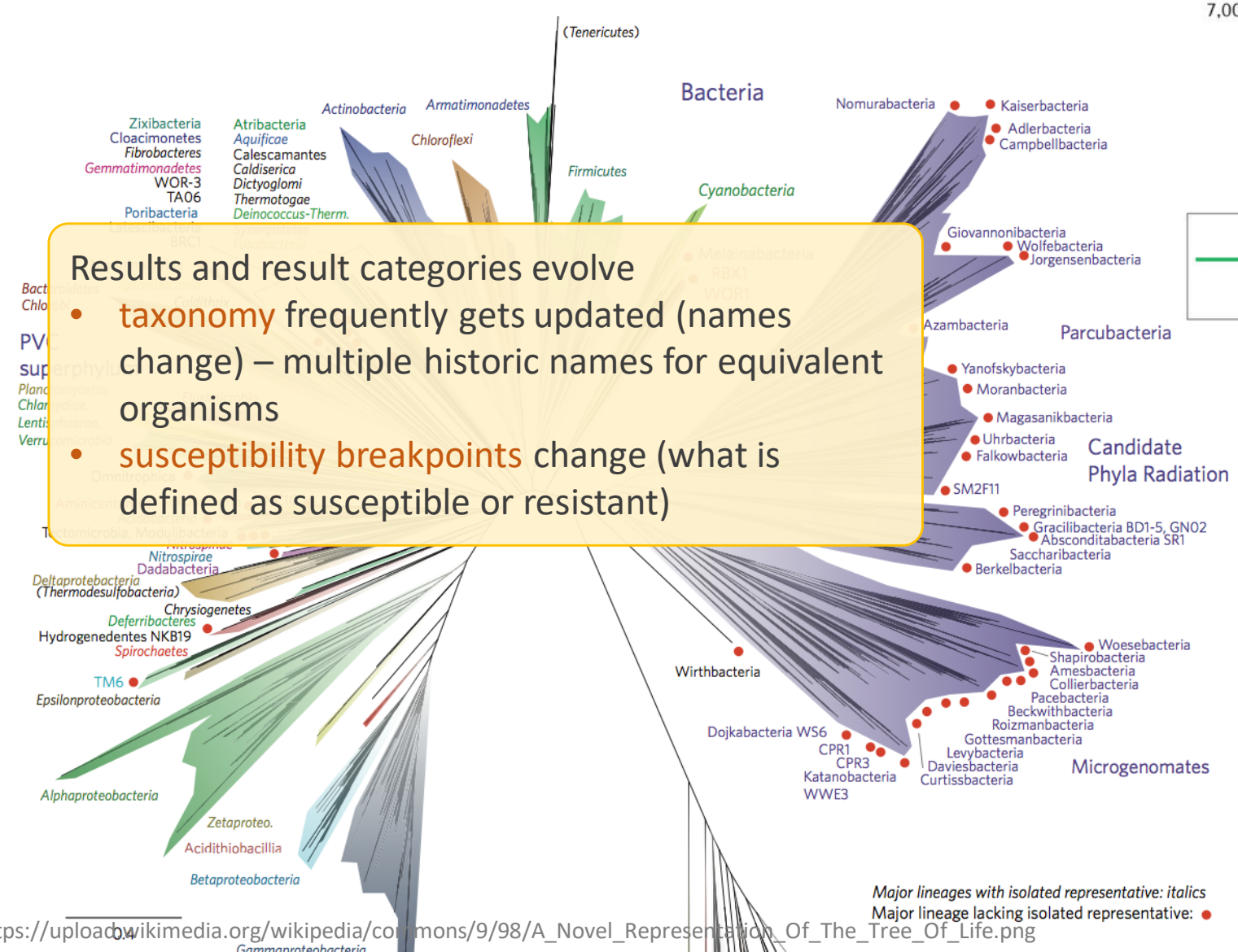
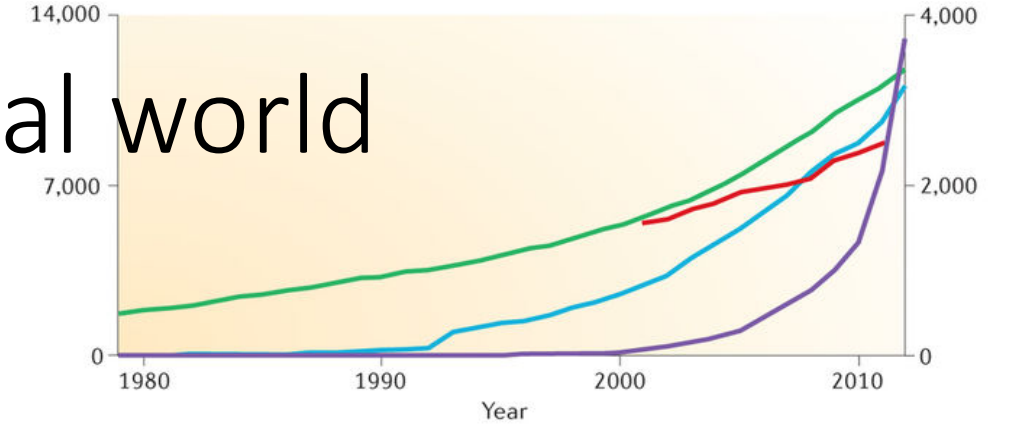
New species, larger microbial world





Results and result categories evolve

- taxonomy frequently gets updated (names change) – multiple historic names for equivalent organisms
- susceptibility breakpoints change (what is defined as susceptible or resistant)

https://upload.wikimedia.org/wikipedia/commons/9/98/A_Novel_Representation_Of_The_Tree_Of_Life.png

Specimen types, and related preparation and sequences for testing, are varied and difficult to completely automate. Results take time (hours to days).

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- from multiple specimens to one patient (e.g., same pathogen isolated from multiple sources)
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- from multiple patients to the same hospital floor or unit
- … to the same institution/city/state (e.g., antibiogram)

Results and result categories evolve

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Microbiology LIS **Best Practices**

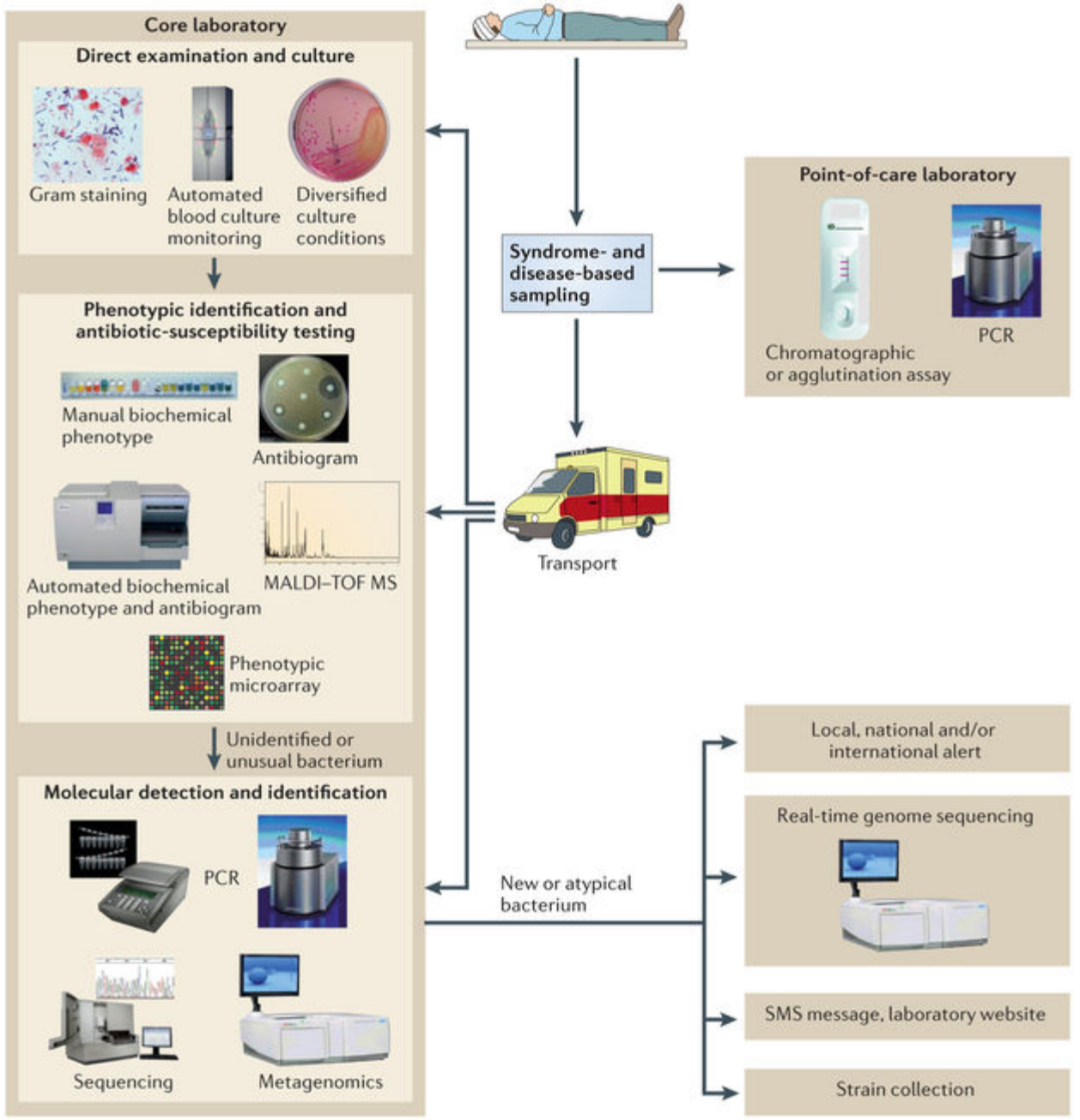
- ✓ Intelligent decision support business rules for routine common tasks (efficiency) as well as sentinel events
- ✓ Preliminary versus final status messages.
- ✓ HL7 2.5.1 OBR/OBX structure, OBX-4-observation sub-ID sequential numbering to link observations to isolates
- ✓ Support structured data being sent to EHR (if it can receive it) versus "text blob"
- ✓ Support viewing related reports
- ✓ Required reporting to public health
- ✓ Update names frequently and connect historic to current names, manage changing interpretation criteria
- ✓ Use of standard nomenclature with LOINC, SNOMED

Faster, smarter

Provider questions for clinical microbiology lab:

1. Is my patient's illness caused by a microbe?
2. If yes, what is it?
3. What is the antibiotic susceptibility profile of that organism so that therapy can be targeted?

Uncertainty drives use of broad-spectrum antibiotics.



npr set station news arts & life music programs shop

shots HEALTH NEWS FROM NPR

PUBLIC HEALTH

Federal Efforts To Control Rare And Deadly Bacteria Working

3:53

+ QUEUE

DOWNLOAD

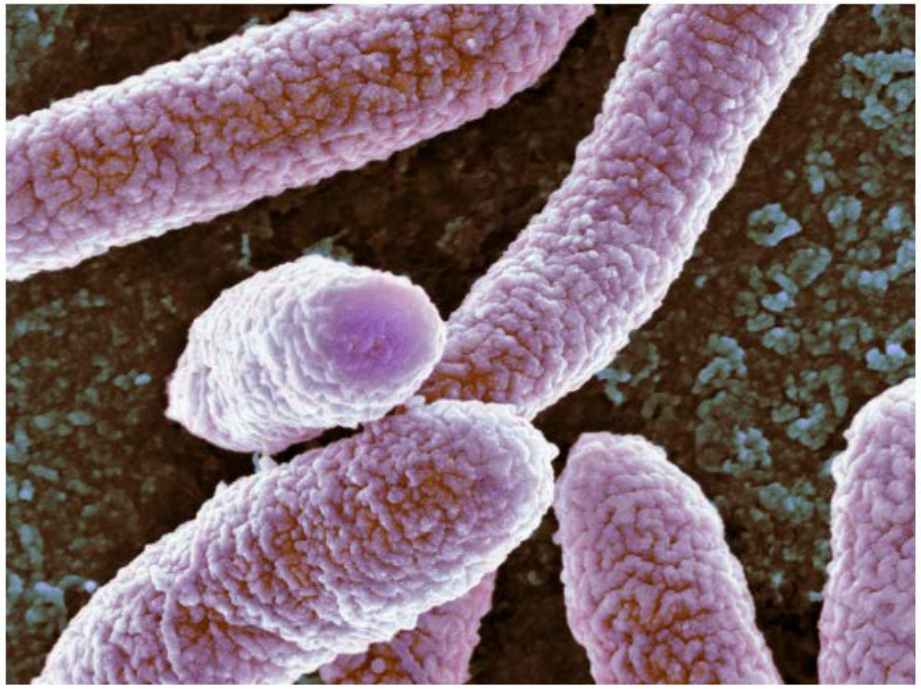
EMBED

TRANSCRIPT

April 3, 2018 · 3:29 PM ET

Heard on All Things Considered

RICHARD HARRIS



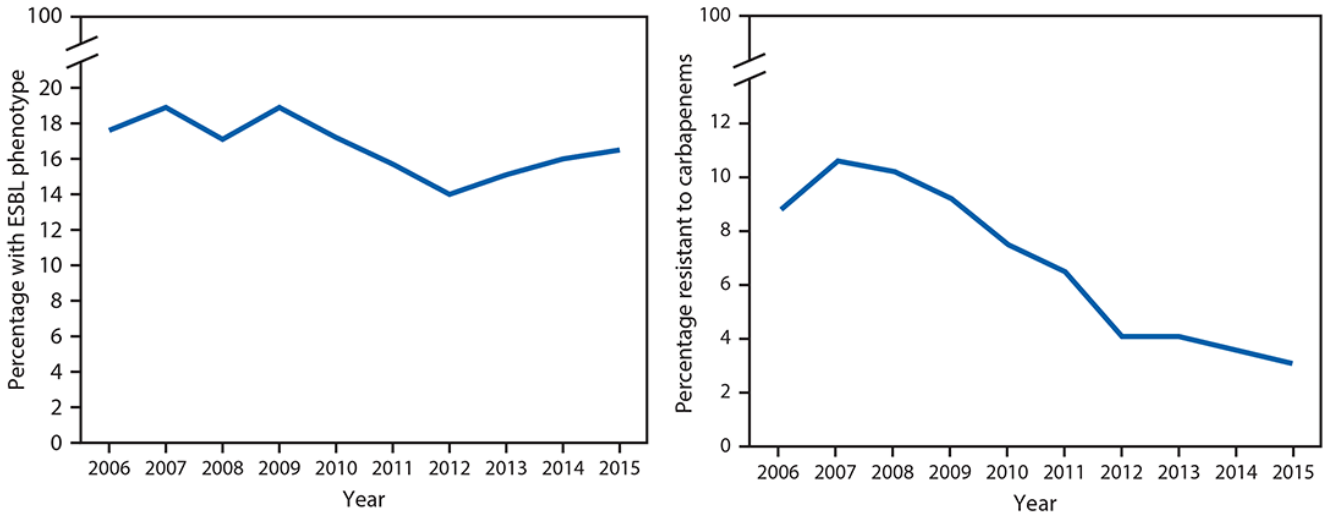
The CDC is trying to stop E. coli and other bacteria that have become resistant to antibiotics because they can cause a deadly infection.

Science Photo Library/Getty Images/Science Photo Libra

Testing… included **carbapenemase production testing** and **molecular detection of genes** encoding for the five carbapenemases of primary public health concern… laboratories were asked to report positive findings to local public health authorities and CDC **within 1 day**…

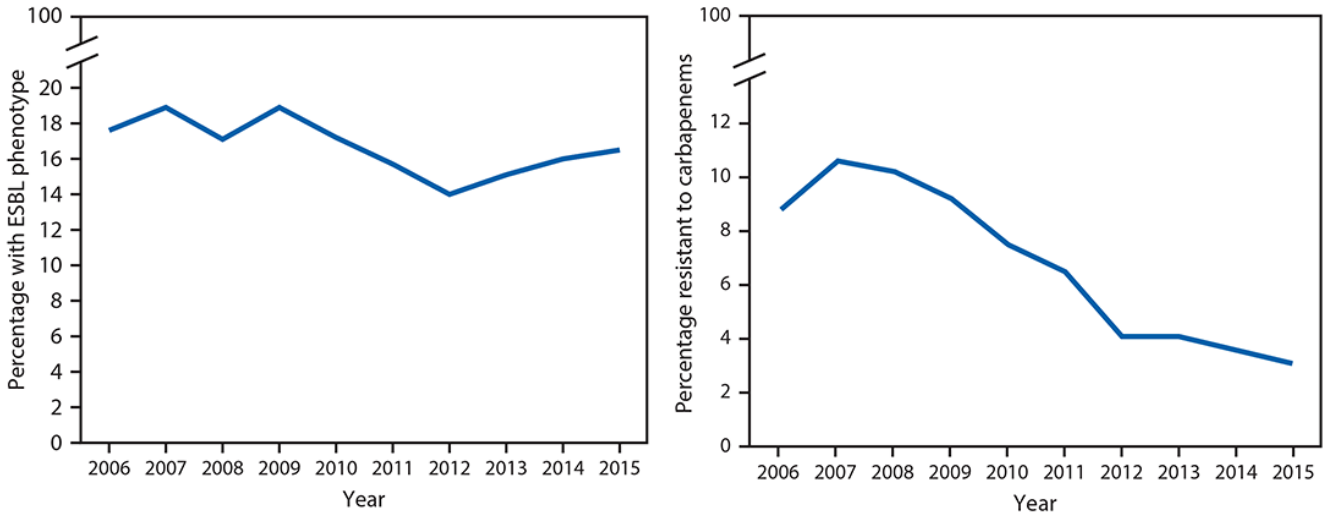
For each carbapenemase-producing isolate detected… state health department staff members contact the health care facility to **review infection control measures** and consider performing **on-site infection control assessments**. If indicated, **contacts of the index patient are screened** to detect transmission... Response activities continue until transmission is **controlled**.

• *The percentage of ESBL phenotype Enterobacteriaceae decreased by 2% per year; by comparison, the CRE percentage decreased by 15% per year.*

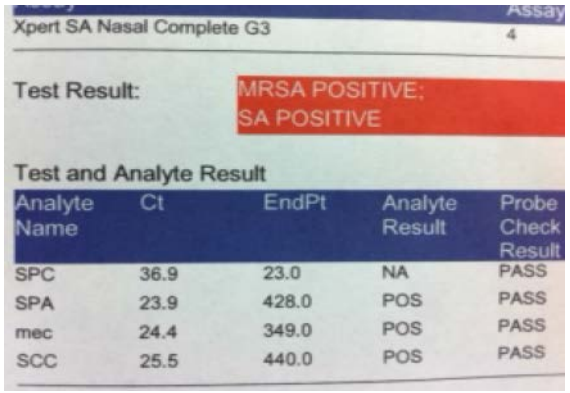


- *The proportion of Enterobacteriaceae infections that were CRE remained lower and decreased more over time than the proportion that were ESBL phenotype. This difference might be explained by the **more directed control efforts implemented** to slow transmission of CRE than those applied for ESBL-producing strains.*

- *These data suggest that an **early aggressive response**, as outlined in CRE-specific infection prevention recommendations released beginning in 2009, can **slow emergence and even decrease the occurrence of infections** from resistant pathogens.*



Faster, smarter



Removing patients from unnecessary contact precautions with single negative PCR compared to 3 consecutively negative MRSA cultures from nasal swabs

Strategy	Passive cultures	Active surveillance	PCR screening
Discontinuation rates of contact precautions	6.6%	26.2%	63.8%
Fewer contact precaution days	104	418	1,841
Cost savings	$86,950	$349,472	$1,539,180

CID 2013 Jul;57(2):176-84

Faster, smarter

Provider questions for clinical microbiology lab:

1. Is my patient's illness caused by a microbe?
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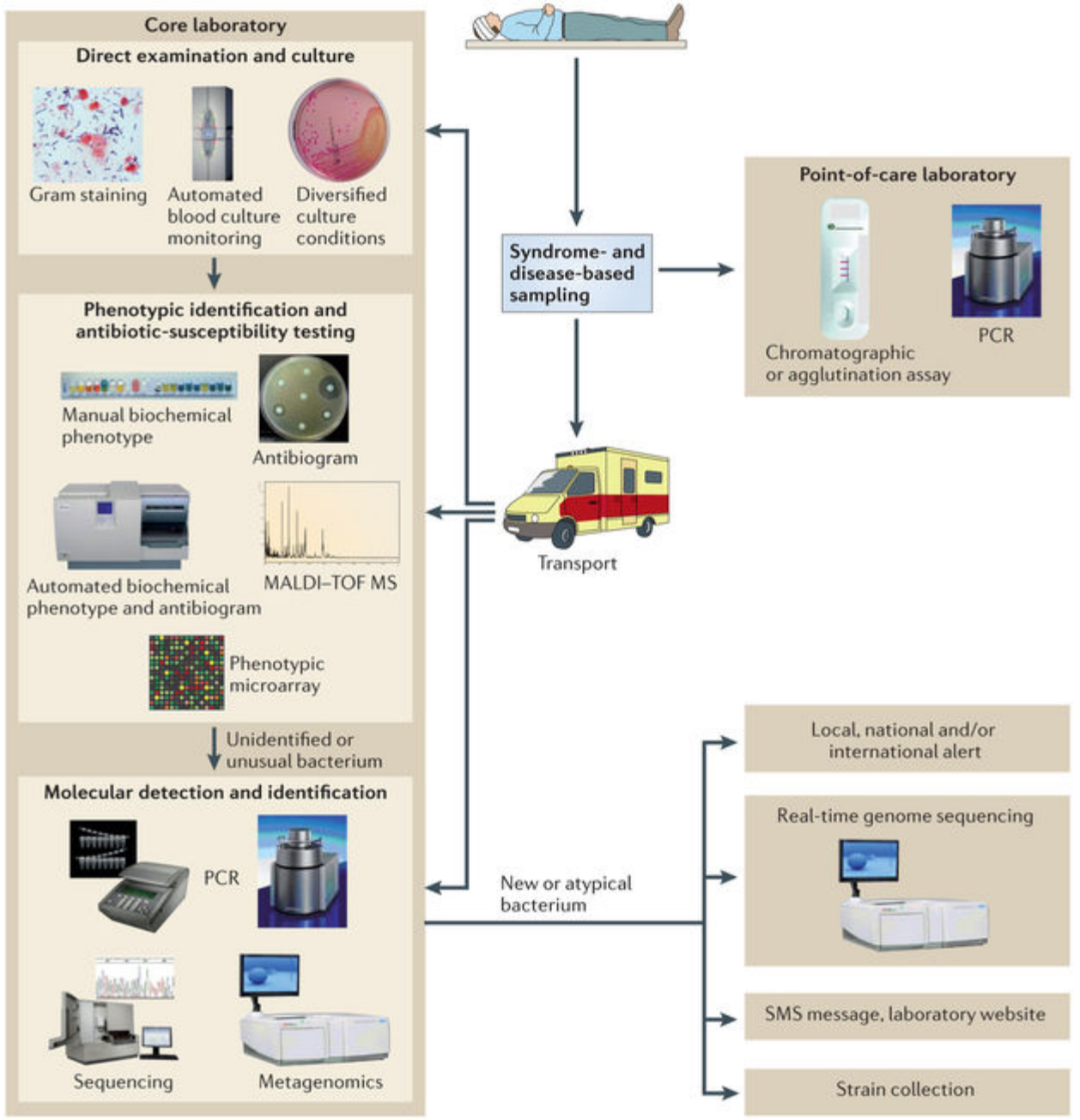
We have actionable data. We need to develop smart message interfaces from the LIS to the pharmacy… From the LIS to ADT for bed management…



Faster, smarter

Provider questions for clinical microbiology lab:

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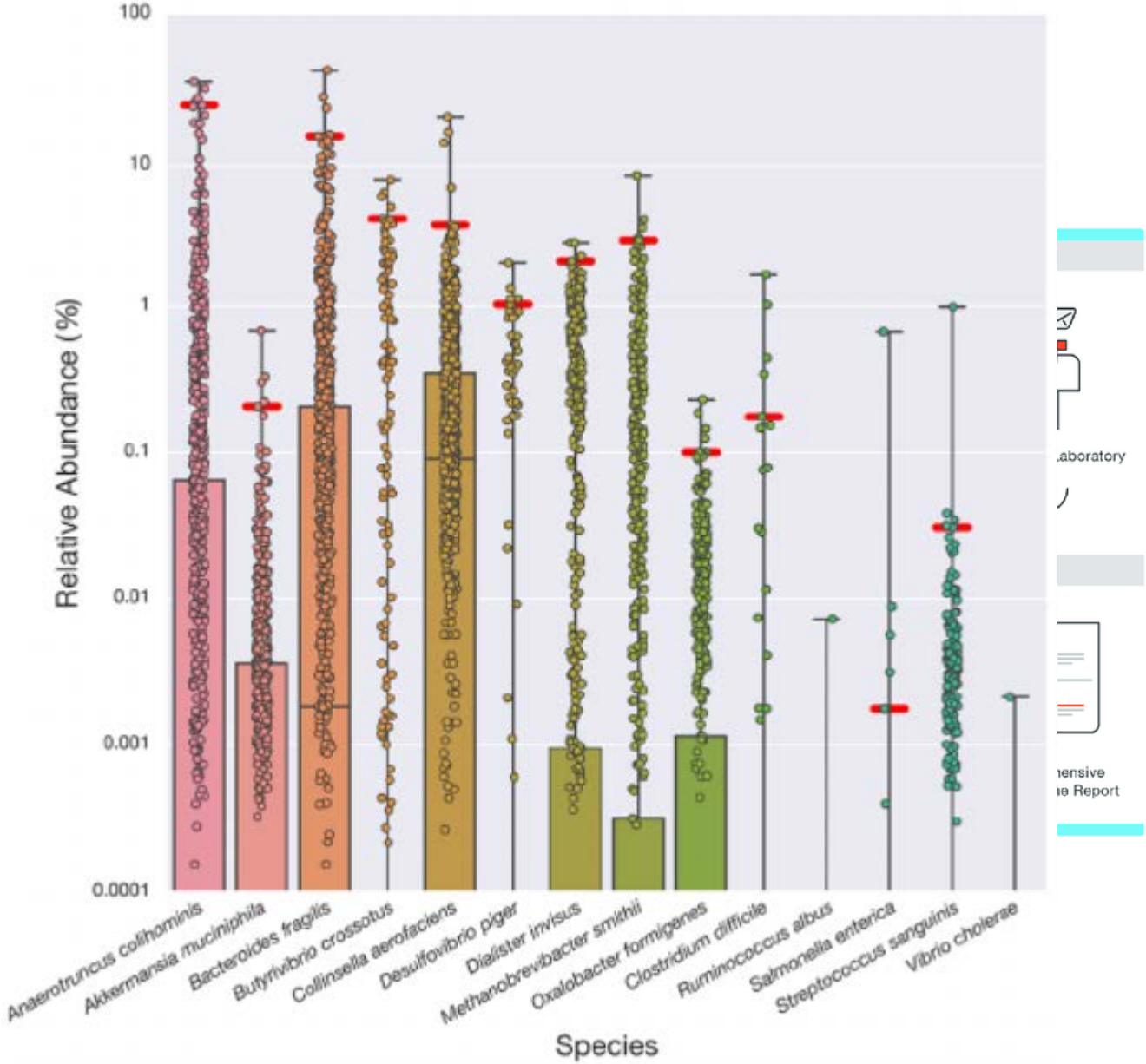
3. What is the antibiotic susceptibility profile of that organism so that therapy can be targeted?

Is it more important to identify organisms or identify resistance quickly?

How to clarify colonization from infection? (Qty?)

How to ingest and report microbiome data? Which are the "good" versus "bad"? Is it important to report both?

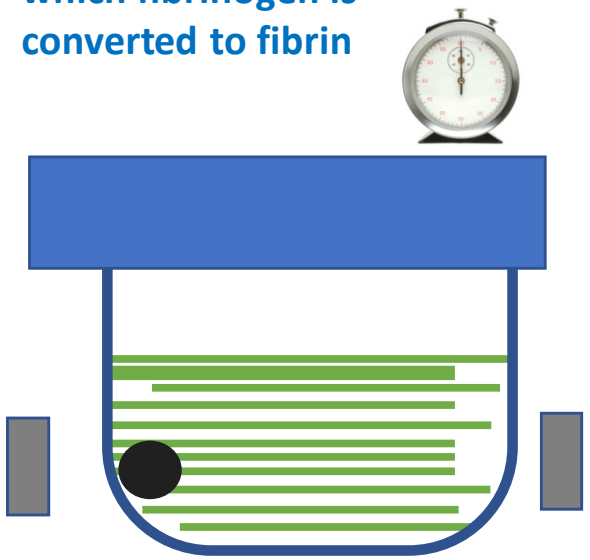


PLoS One. 2017 May 3;12(5):e0176555

Coagulation LIS

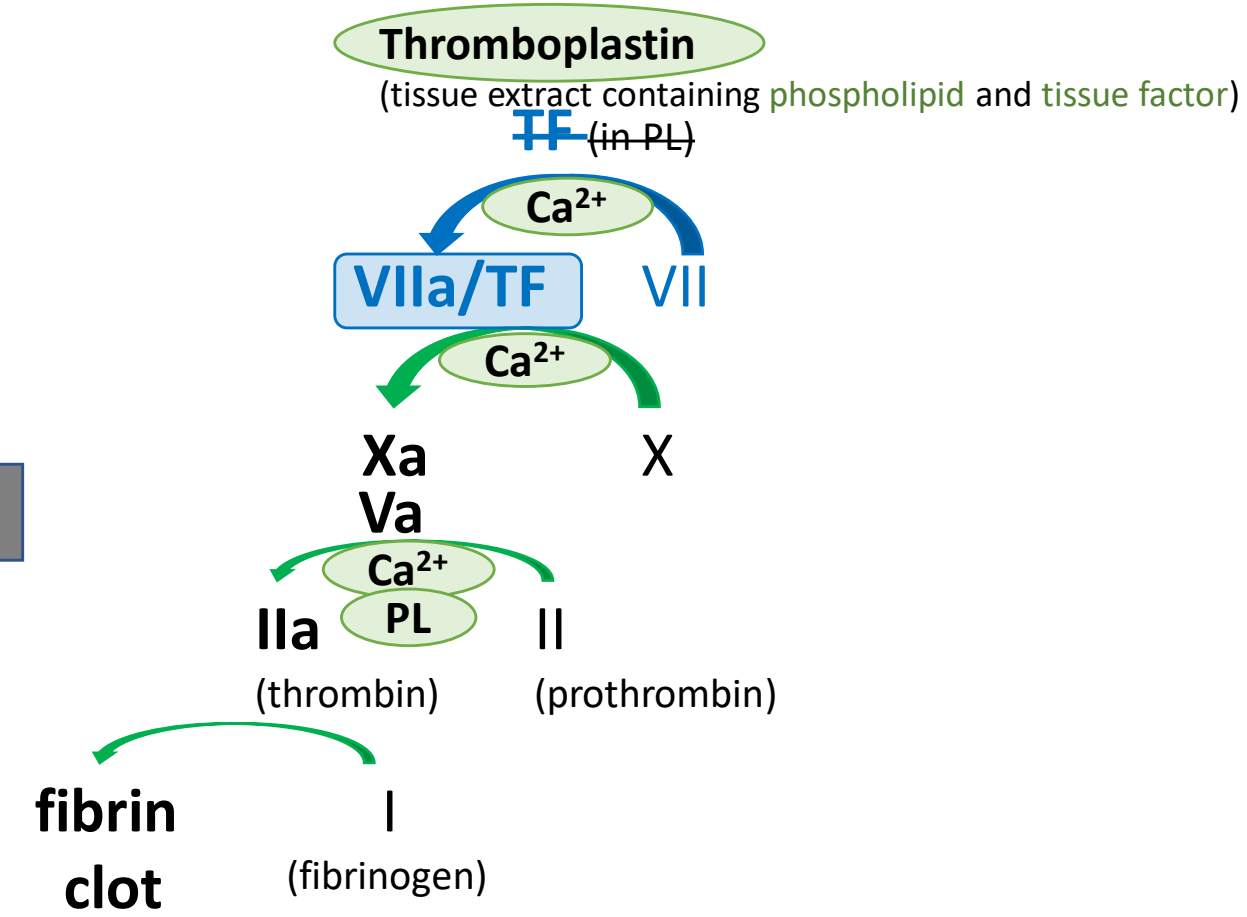
Prothrombin Time

Measures time of fibrin clot formation, beginning with factor VII activation, through the final step in which fibrinogen is converted to fibrin

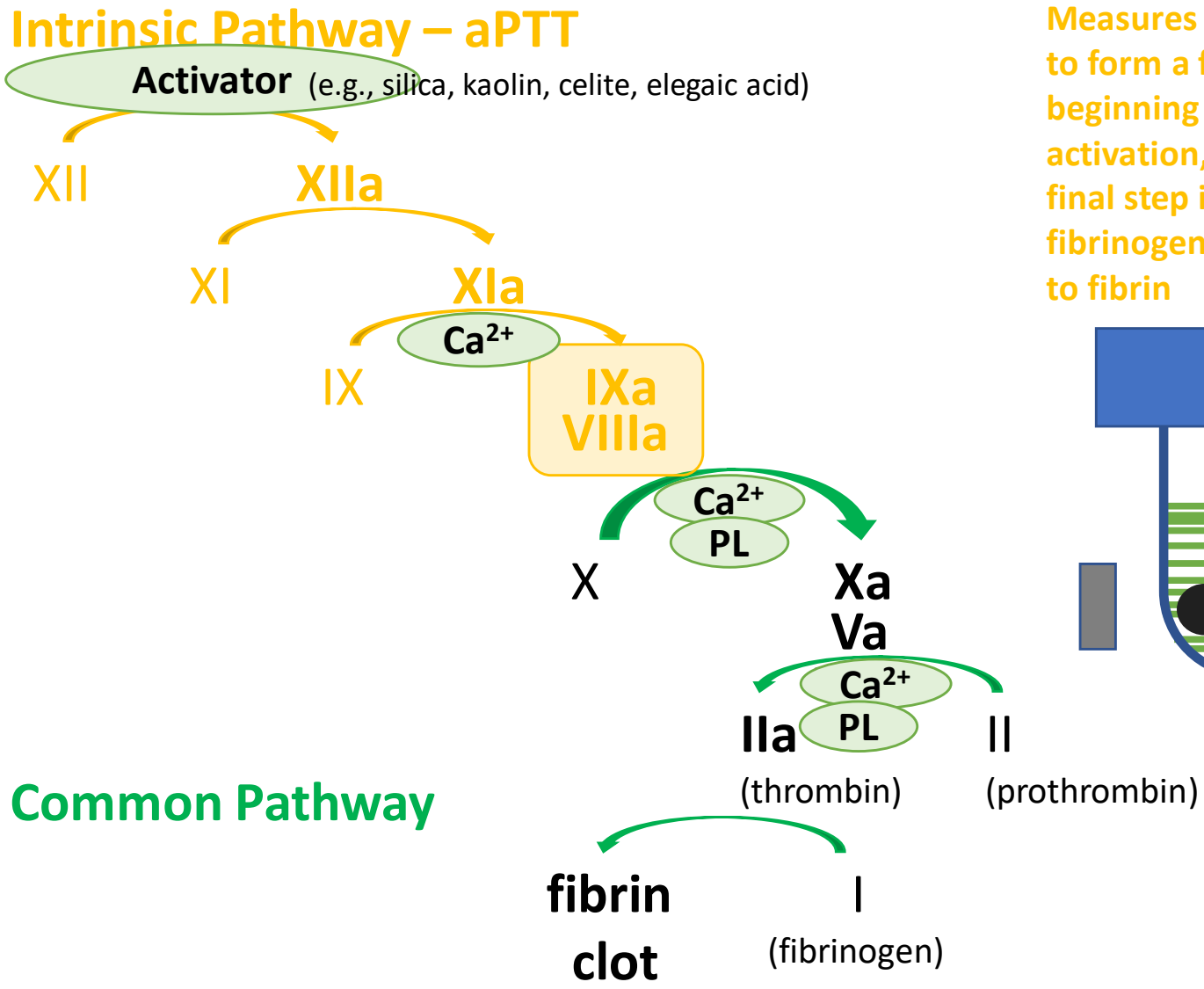


Common Pathway

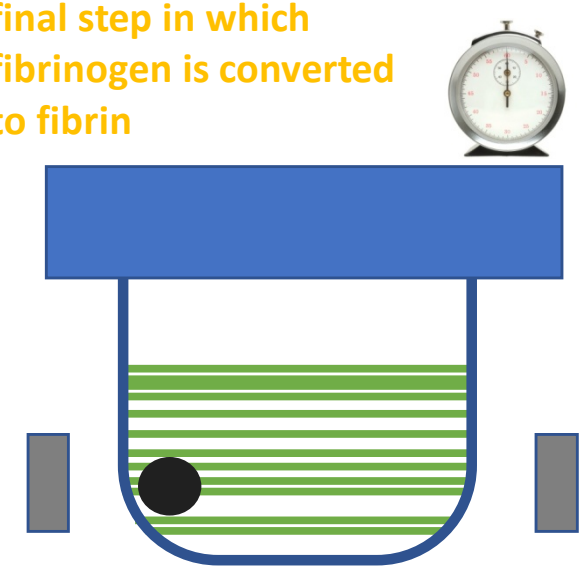
Extrinsic Pathway – PT



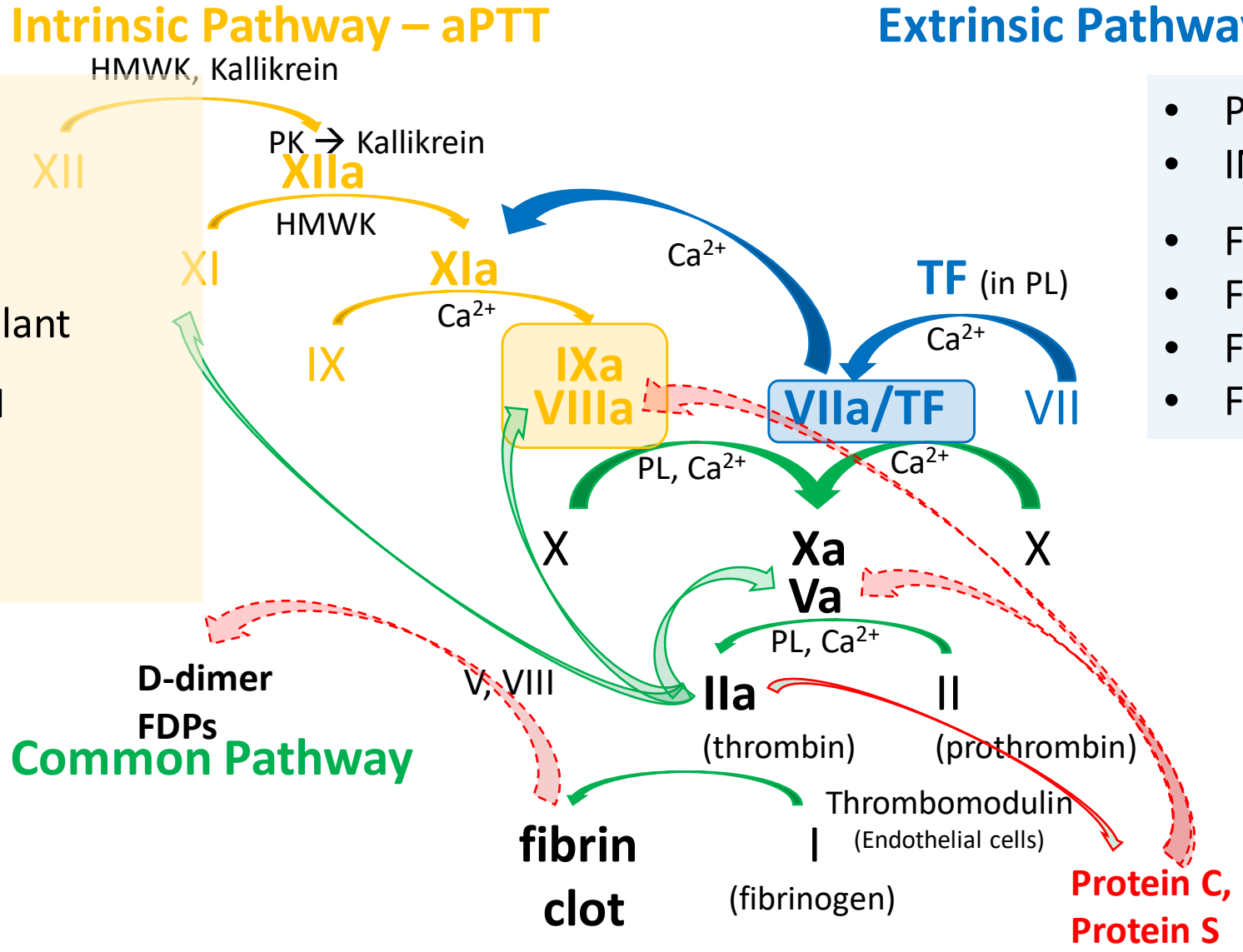
Activated Partial Thromboplastin Time



Measures time it takes to form a fibrin clot, beginning with factor XII activation, through the final step in which fibrinogen is converted to fibrin



Clot-based tests



- aPTT
- Protein C
- Protein S
- Lupus anticoagulant

- Factor VIII
- Factor IX
- Factor XI
- Factor XII

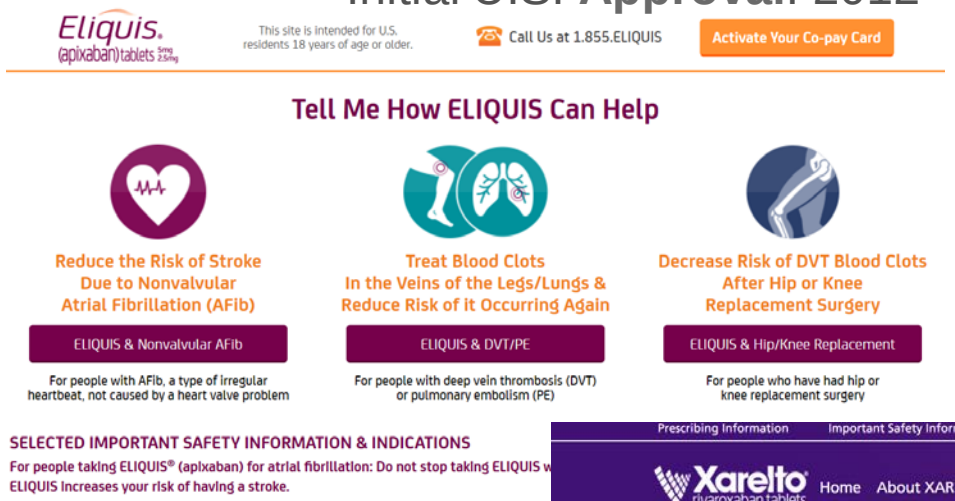
- PT
- INR

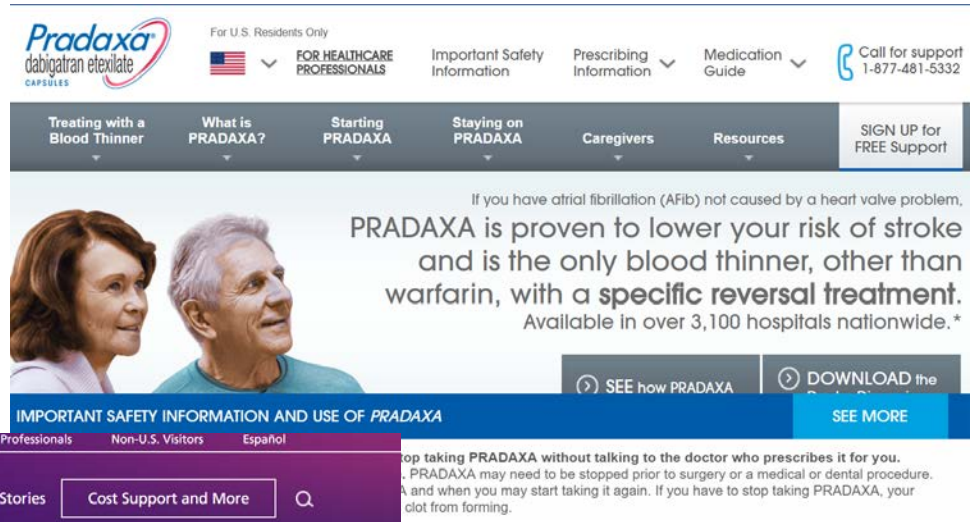
- Factor II
- Factor V
- Factor VII
- Factor X

- Thrombin time

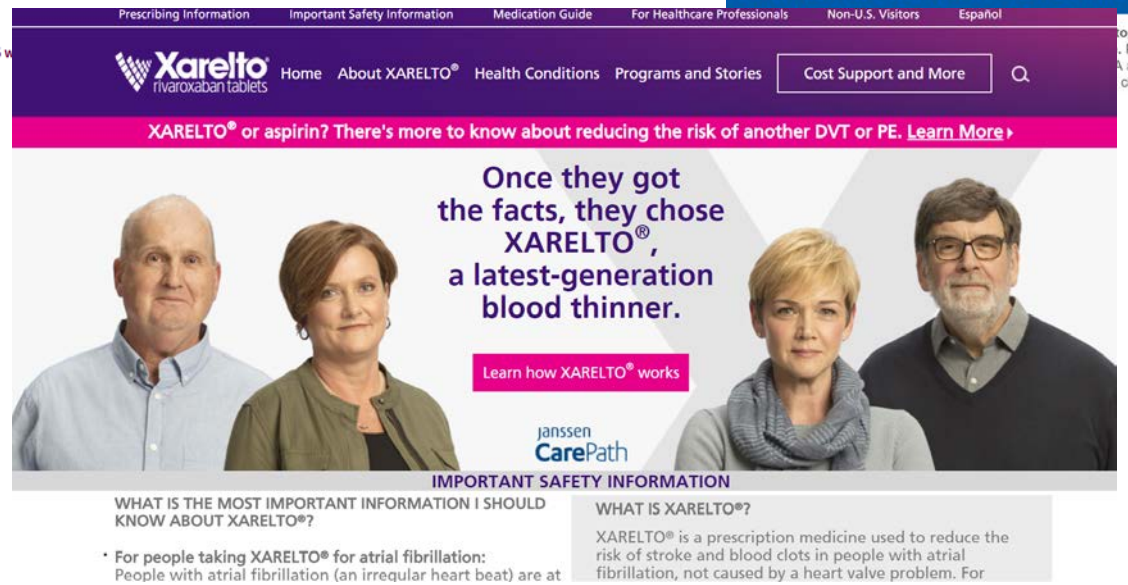
New oral anticoagulants

Initial U.S. **Approval**: 2012



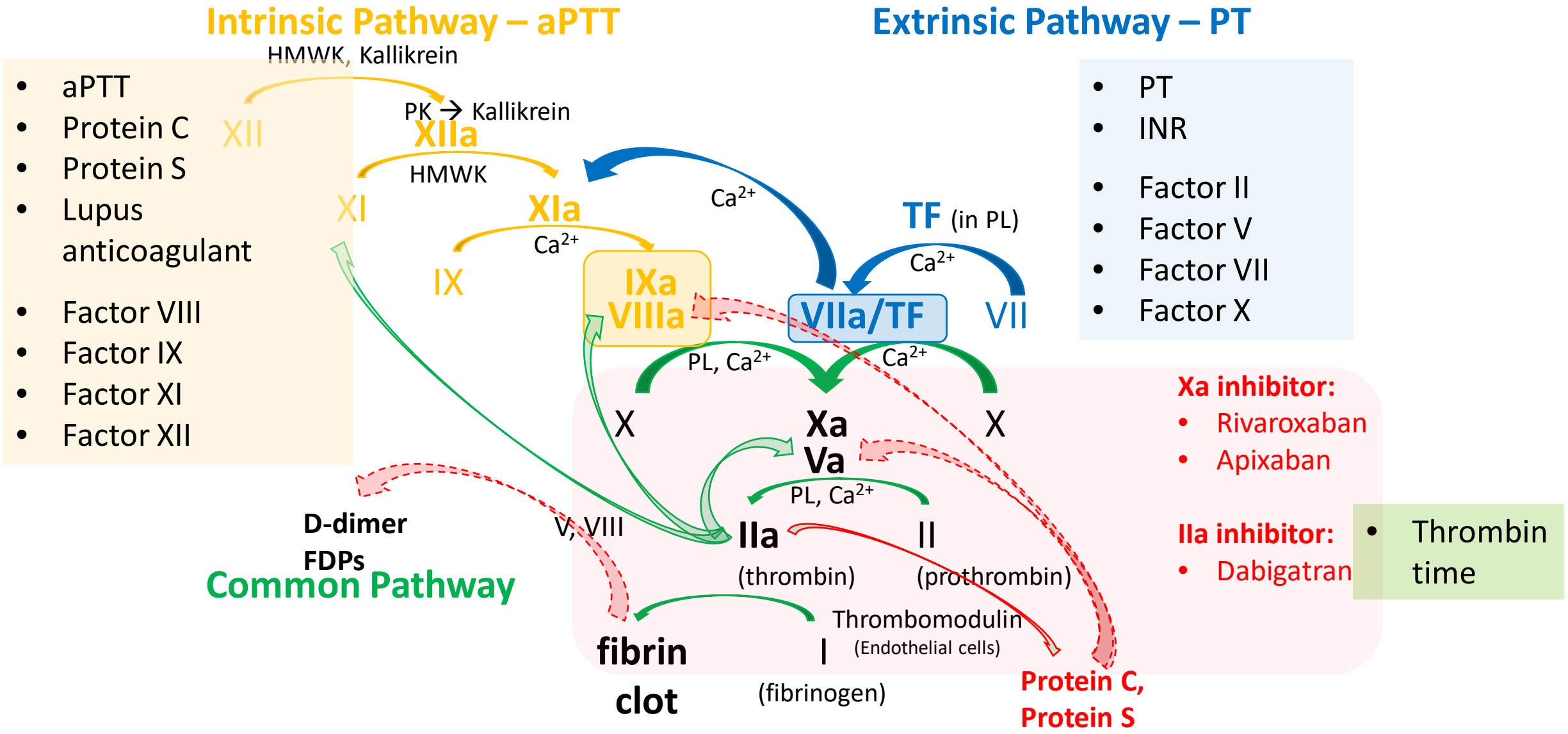


Initial U.S. **Approval**: 2014

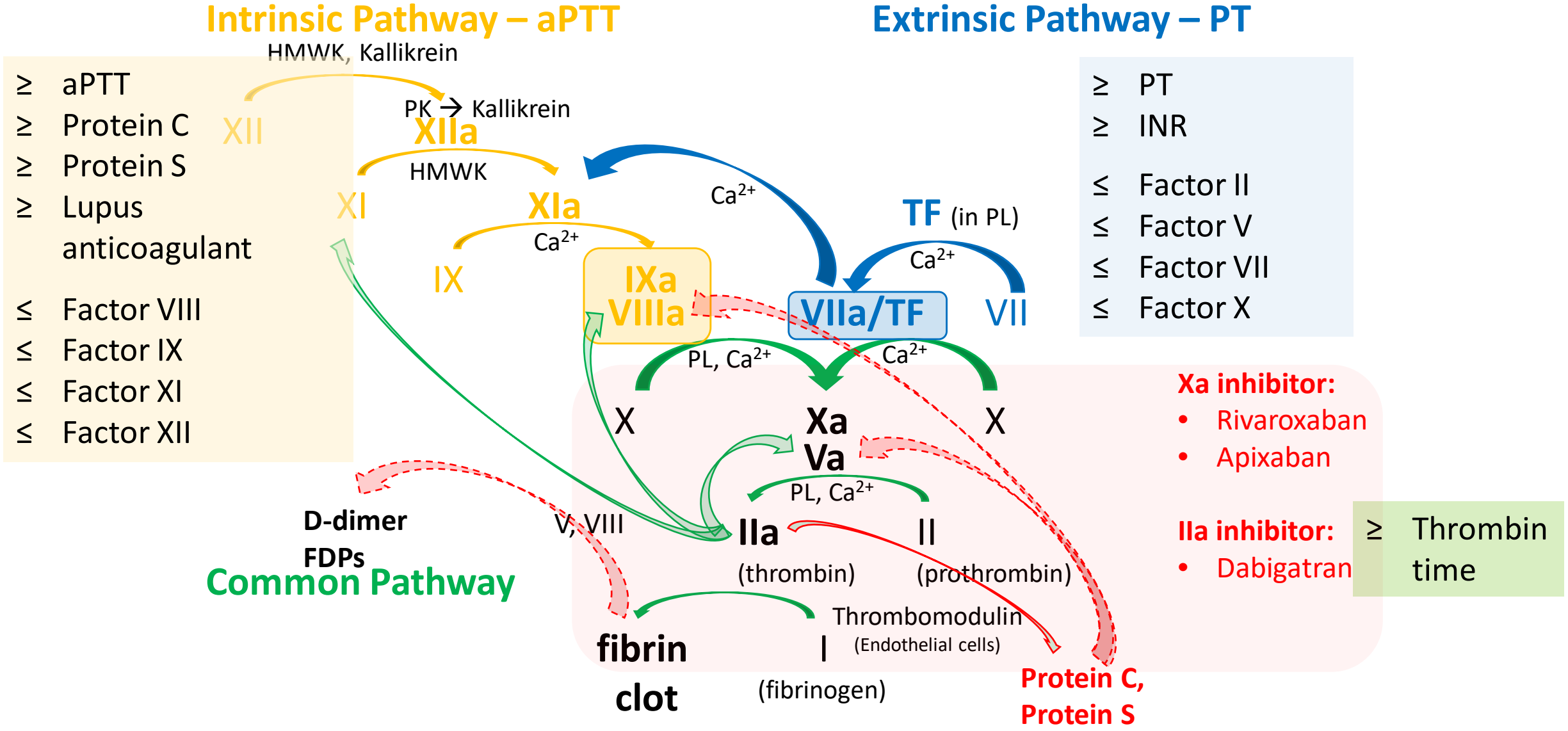


Initial U.S. **Approval**: 2017

Clot-based tests



Clot-based tests: "open-ended" cascades



Effect of Various Anticoagulants On Commonly Used Coagulation Assays.

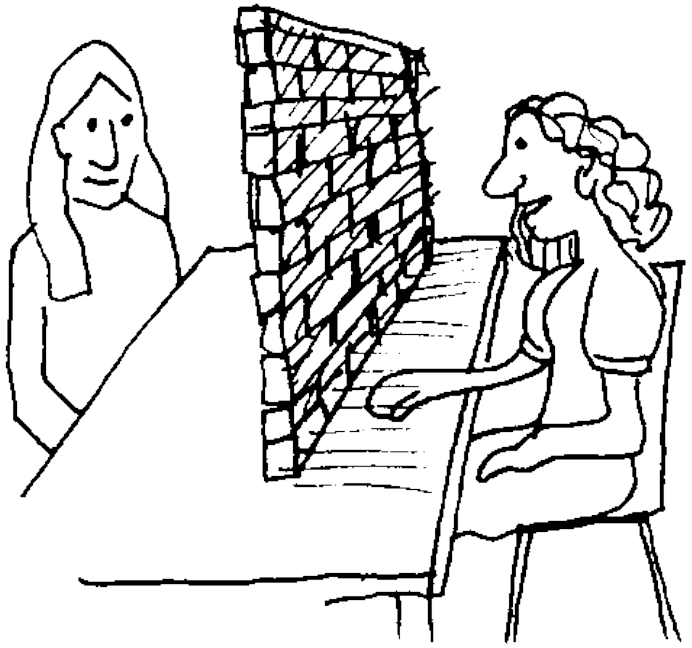
Source: Dorothy Adcock MD, Chief Medical Officer, LabCorp Diagnostics

Coagulation Assays	VKA (Influence)	UFH (Influence)	LMWH (Influence)	Rivaroxaban (Influence)	Apixaban (Influence)	Edoxaban (Influence)	Dabigatran (Influence)
PT	↑	no effect or ↑[1]	=	↑	no effect or ↑ (weak)	↑ (weak)	↑
aPTT	↑	↑	no effect or ↑ (weak)	↑	no effect or ↑ (weak)	↑ (weak)	↑
Fibrinogen (Clauss Method)	=	↓	=	=	=	=	= / ↓
Thrombin Time TT	=	↑	↑	=	=	=	↑
Factor Assays (clotting assays)	↓ (FIX,VII,X and II) no effect for the others	aPTT based: ↓[2] PT based: =	aPTT based: ↓[2] (weak) PT based: =	↓[2]	↓[2] (weak) / =	↓[2]	↓[2]
DDi, VWF: Ag, VWF: RCo							
Anti-Xa Activity (UFH or LMWH)							
Antithrombin Activity FXa-based Assay							
Antithrombin Activity FIIa-based Assay							
Protein C Activity Clot-based Assay							
Protein C Activity Chromogenic Assay							
Protein S Activity Clot-based Assay							
Free Protein S Ag (Immunological Assay)	↓	=	=	=	=	=	=
Lupus Anticoagulant Testing: "sensitive" aPTT and dRVVT (screening, mixing, confirmation)	↑[4]	↑[4]	=	↑[4]	↑[4]	↑[4]	↑[4]
Resistance to Activated Protein C	↑[5]	↑[1]	=	↑[3]	↑[3]	↑[3]	↑[3]
Reptilase Time	=	=	=	=	=	=	=

40% false-positive lupus anticoagulant test results at KPSC – new "indeterminate" result category; using chart review to check medication history for some cases

LIS needs Pharmacy and Vice Versa

- Many potential areas for connecting and improving patient care:
  - Oncology and pharmacogenetic testing
  - Antibiotic stewardship activities
  - Therapeutic drug monitoring (e.g., methotrexate)
  - Opioid / pain management drug prescription monitoring (adherence)
  - Safe renal dosing of medications
  - Anticoagulation interference in diagnostic work-up of hypercoagulability conditions
  - Etc…
- Some pharmacy systems are able to receive laboratory results, enabling rules-based review (e.g., therapeutic drug monitoring)
- However, in most cases, pharmacy and laboratory systems rarely communicate



http://yuanyuanliang.blogspot.com

Thank you!

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Clot-based tests: “open-ended”