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# Fluorescence in Situ Hybridization (FISH) Optimization for Bone Marrow Specimens

Michael Tiffert

*Loyola Marymount University*

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# Fluorescence In Situ Hybridization (FISH) Optimization for Bone Marrow Specimens

Michael Tiffert, M.S.

Section Manager Cytogenetics and FISH  
SCPMG Regional Genetics Laboratory, 4580  
Electronics Place, Los Angeles, CA 90039  
Course SELP 695-02, Semester: Spring 2014  
Advisor: Bohdan W. Oppenheim, PHD

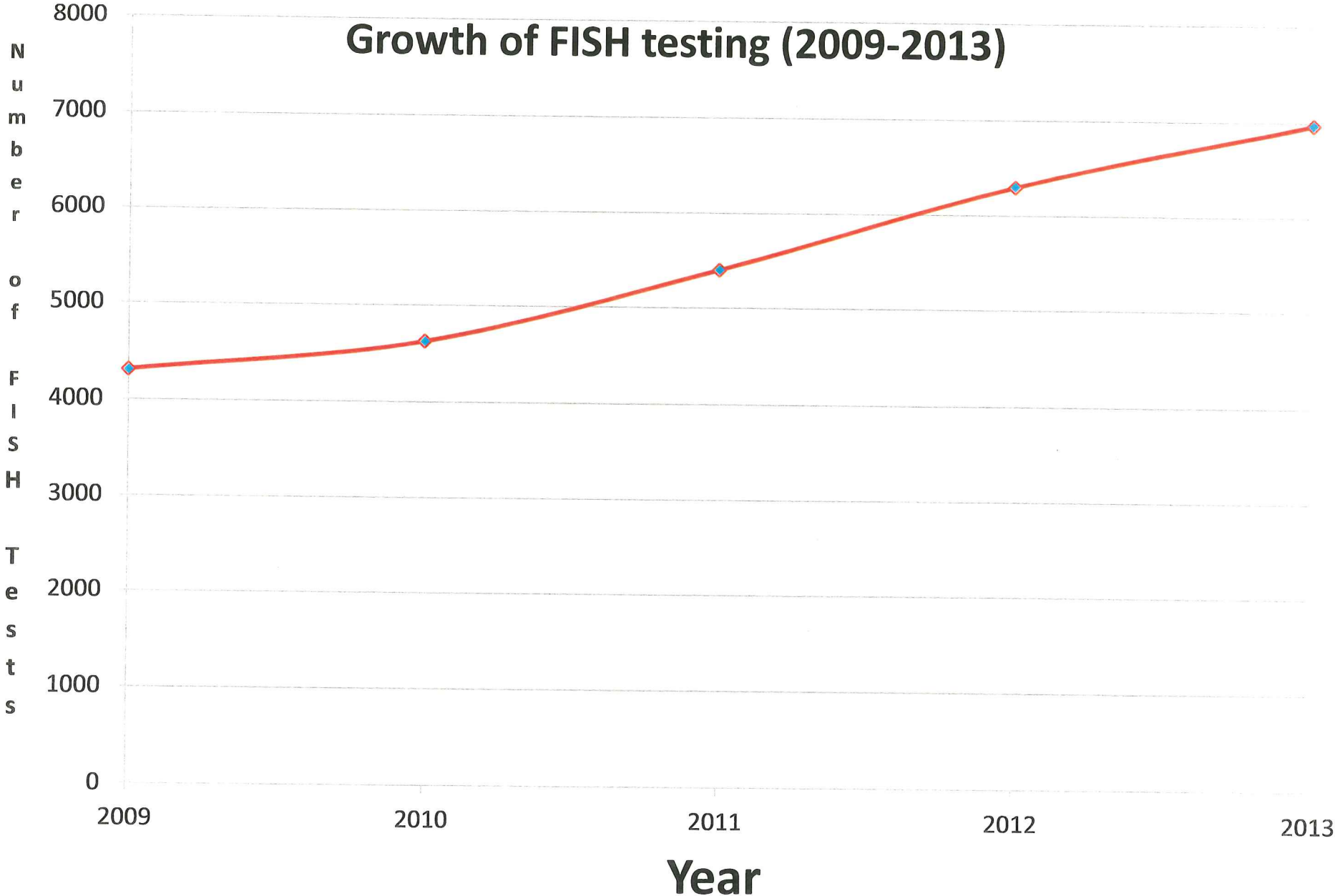
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# Background

- Fluorescence In Situ Hybridization (FISH) is a cytogenetic technique that detects specific DNA sequences on chromosomes
- Used to detect submicroscopic chromosomal abnormalities such as cryptic deletions and translocations of genes
- Cancer incidence will increase by approximately 45%, from 1.6 million in 2010 to 2.3 million in 2030 ([J Clin Oncol.](#) 2009 Jun)

# Growth of FISH testing (2009-2013)



# REGIONAL GENETICS LABORATORY DEPARTMENTS

- **CYTOGENETICS** includes FISH Department
  - Hematological (Bone Marrow/Unstimulated Peripheral Blood)
  - Prenatal (Amniotic Fluid/CVS/POC)
  - Postnatal(Peripheral Blood)
- Molecular Genetics
- Biochemical Genetics (Metabolic)
- Neonatal and Prenatal Screening (NAPS Department)



# FISH Performed on a Variety of Tissue Types

- Bone Marrow/Unstimulated Peripheral Blood
- Amniotic Fluid, POC, CVS, Tissue
- Peripheral Blood
- Lung Tissue for ALK FISH
- Breast/Stomach Tissue for HER-2 neu FISH
- Tumors (mostly paraffin embedded tissue slides)



# Technical Bulletin

SCPMG LABORATORY SYSTEM – REGIONAL REFERENCE LABORATORIES

Congenital Probes	Syndrome/Chromosomal Abnormality
LSI ELN (7q11.23) Deletion LSI RB1 (13q14) Enumeration LSI SNRPN (15q11.2) Deletion CEP 18 (centromere) Enumeration LSI D21S259/D21S341/D21S342 (21q13) Enumeration LSI HIR/VTUPLE1 (22q11.2) Deletion/Duplication LSI STS (Xp22.3) Deletion CEP X (centromere) / CEP Y (centromere) Enumeration LSI SRY (Yp11.3) Translocation/Deletion	Williams syndrome Trisomy 13 Prader-Willi/Angelman Syndrome Trisomy 18 Trisomy 21 VCFS/DiGeorge syndrome Steroid Sulfatase Deficiency Turners and Klinefelters syndrome Gonadal Dysgenesis XX males, XY females
Hematological	Panels
LSI ALK (2p23) Translocations LSI BCL6 (3q27) Rearrangement LSI IgH (14q32) / LSI FGFR3 (4p16) Translocation CEP 4 / CEP 10 / CEP 17 (centromeres) Enumeration LSI 4q12 (FIP1L1-PDGFR) Rearrangement LSI EGR1 (5q31) Deletion LSI PDGFRB (5q32-q33) Rearrangement LSI D7S486/D7S522 Deletion (7q31) CEP 8 (centromere) Enumeration LSI RUNX1 (21q22) / LSI RUNX1T1 (8q21.1) Translocation LSI MYC (8q24) Translocations LSI IgH (14q32) / LSI MYC (8q24) Translocation LSI BCR (22q11.2) / LSI ABL1 (9q34) Translocation LSI IgH (14q32) / LSI CCND1 (11q13) Translocation LSI BIRC3 (11q21) / LSI MALT1 (18q21) Translocation LSI ATM (11q22.3) Deletion LSI MLL (11q23) Rearrangement CEP 12 (centromere) Enumeration LSI D13S319 (13q14.3) / LSI 13q34 (LAMP1) Deletion LSI ETV6 (12p13) / LSI RUNX1 (21q22) Translocation LSI TRAFD (14q11.2) Inversion/Translocation LSI IgH (14q32) Translocations LSI IgH (14q32) / LSI MAF (16q23) Translocation LSI IgH (14q32) / LSI BCL2 (18q21) Translocation LSI PML (15q22) / LSI RARA (17q21) Translocation LSI CFB (16q22) Inversion/Deletion LSI TP53 (17p13.1) Deletion LSI RARA (17q21) Translocations LSI D20S108 (20q12) Deletion CEP X (centromere) / CEP Y (centromere) Enumeration	<p style="text-align: center;"><b>Myeloma</b></p> Deletion 13q (13q14 + 13q34) IGH rearrangement (14q32) TP53 deletion (17p13) <i>Reflex panel if IGH positive</i> FGFR3 IGH Translocation (4p16-14q32) CCND1, IGH Translocation (11q13-14q32) IGH, MAF Translocation (14q32-16q23)
	<p style="text-align: center;"><b>CLL</b></p> ATM deletion (11q23) + TP53 Deletion (17p13) Trisomy 12 (centromere) Deletion 13q (13q14 + 13q34)
	<p style="text-align: center;"><b>Follicular lymphoma</b></p> IGH BCL2 Translocation (14q32-18q21) <i>If normal reflex to</i> BCL6 Rearrangement (3q27)
	<p style="text-align: center;"><b>Diffuse Large B-cell Lymphoma</b></p> MYC Rearrangement (8q24) IGH BCL2 Translocation (14q32-18q21) BCL6 Rearrangement (3q27)
	<p style="text-align: center;"><b>Marginal Zone Lymphoma</b></p> BIRC3, MALT1 Translocation (11q21-18q21)
	<p style="text-align: center;"><b>Burkitt's Lymphoma</b></p> cMYC rearrangement (8q24)
	<p style="text-align: center;"><b>T-cell Lymphoma</b></p> ALK Translocations (2p23) TCR AVD Rearrangement (14q11)
	<p style="text-align: center;"><b>Adult B-ALL</b></p> MLL Rearrangement (11q23) BCR, ABL1 Translocation (9q34-22q11.2)
	<p style="text-align: center;"><b>MDS</b></p> 5q Deletion (5q31) 7q Deletion (7q31) Trisomy 8 (centromere) + 20q Deletion (20q11.2)
	<p style="text-align: center;"><b>Adult AML</b></p> RUNX1T1, RUNX1 Translocation (8q22-21q22) PML, RARA Translocation (15q22-17q21) CFB Inversion/Deletion (16q22) MLL Rearrangement (11q23)
Solid Tumors	
LSI ALK (2p23) Inversion LSI DDIT3 (12q13) Rearrangement LSI MDM2 (12q15) Gene Amplification LSI FOXO1 (13q14) Translocations LSI FUS (16p11) Translocations HER2 Gene Amplification LSI SS18 (18q11.2) Translocations LSI EWSR1 (22q12) Translocations	



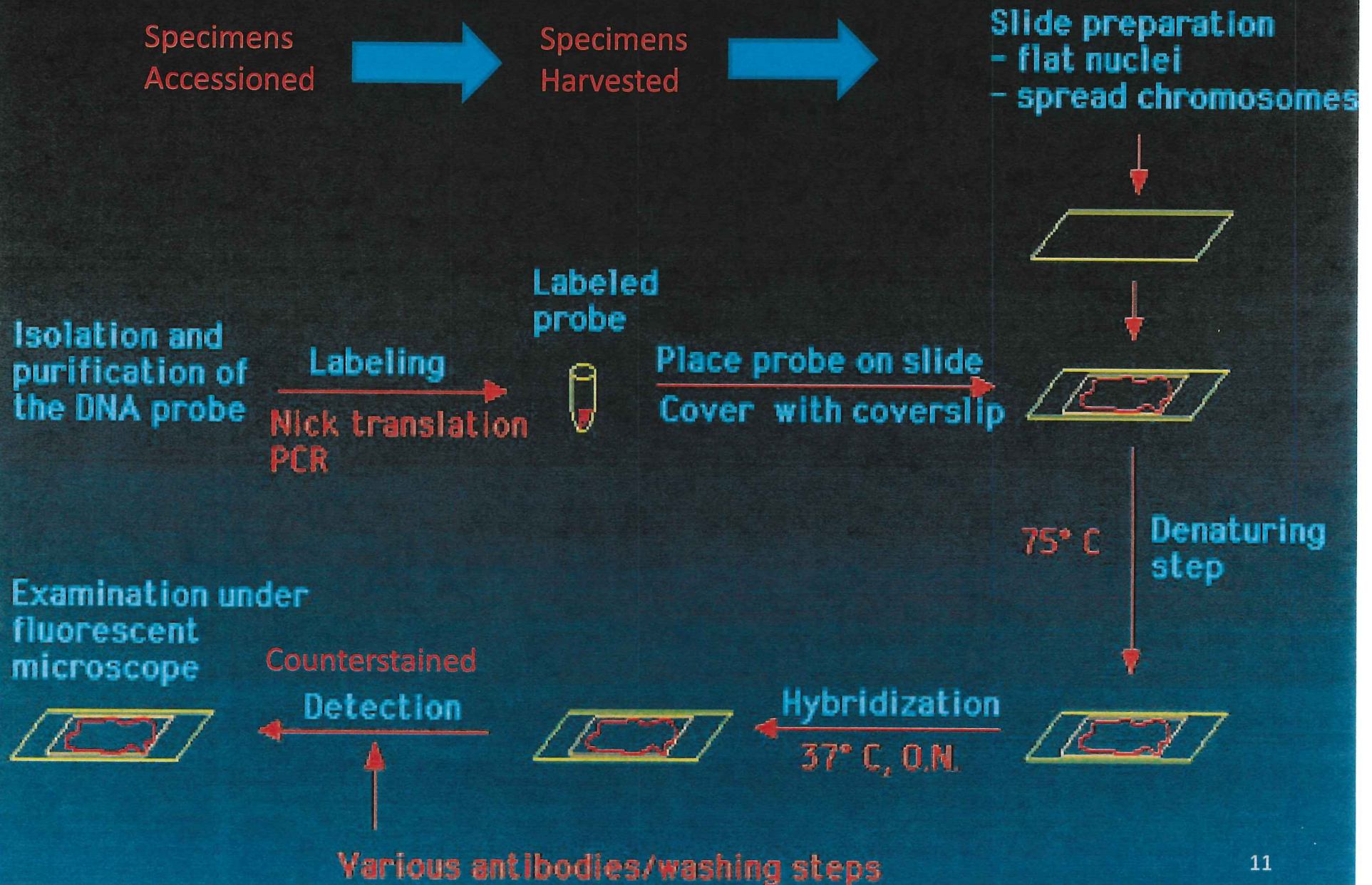
# Customer and Value

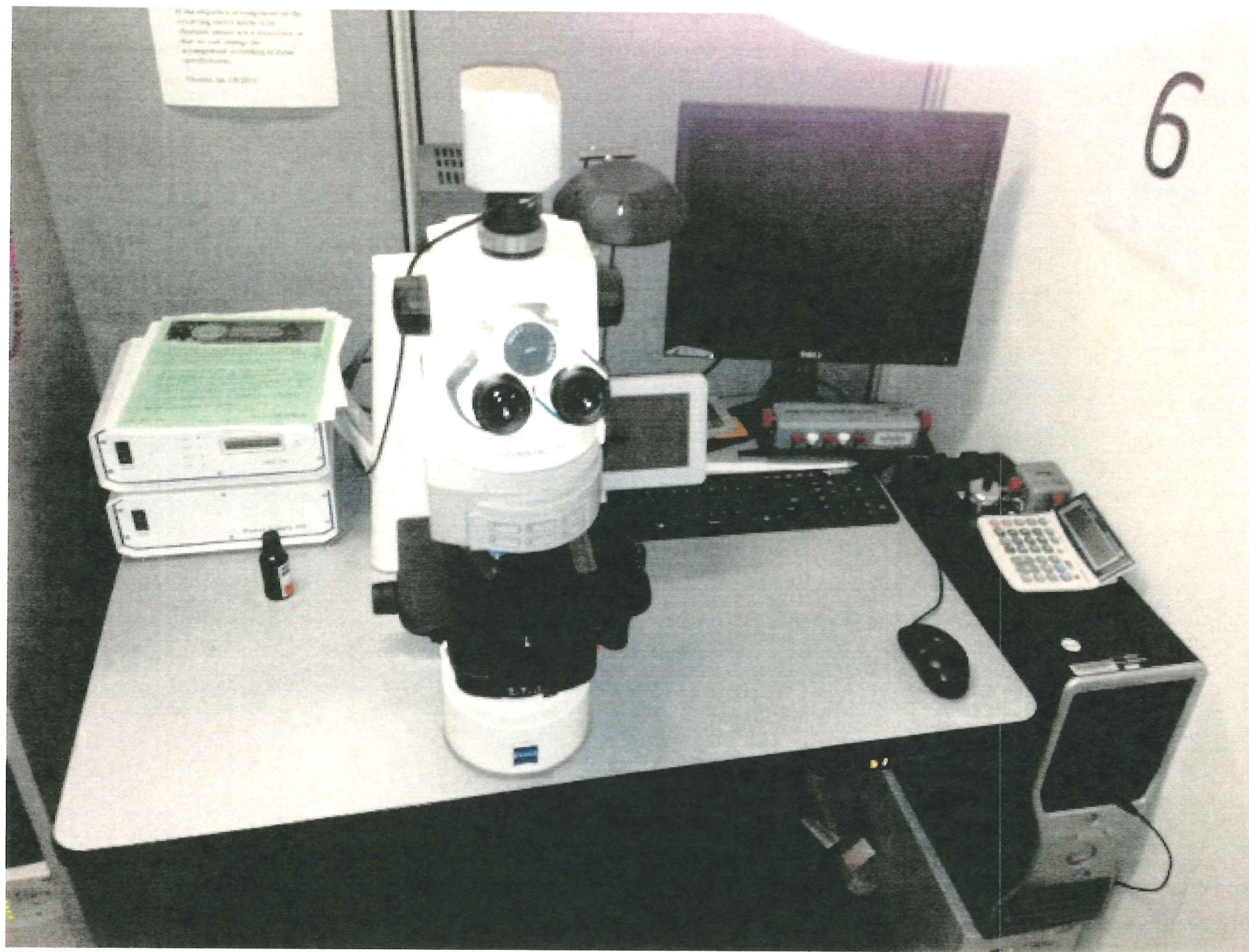
- Primary Customers: Patients and their physicians
- Value: Minimize throughput time and accurate test results every time
- Secondary Customers: KP Enterprise
- Value: Greater competitiveness, greater productivity, and reduced cost overall

# Scope of Project

- To reduce bone marrow FISH turn around time (TAT), thereby indirectly reducing overall cost
- To increase patient and physician satisfaction by providing accurate, timely, and high quality results
- To obtain consistent and high quality results by streamlining operations to eliminate variability and waste
- Boost employee morale by decreasing backlog

# General FISH protocol

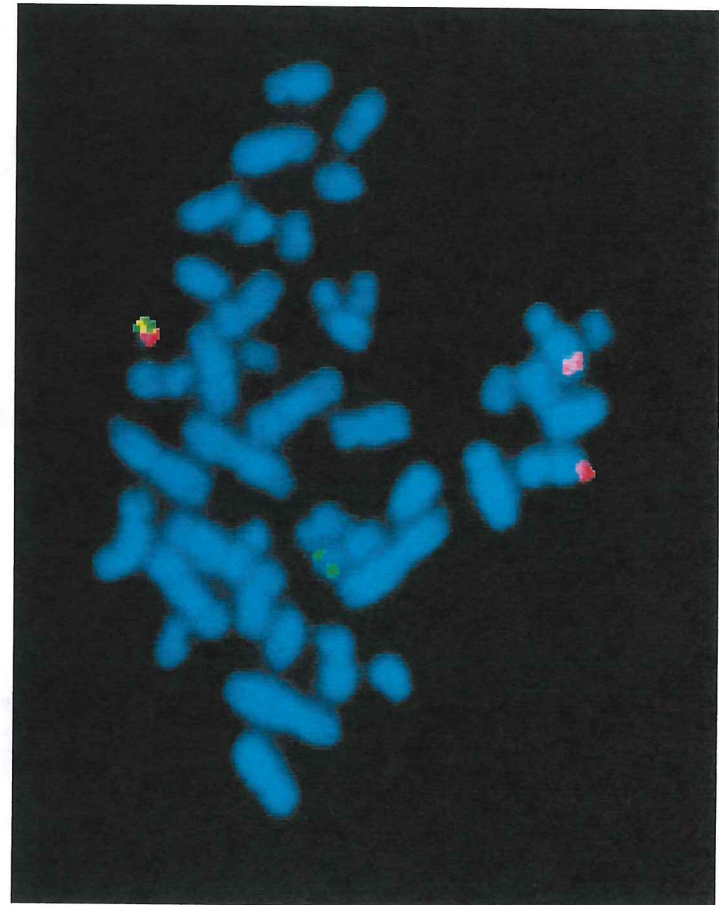
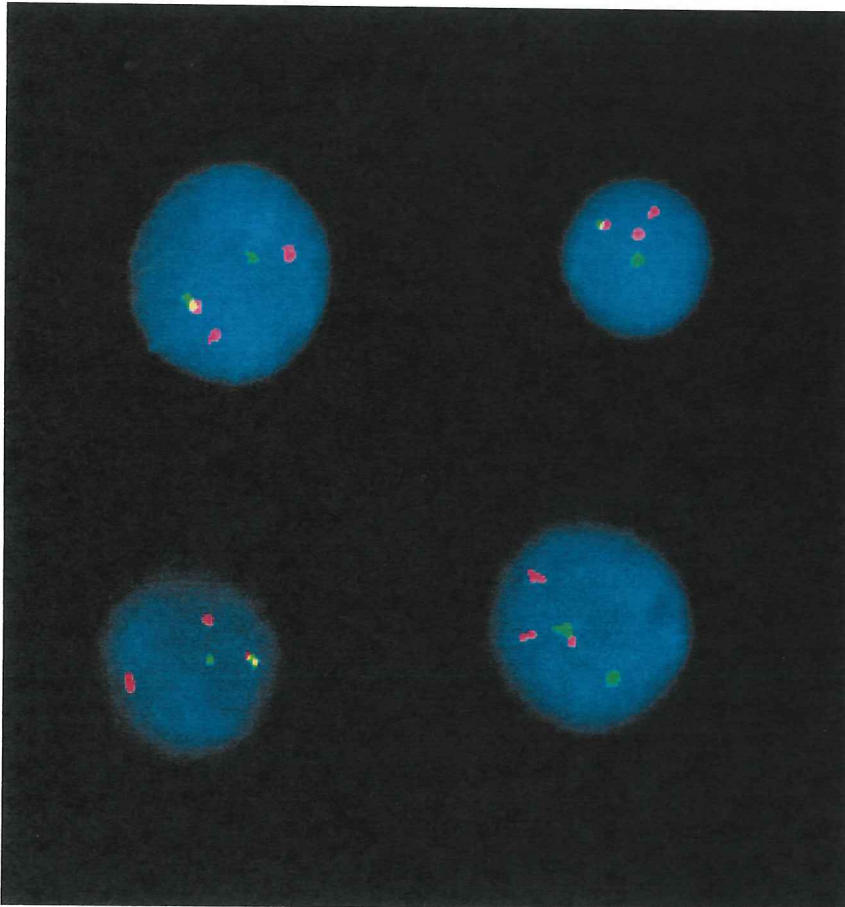




# Fluorescence In Situ Hybridization (FISH)

Probes are quantified based on  
Fluorescent colors

A total of 200 cells should be counted  
2 Cytogenetic techs perform analysis (100 cells each)



# Overview of Value Streams

- Current State Map with three Phases
  - (Prenalytical, Analytical, Post-analytical)
- Future State Map with three Phases
  - (Prenalytical, Analytical, Post-analytical)
  - Without Genetics Laboratory Information System (Genetics LIS)
  - With a Genetics LIS
- Ideal State Map

# What is a Genetics LIS?

- Series of computer programs that process, store, and manage data from all stages of medical processes and tests
- Primarily designed for processing and reporting data related to individual patients in a clinical setting
- Patient and specimen oriented
- Must satisfy the needs of reporting and auditing agencies and HIPAA



# Current State Observations

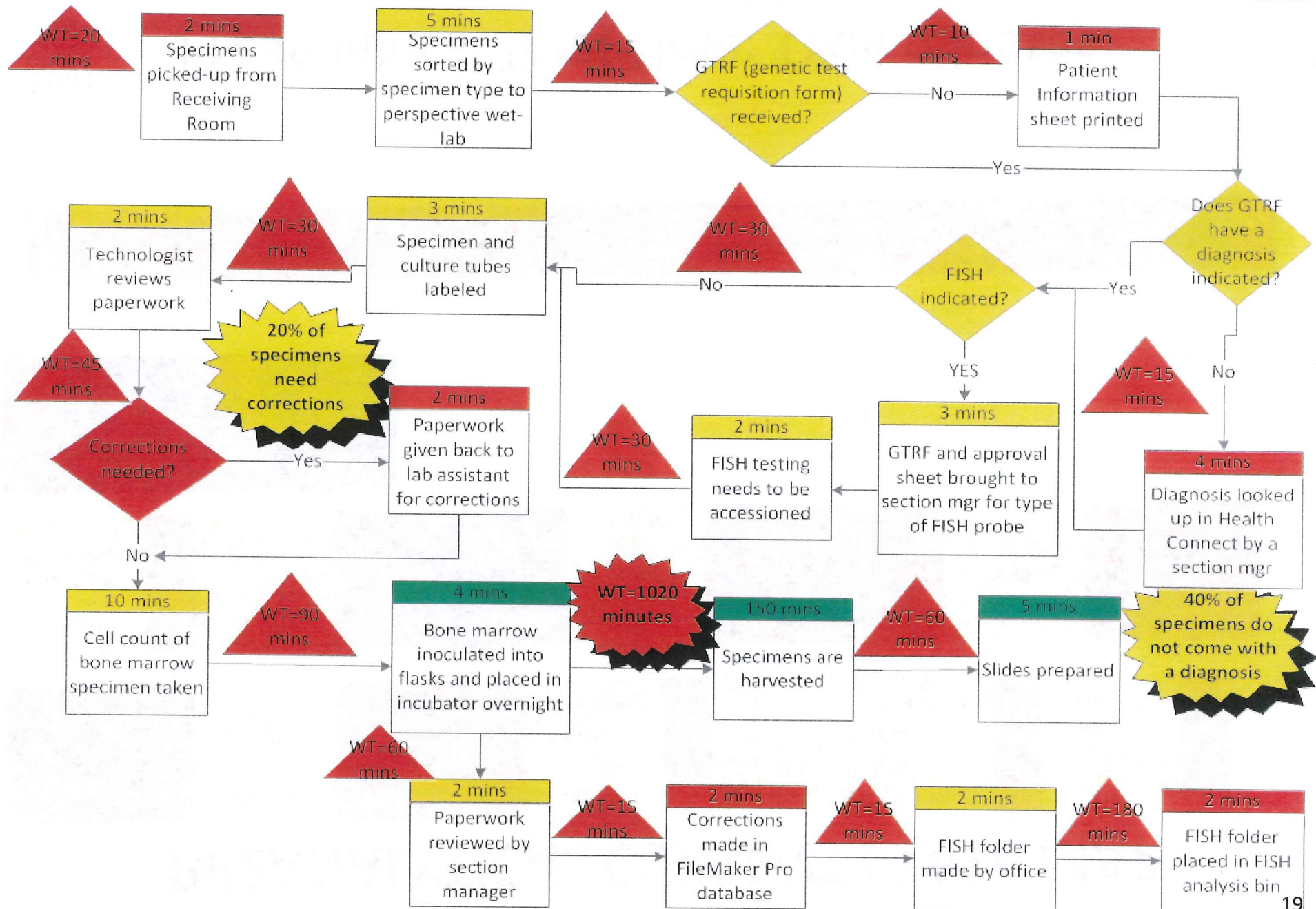
- Current laboratory set-up is geared more towards a university based setting instead of a high volume clinical laboratory
- FISH testing currently cannot be ordered in Health Connect
- Current process takes three days **before** slides are ready for analysis at the microscope (both labor intensive and time consuming)
- All processes are manual that are mistake prone throughout (rework required)
- Large backlog of FISH cases waiting to be analyzed (average FISH TAT is around 10 days)
- Numerous phone calls from physicians fielded by section managers on a daily basis regarding the status of their patient's bone marrow FISH results
- Set-up of FISH currently done only Monday-Friday
- Limited staff on evening shift-eight technologists



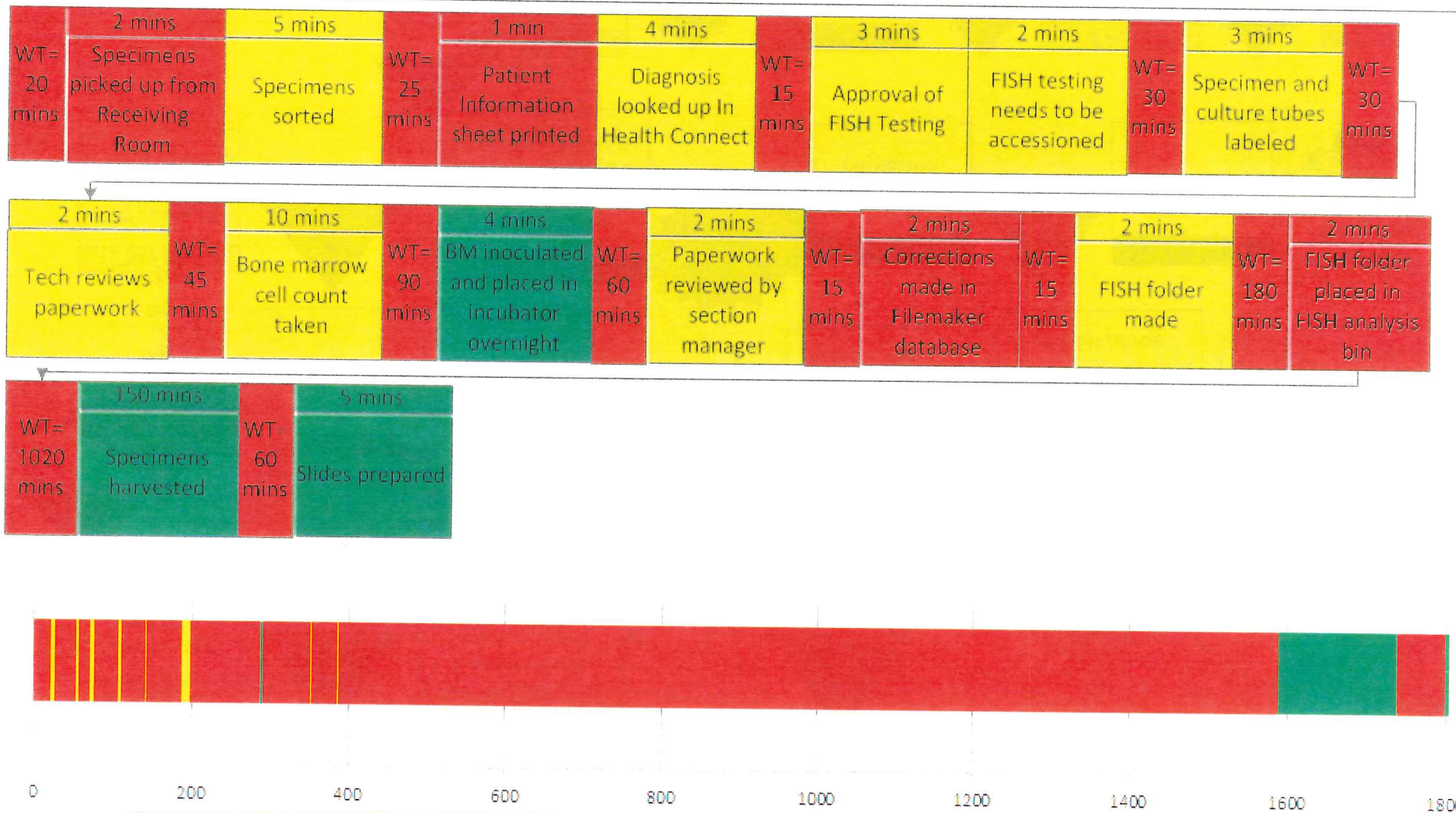
# Lack of Major Lean Tools in Current State

- Lack of Poka-Yoke (error proofing of processes)
- Lack of visual controls-state of testing
- Lack of Heijunka (load leveling)
- Large batch sizes used- no single piece work flow
- Limited report generation in regards to TAT metrics

# PREANALYTICAL CURRENT STATE MAP

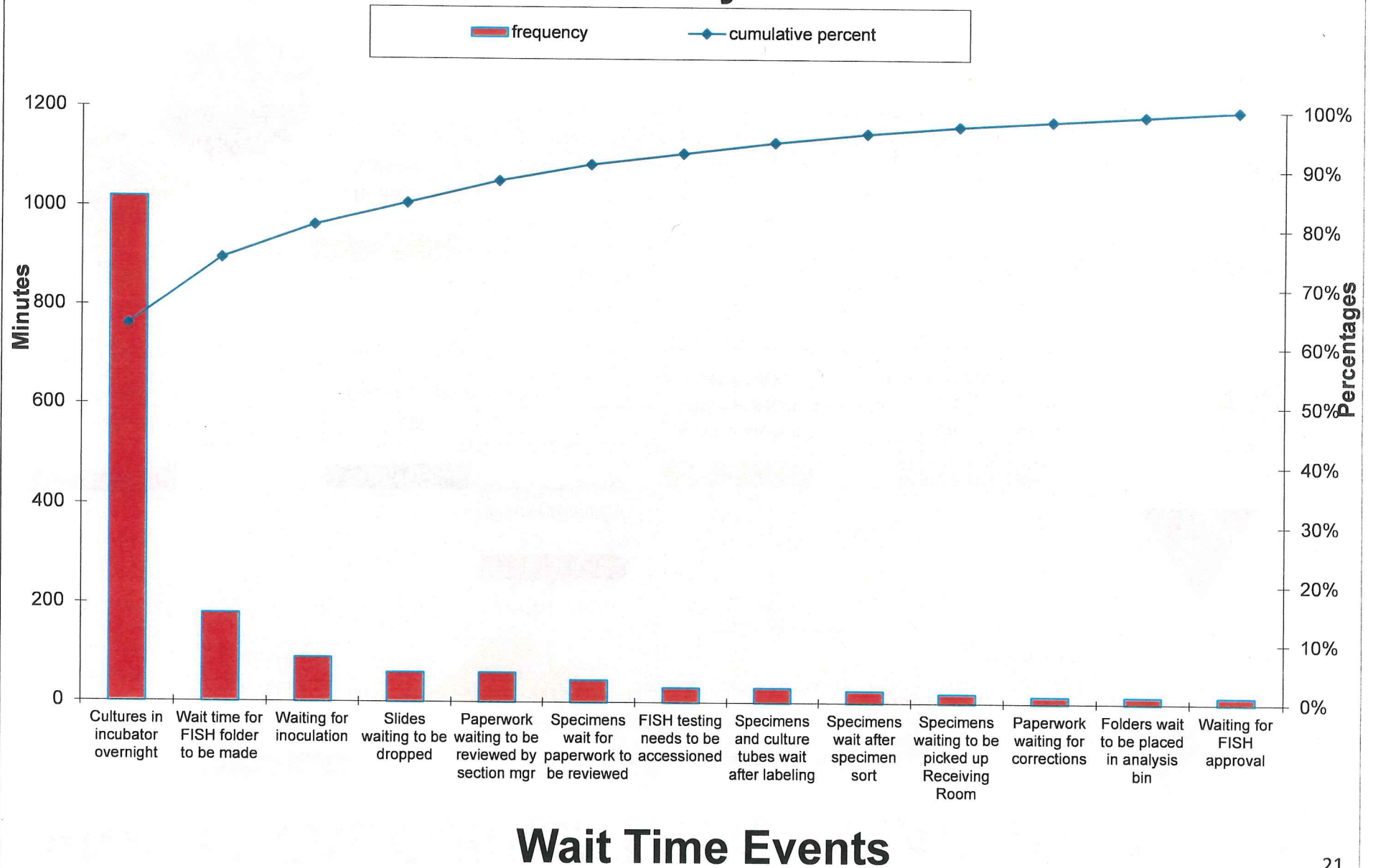


# PREANALYTICAL CURRENT STATE MAP

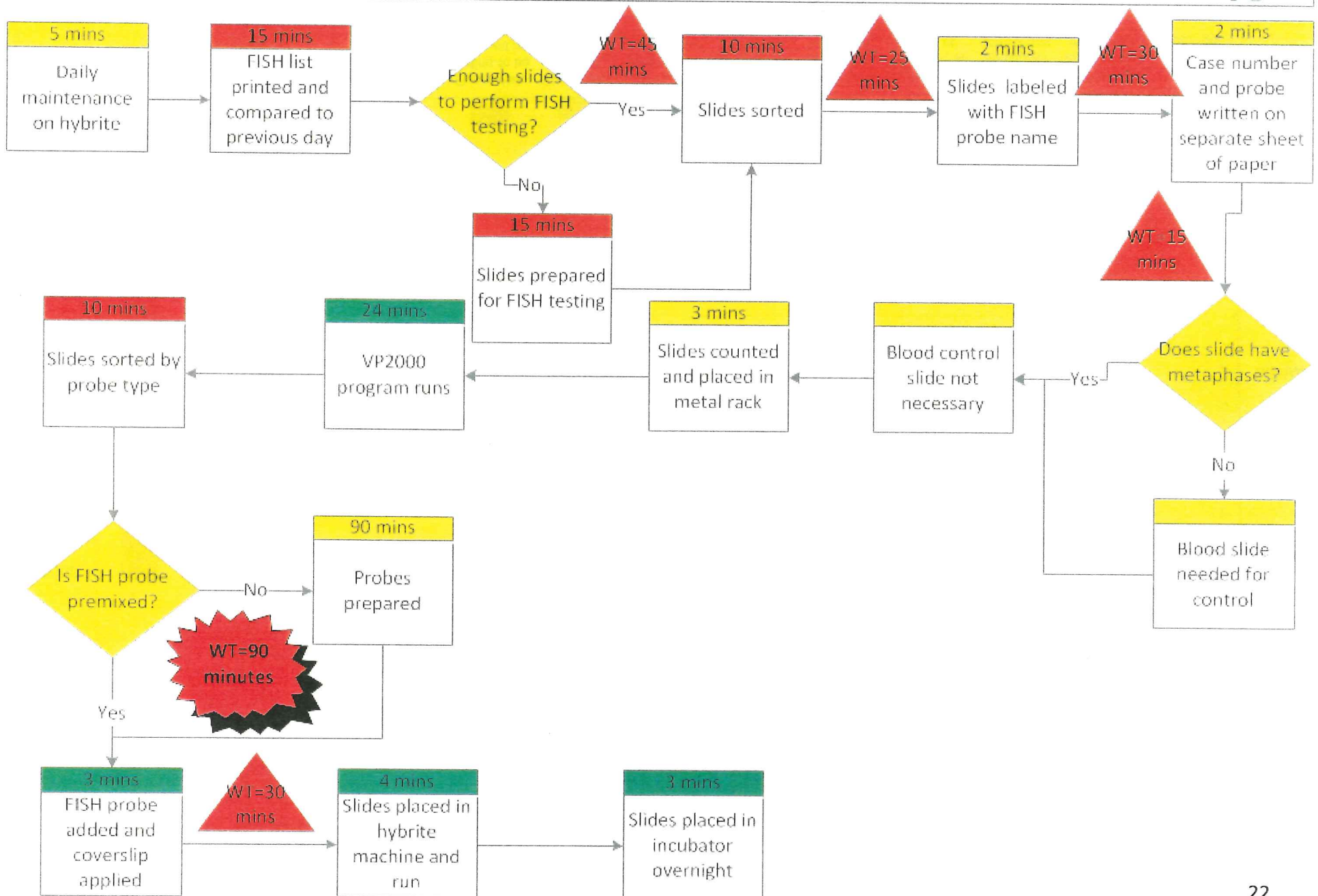


Preanalytical Total Time: 1804 minutes  
(approximately 30 hours)

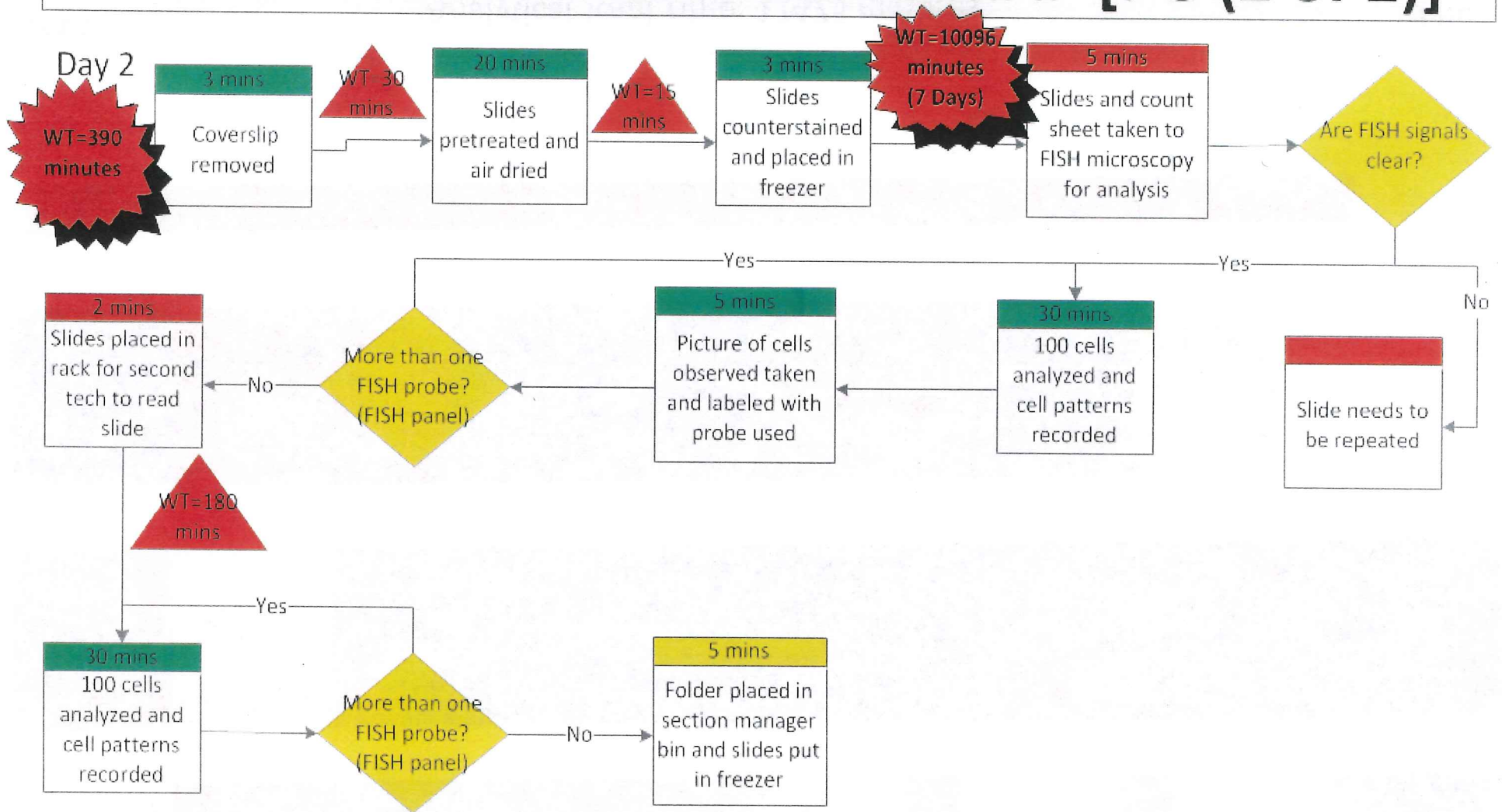
# Pareto Chart Showing Wait Times for BM FISH Preanalytical



# ANALYTICAL CURRENT STATE MAP [PG (1 of 2)]

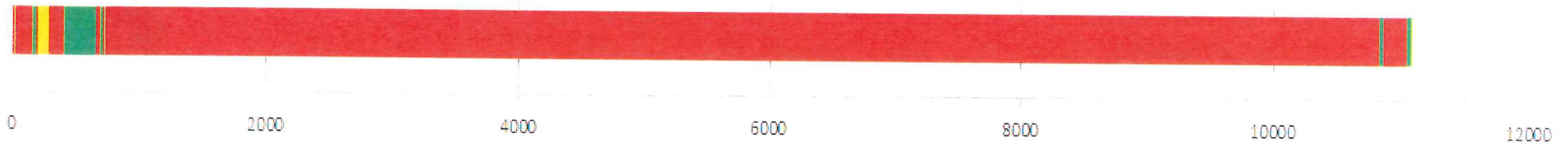
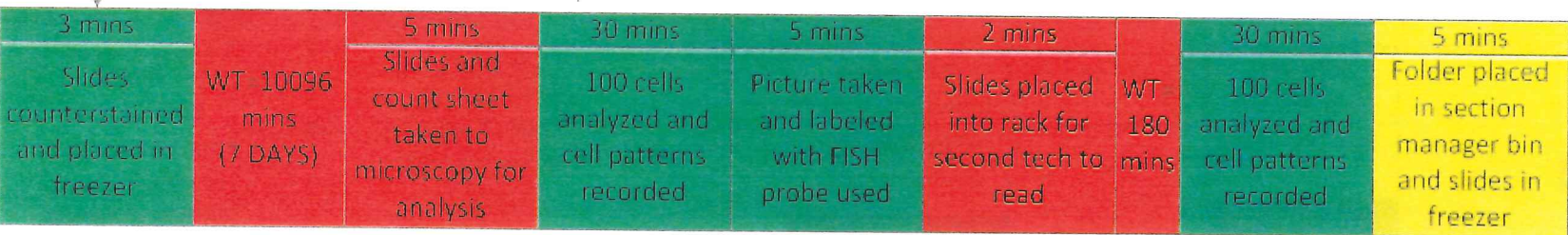
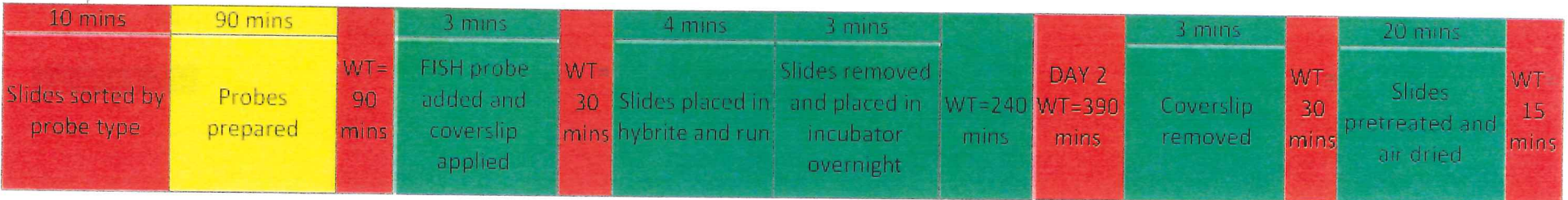
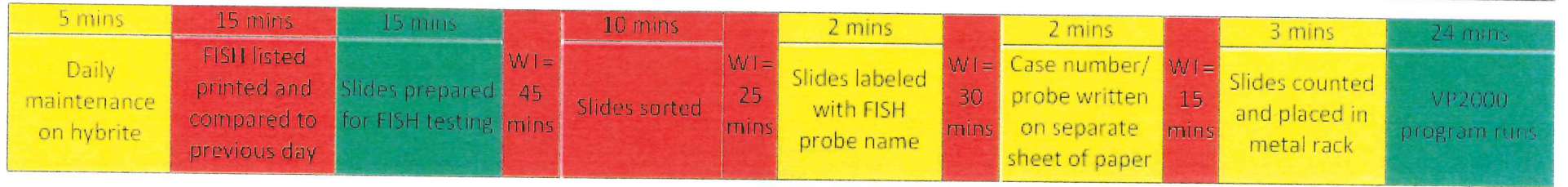


# ANALYTICAL CURRENT STATE MAP [PG (2 of 2)]



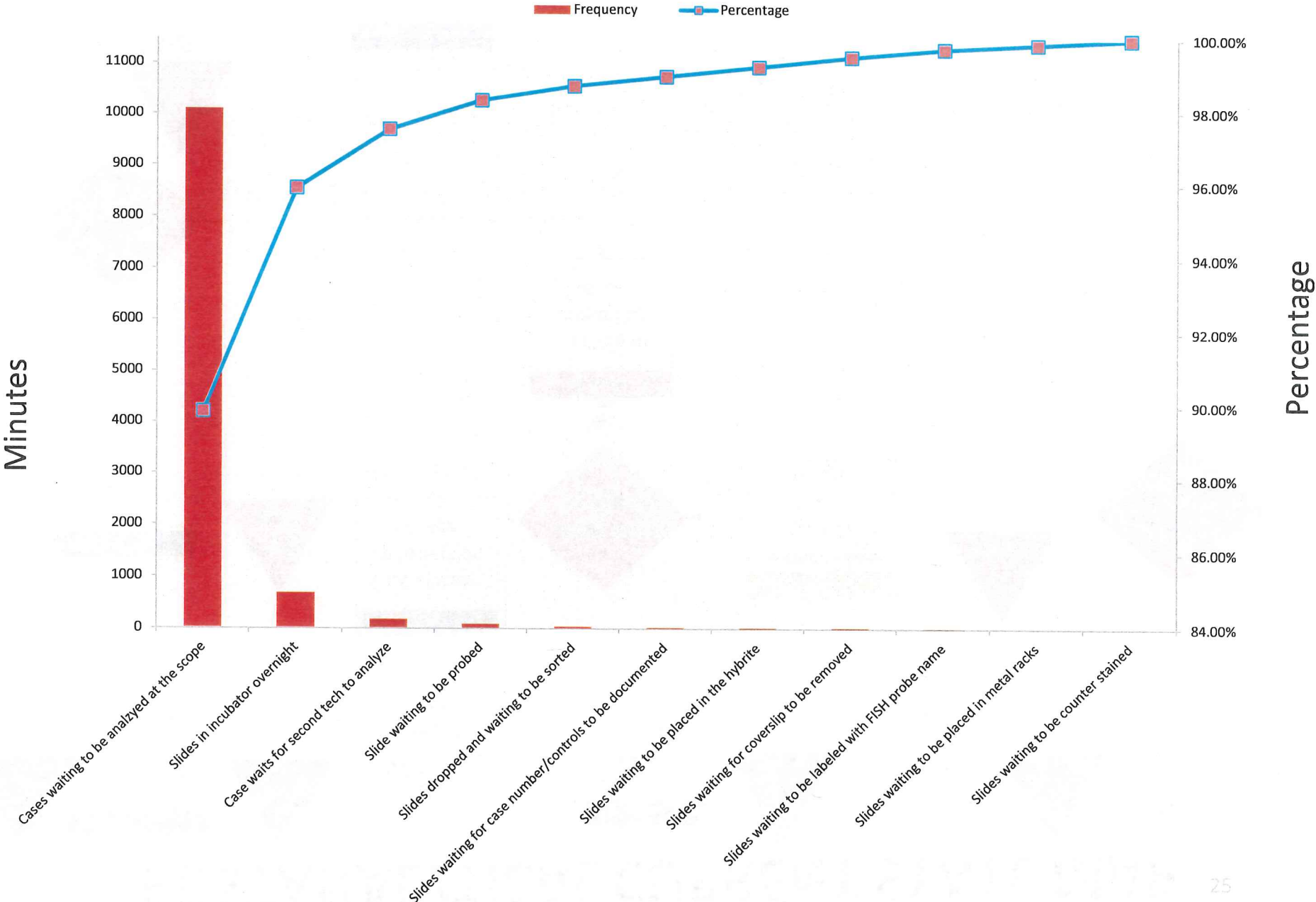


# ANALYTICAL CURRENT STATE MAP

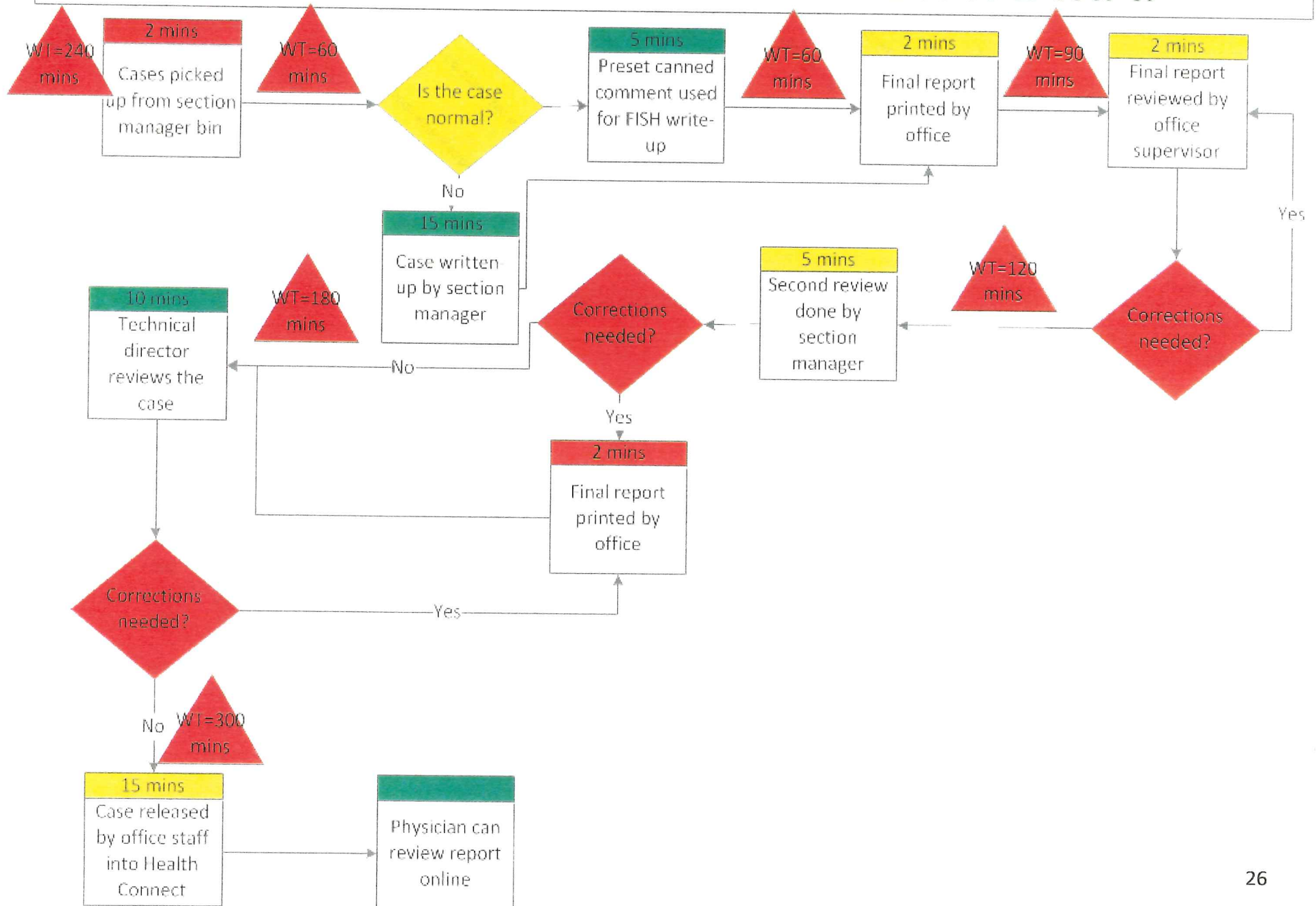


Start Analytical Total Time: 11475 minutes End  
(approximately 8 days)

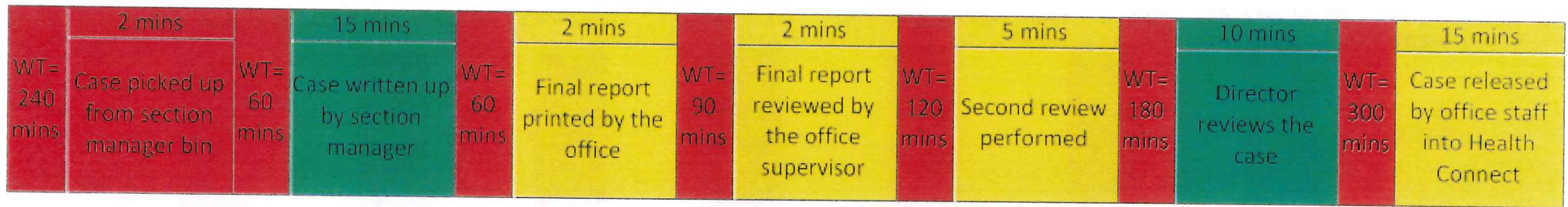
# Pareto Chart Showing Wait Times for Bone Marrow FISH Analytical



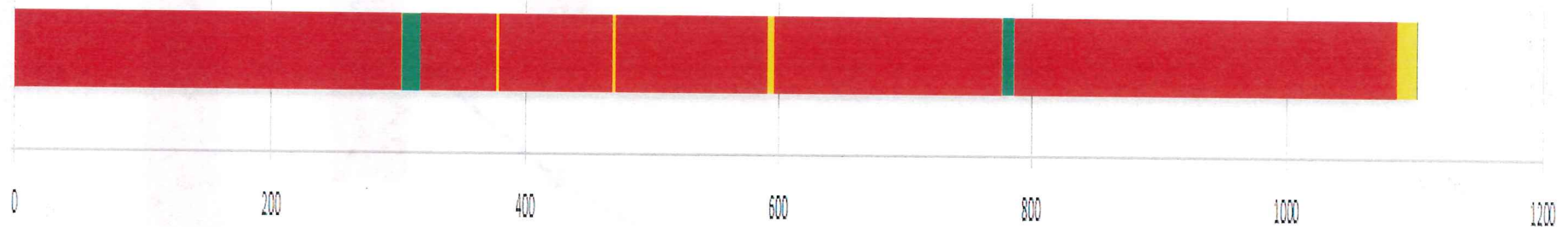
# POSTANALYTICAL CURRENT STATE MAP



# POSTANALYTICAL CURRENT STATE MAP



Physician can review the report online

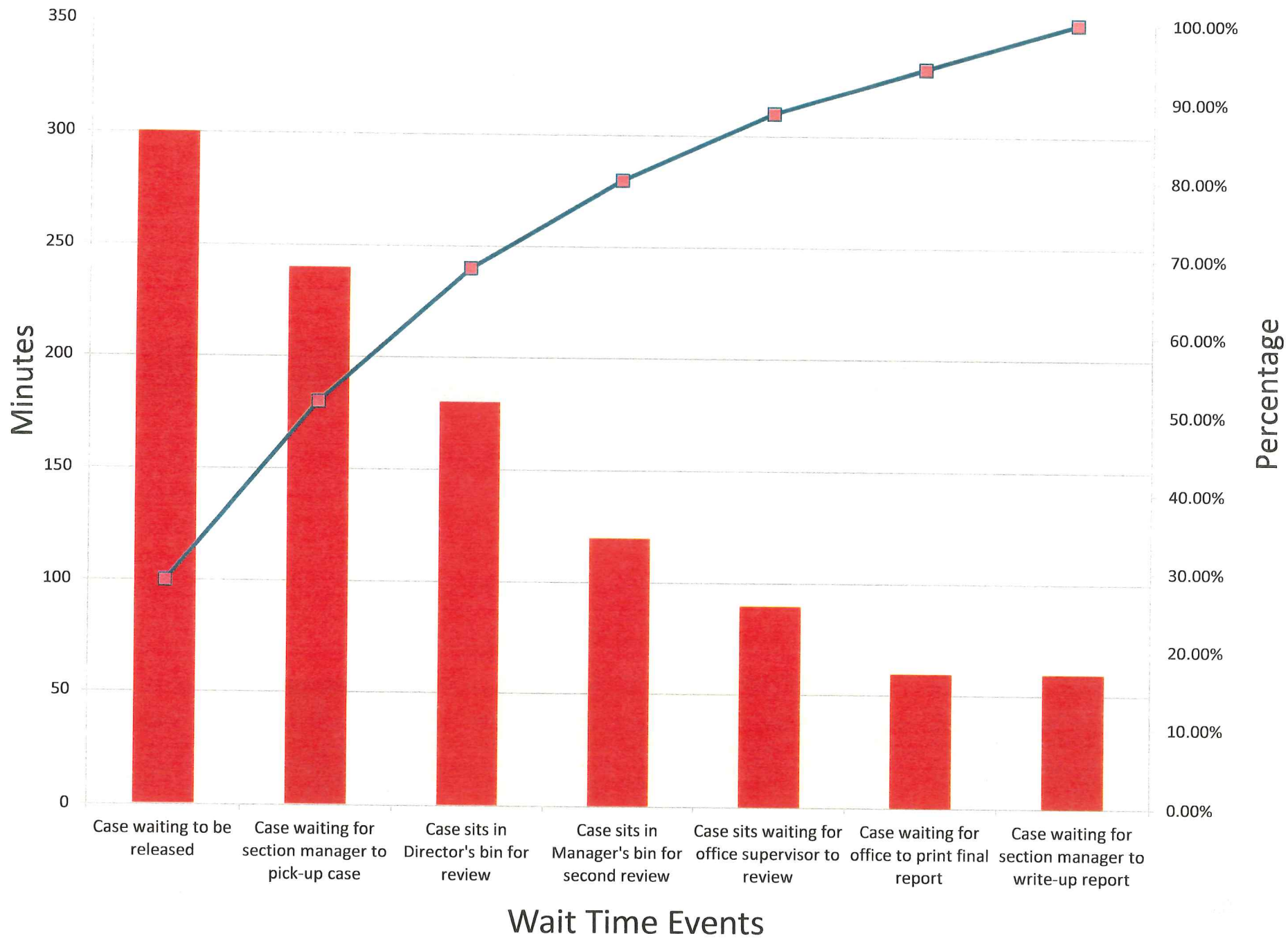


Start

End

Postanalytical Total Time: 1101 minutes  
(approximately 18.35 hours)

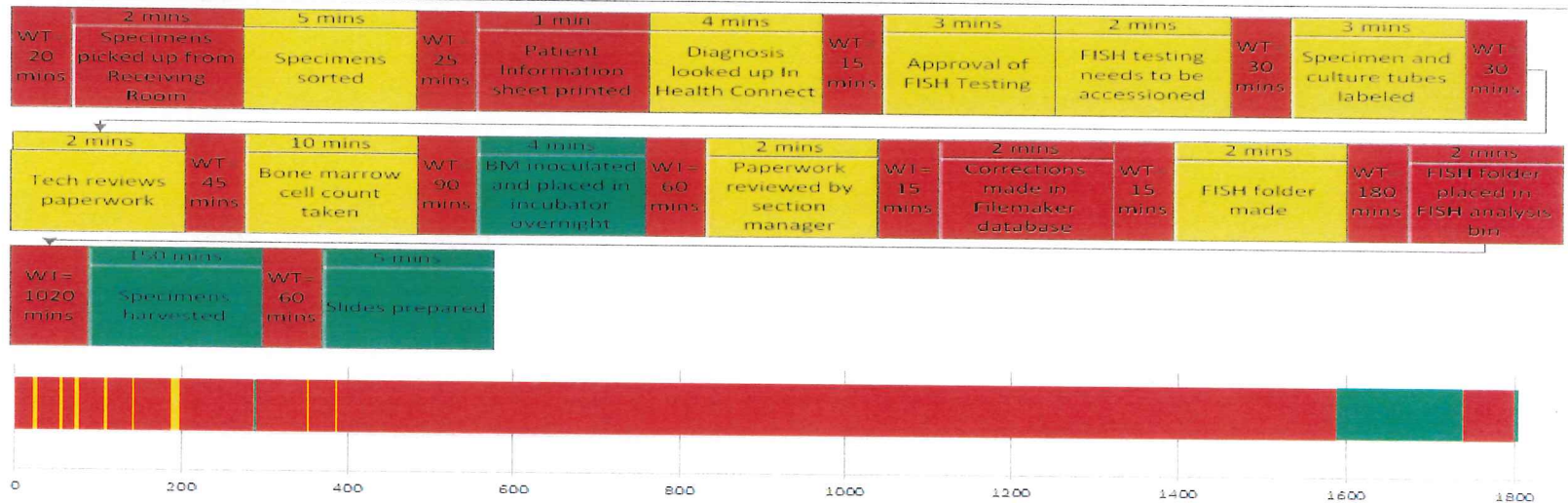
# Pareto Chart Showing Wait Times BM FISH Postanalytical Phase



# SUMMARY of CURRENT STATE

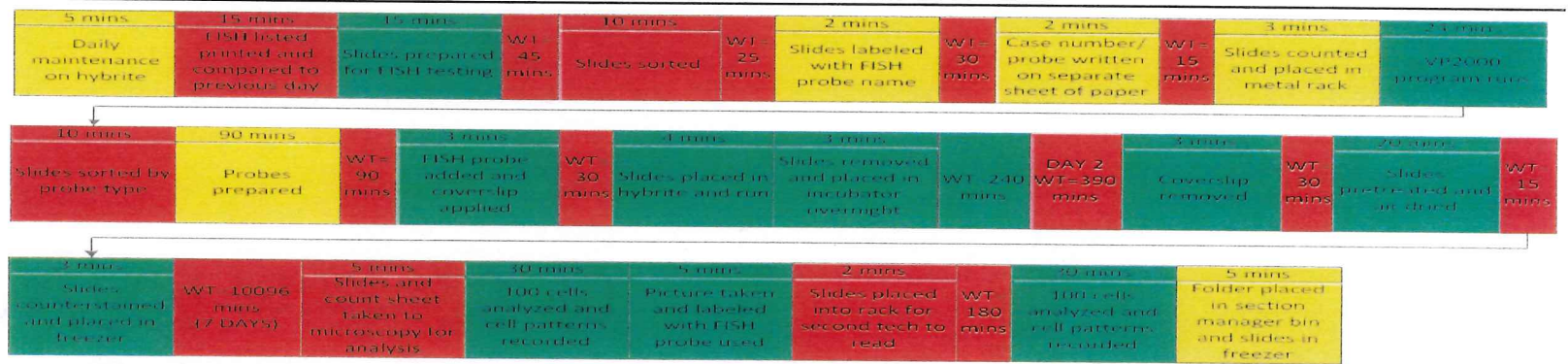
## Preanalytical

Total Time: 1804 minutes  
(approximately 30 hours)



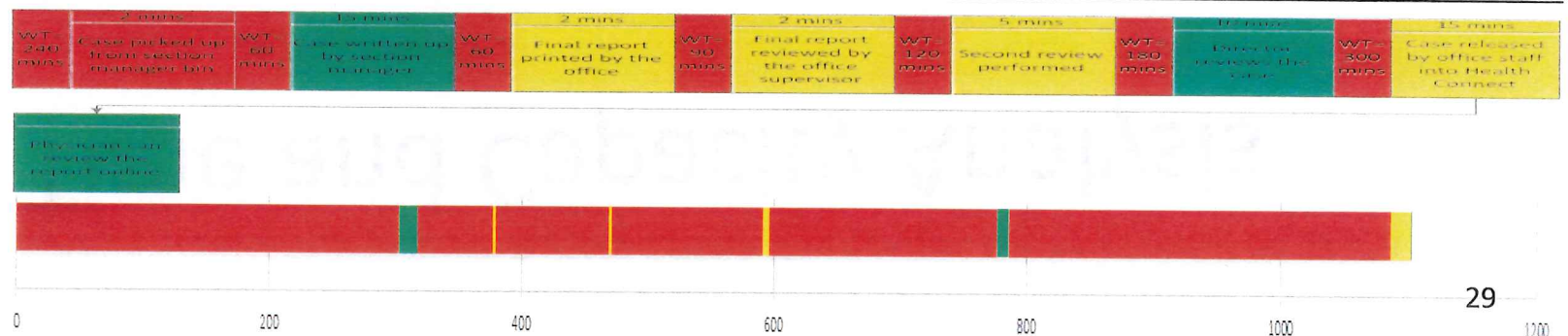
## Analytical

Total Time: 11475 minutes  
(approximately 8 days)



## Postanalytical

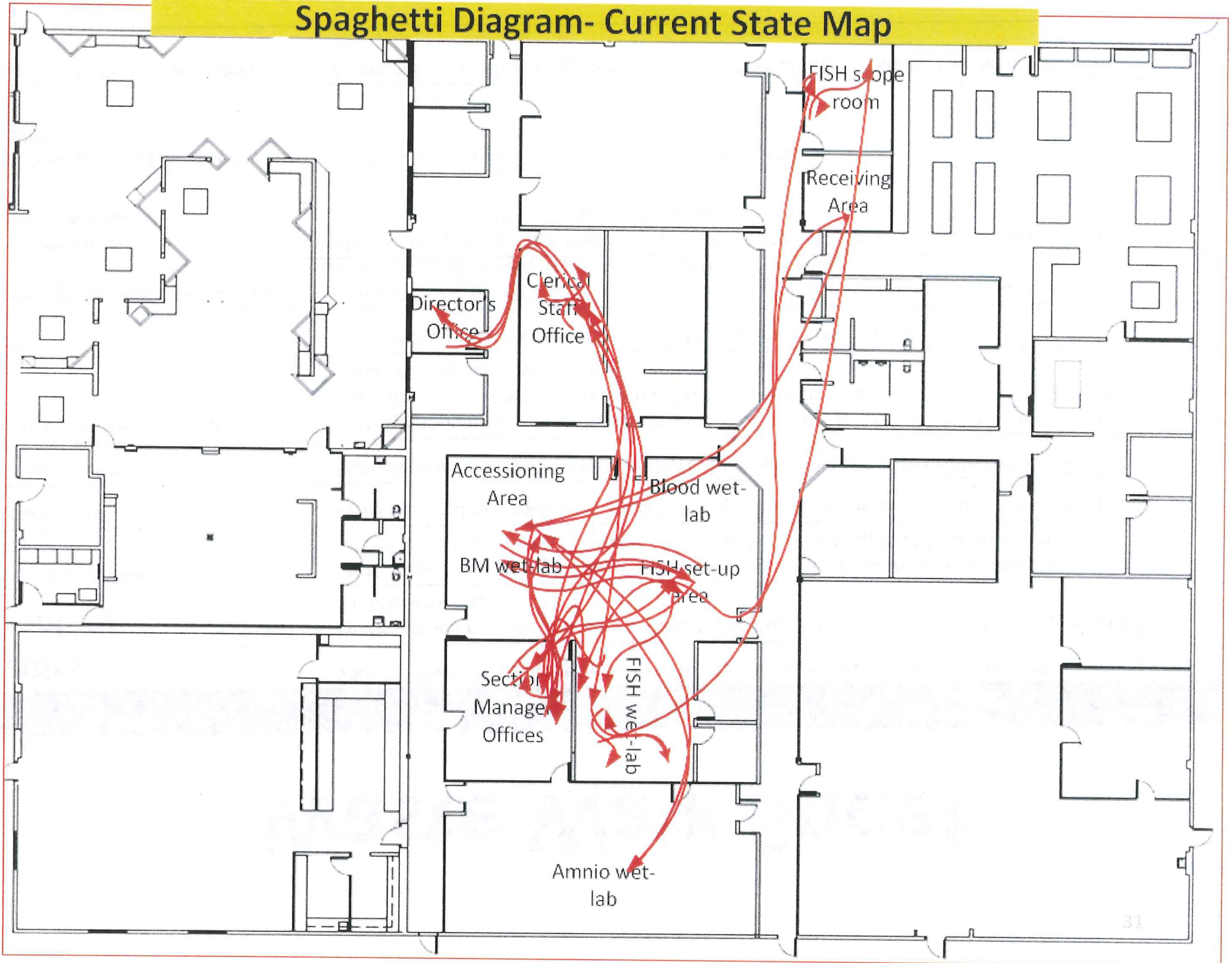
Total Time: 1101 minutes  
(approximately 18.35 hours)



# Time and Capacity Analysis

- Throughput Time/Value Added Time=14380 mins/564 mins=25.50

# Spaghetti Diagram- Current State Map

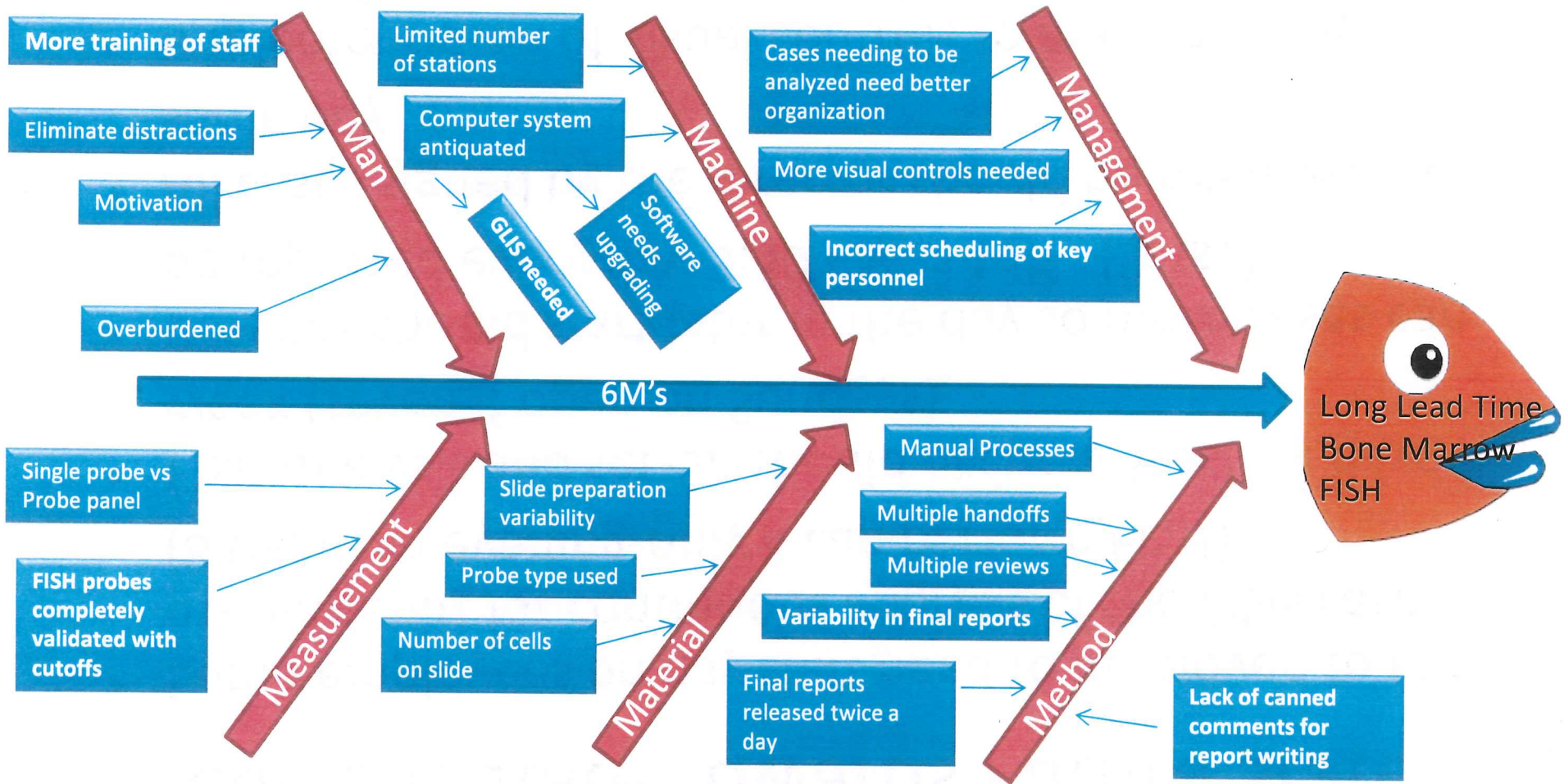




# Waste Walk Sheet

Waste Type	Waste Description
<b>Waiting</b>	Specimens wait to be processed, analyzed, written-up, signed out, and released into Health Connect.
<b>Inventory</b>	Specimens are processed in large batches throughout the entire process creating inventories at almost every step.
<b>Unnecessary Motion</b>	Case folders travel through multiple bins and offices. Paper system that requires approval of FISH testing by section manager because FISH cannot be ordered in Health Connect currently.
<b>Transportation</b>	Paperwork and case folders are passed through several offices and locations throughout the lab.
<b>Over-Production</b>	Multiple slides are made for FISH testing even though only one slide needed per probe set.
<b><u>Excessive Processing / Rework</u></b>	Missing information such as diagnoses need to be looked up if not written on GTRF (genetic test requisition form) originally. Numerous data entry corrections made daily for spelling errors and simple demographics such as name, dob, etc.
<b>Defects</b>	Probe hybridization not ideal (signals weak), FISH probe needs to be repeated.
<b>Waste of Human Potential</b>	Trying to locate patient folders when a doctor calls for their patient results or when information needs to be verified such as a collection date or a previous result.
<b>Muri – overburden / unreasonableness</b>	Many of the processes are manual and are time consuming. FISH samples not set-up on the weekend creating heavier loads for Monday.
<b>Mura – unevenness / variation / instability</b>	Due to specimen variability unevenness is a daily occurrence.
<b>Others (Handoffs, Re-Invention...)</b>	Numerous hand-offs and approvals needed for FISH probes by section managers or directors.

# Causes for Long Lead Times Bone Marrow FISH Fishbone Analysis Diagram for 6M's



# Recommendations to Move from Current State Towards Future State

- Some employees on day shift need to be moved to the evening shift for continuous analysis of the FISH cases (8 techs on evening-only 4 can perform FISH)
- FISH analysis and set-up should occur at least six days a week (seven if open on Sundays)
- Director should start later in the day so more cases can be reported every day-3:30 PM cutoff (Sats?)
- All cases signed by the director should be released the same day
- Implementation of visual controls to make employees aware of the number of cases that need to be analyzed

# Visual Control

TEST \ DAYS	>10	10	9	8	7	6
CANCER	6	0	2	13	21	10

TEST \ DAYS	>14	14	13	12	11	4-10
BLOOD	12	14	11	9	13	61
AMNIOTIC FLUID	0	0	0	3	0	8
CVS	0	0	0	0	0	5

TEST \ DAYS	>28	25-28	20-24	15-19	10-14	5-9
TISSUE	0	0	0	1	3	6

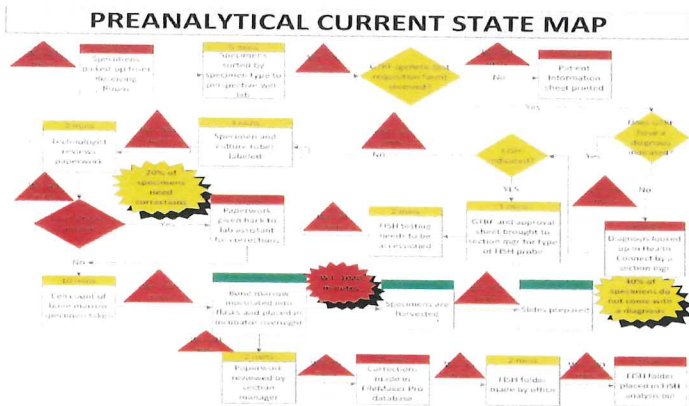
# Preanalytical Recommendations in Future State

## Without Genetics LIS

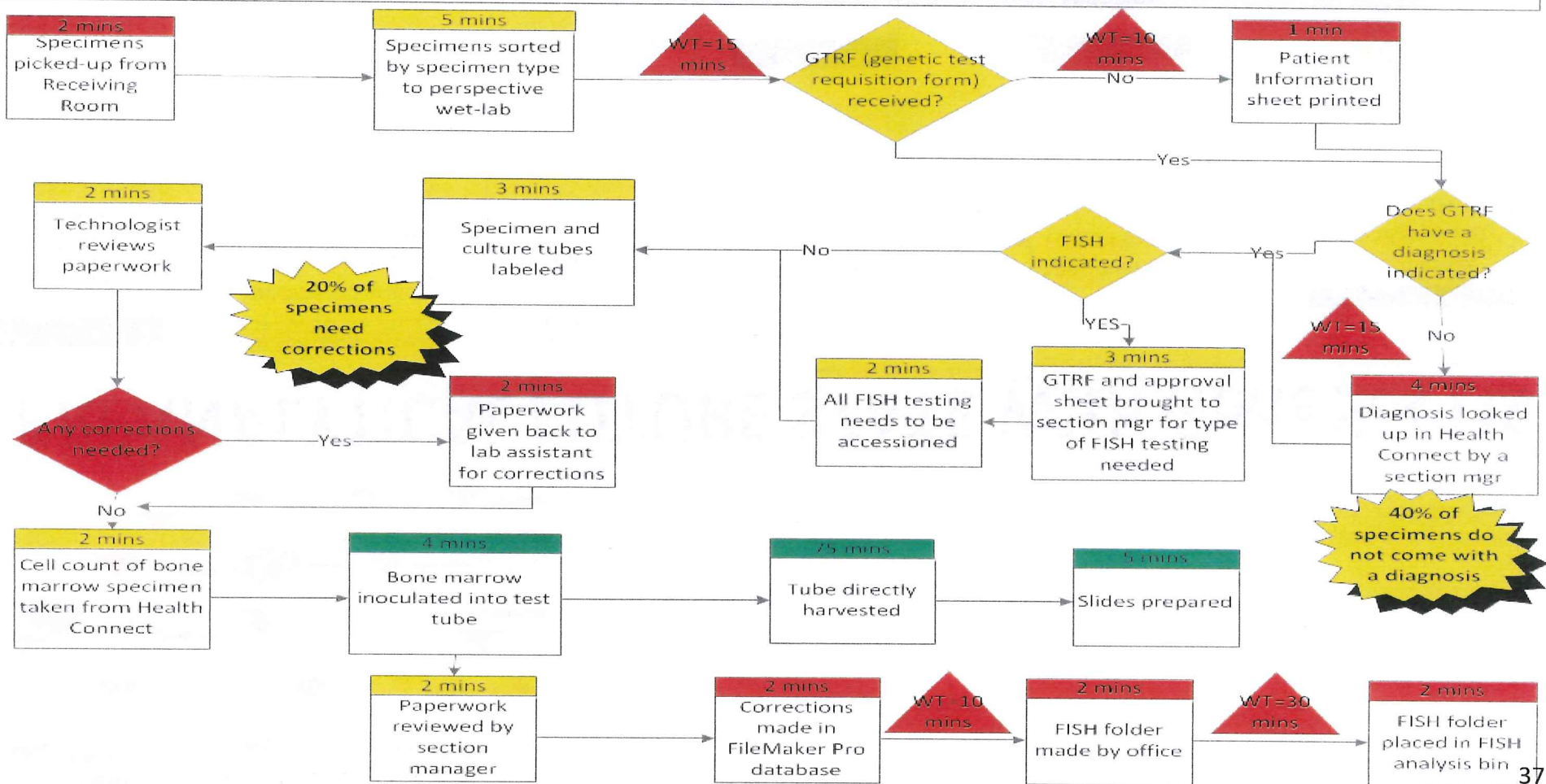
- Lab assistants should pick up specimens as soon as door bell rings
- Move to smaller batch sizes and ideally single piece flow decreasing wait times
- Perform direct harvest same day specimens received-overnight incubation eliminated

## With Genetics LIS

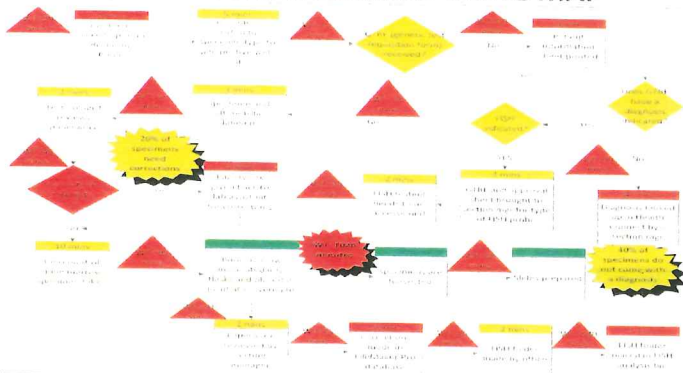
- Minimal data entry-minimize rework and ergonomic injuries
- FISH testing already accessioned, approvals from section manager no longer needed
- Easier tracking of specimens throughout the entire process
- Diagnoses no longer needed to be looked up by section manager
- Folders become obsolete
- Cell count can be autopopulated from flow result when available



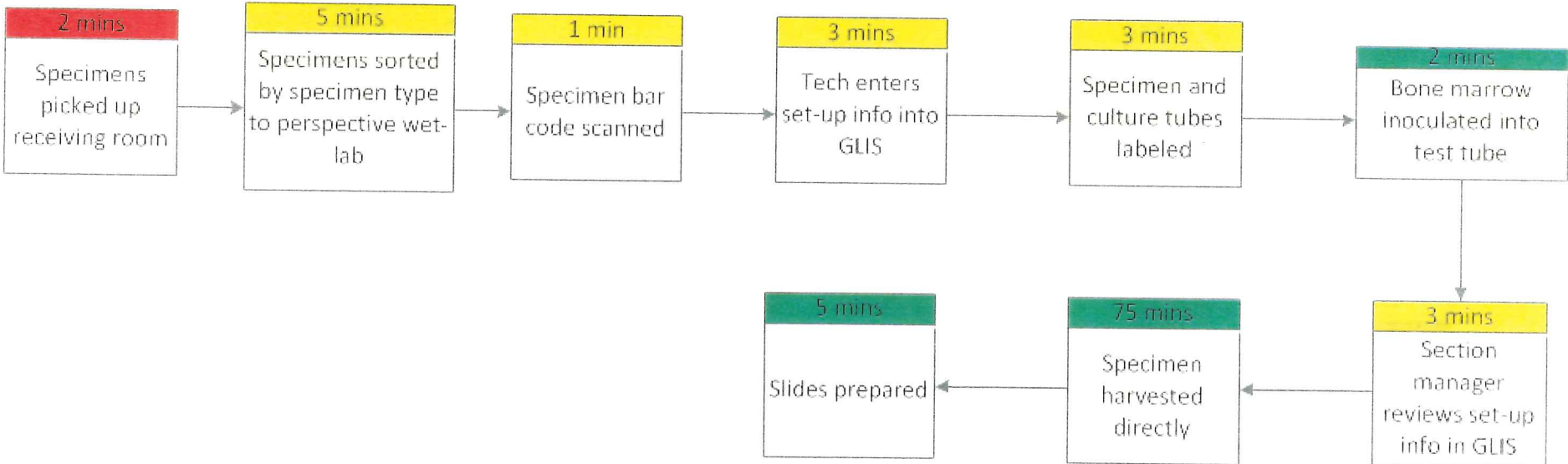
## PREANALYTICAL FUTURE STATE MAP WITHOUT GENETICS LIS



### PREANALYTICAL CURRENT STATE MAP



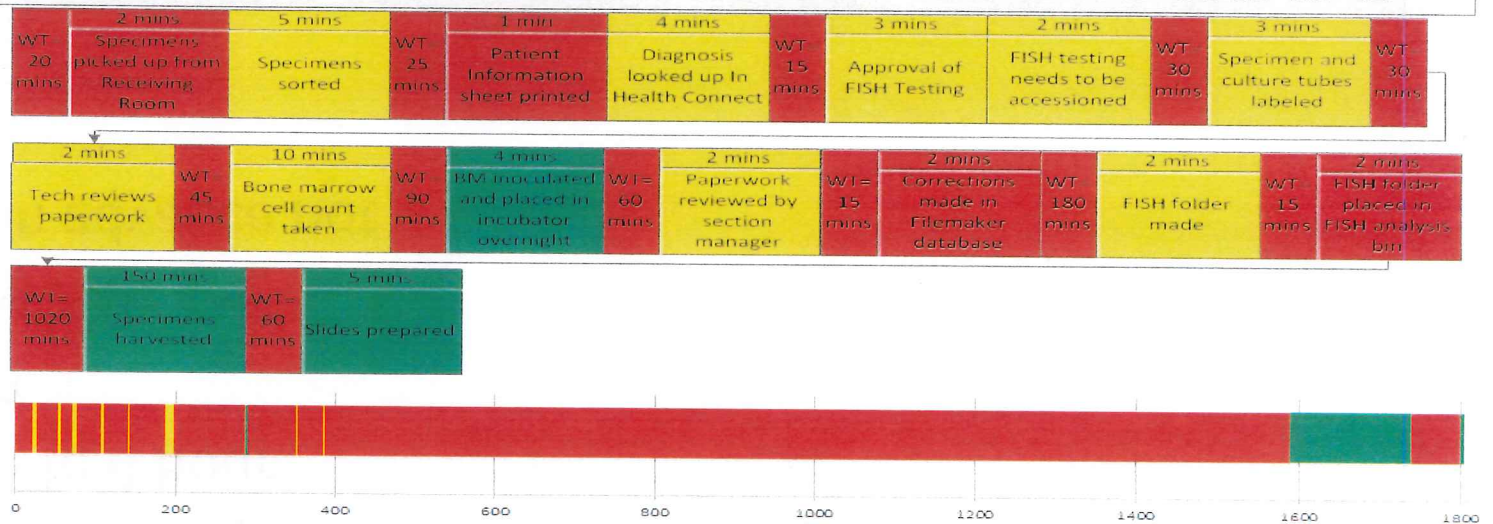
# PREANALYTICAL FUTURE STATE With Genetics LIS



# COMPARISON of PREANALYTICAL STATE MAPS

Current State Map

Total Time=1804 minutes



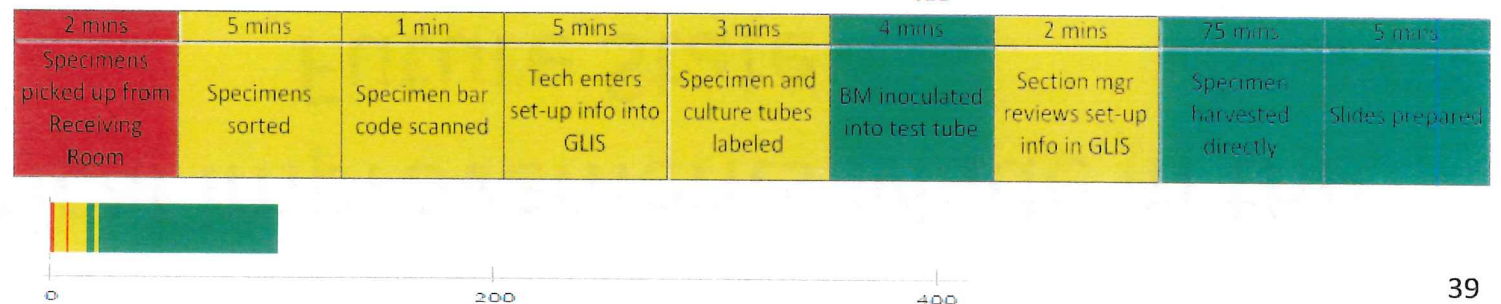
Future State Map *without* Genetics LIS

Total Time=231 minutes



Future State Map *with* Genetics LIS

Total Time=102 minutes





# Analytical Improvements Made in the Future State

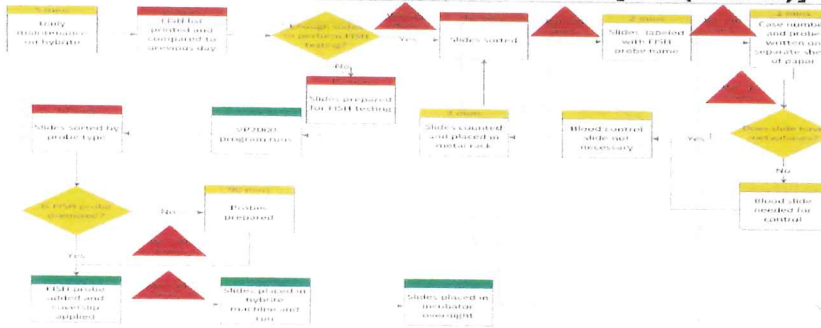
## Without Genetics LIS

- Wait times diminished due to same day set-up and smaller batch sizes wait times diminished
- Move from overnight incubation to 4 hour incubation
- FISH probe vials are prepared in advance not same day

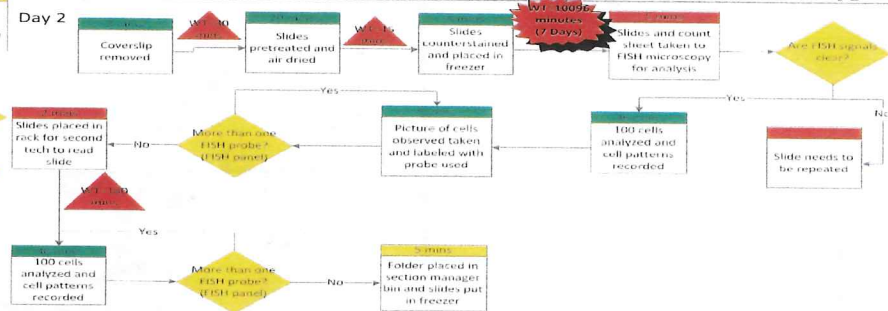
## With Genetics LIS

- Worklists are readily available
- Ability to track specimens throughout the entire process

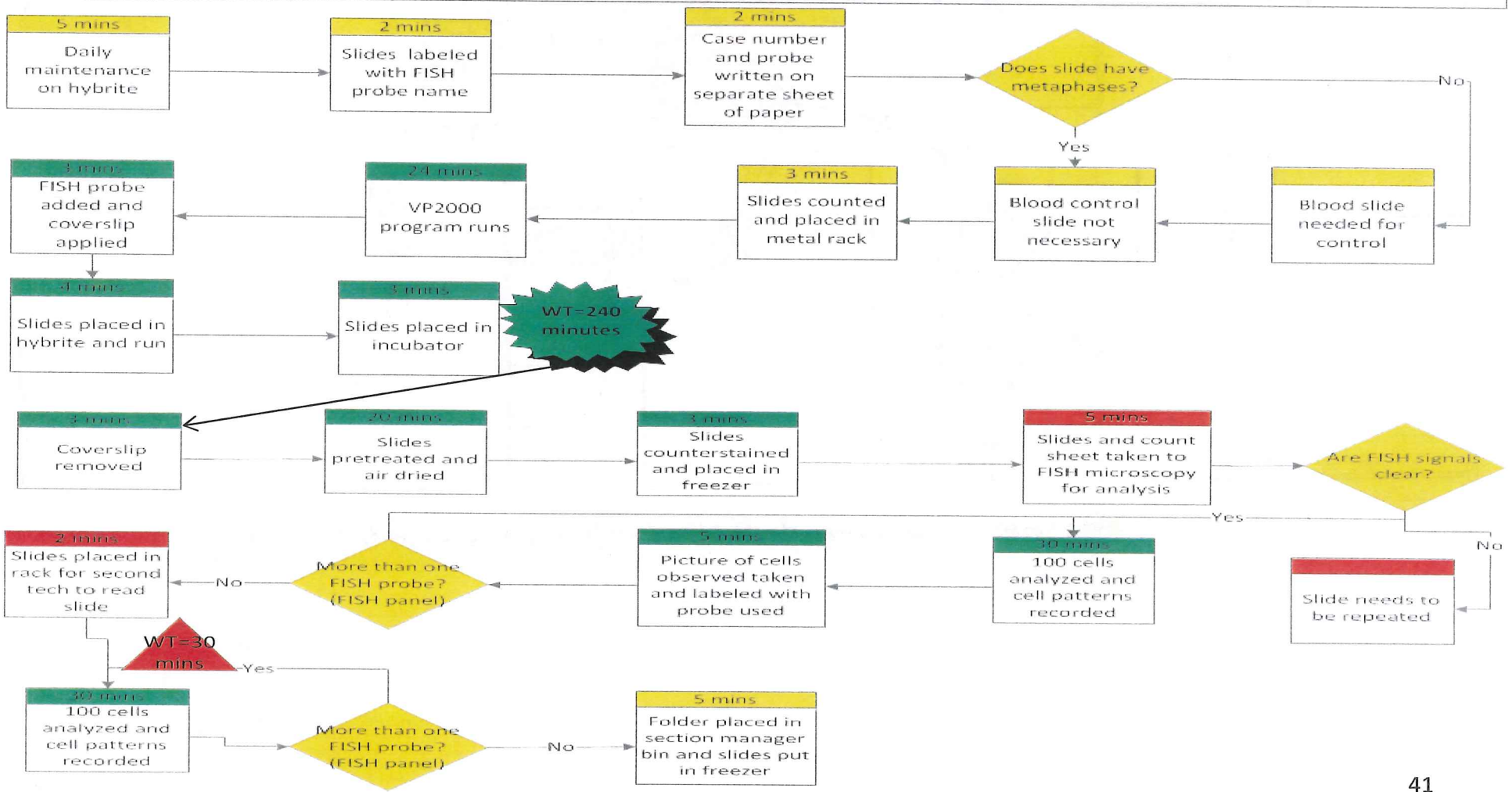
### ANALYTICAL CURRENT STATE MAP [PG (1 of 2)]



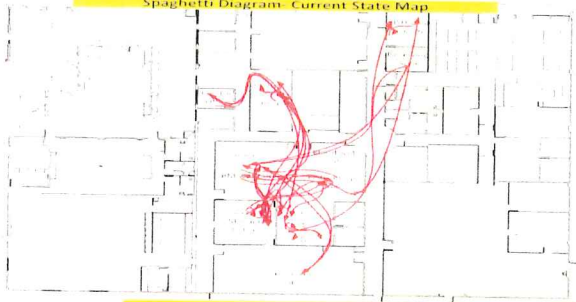
### ANALYTICAL CURRENT STATE MAP [PG (2 of 2)]



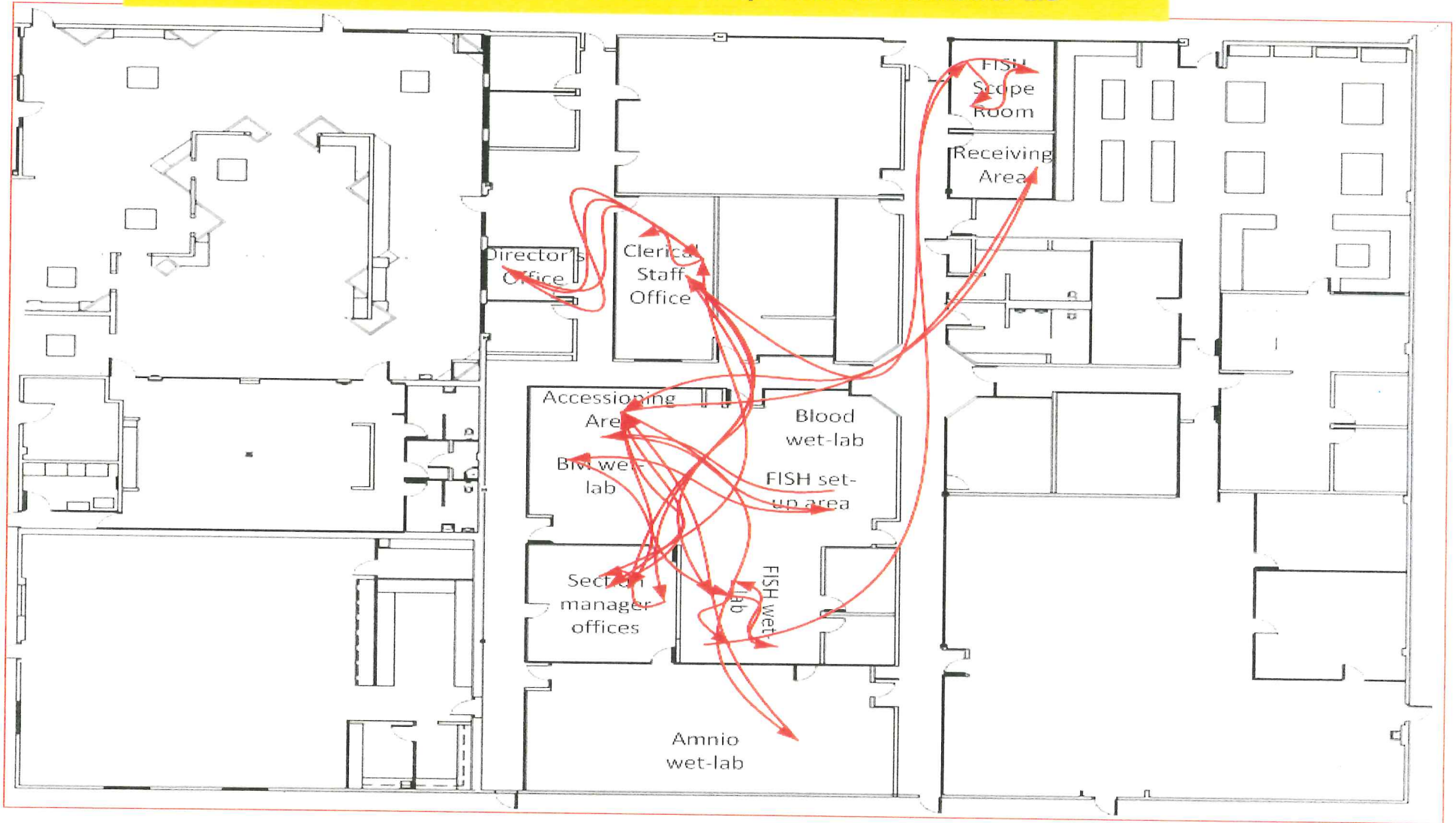
### ANALYTICAL FUTURE STATE MAP WITHOUT GENETICS LIS



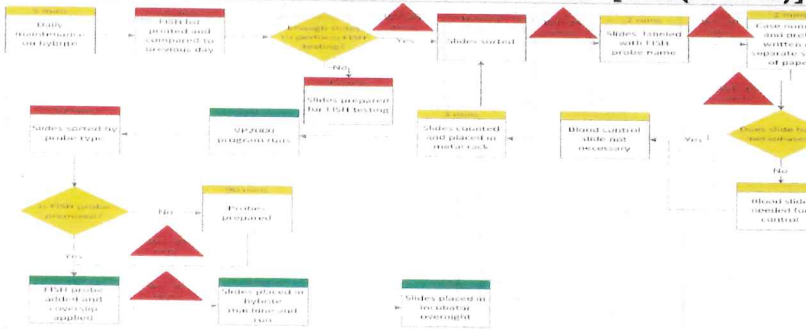
Spaghetti Diagram- Current State Map



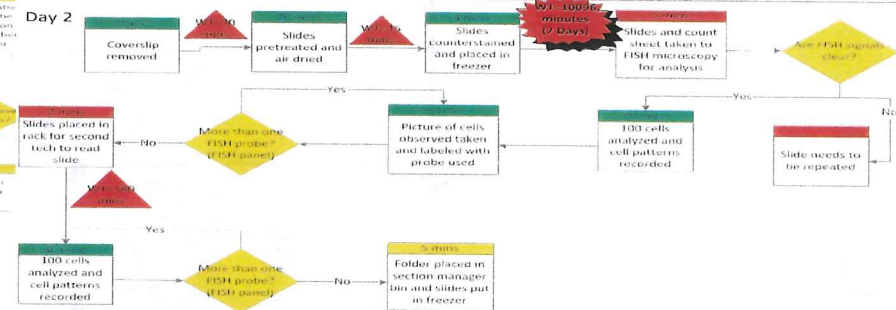
Spaghetti Diagram- FUTURE State Map Without Genetics LIS



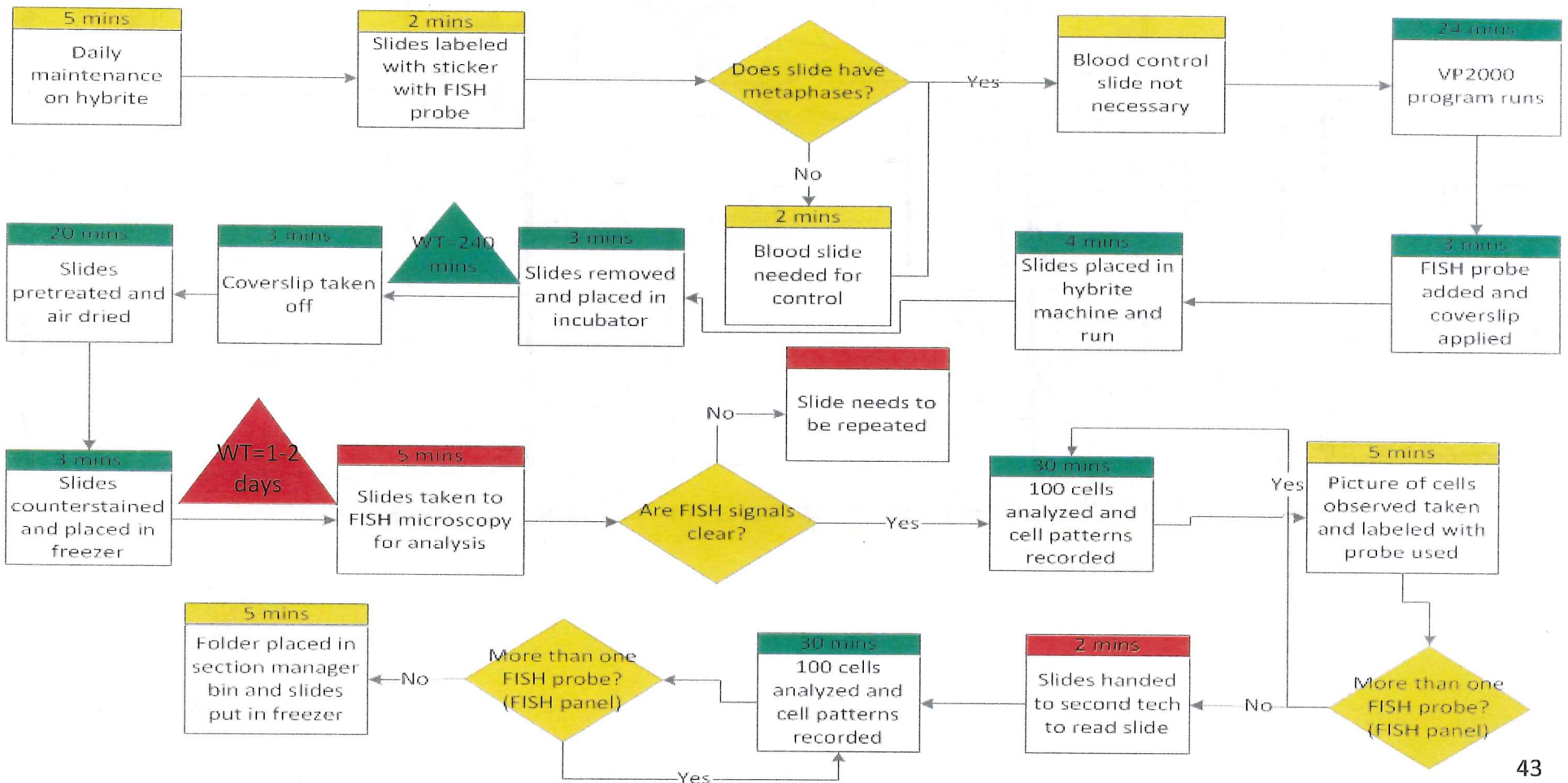
**ANALYTICAL CURRENT STATE MAP [PG (1 of 2)]**

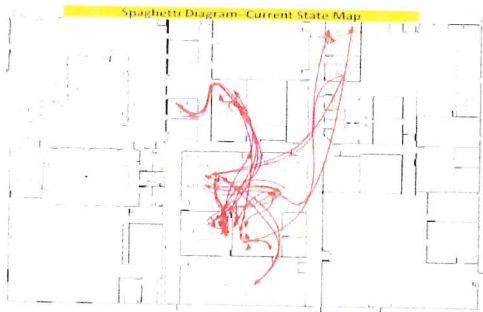


**ANALYTICAL CURRENT STATE MAP [PG (2 of 2)]**

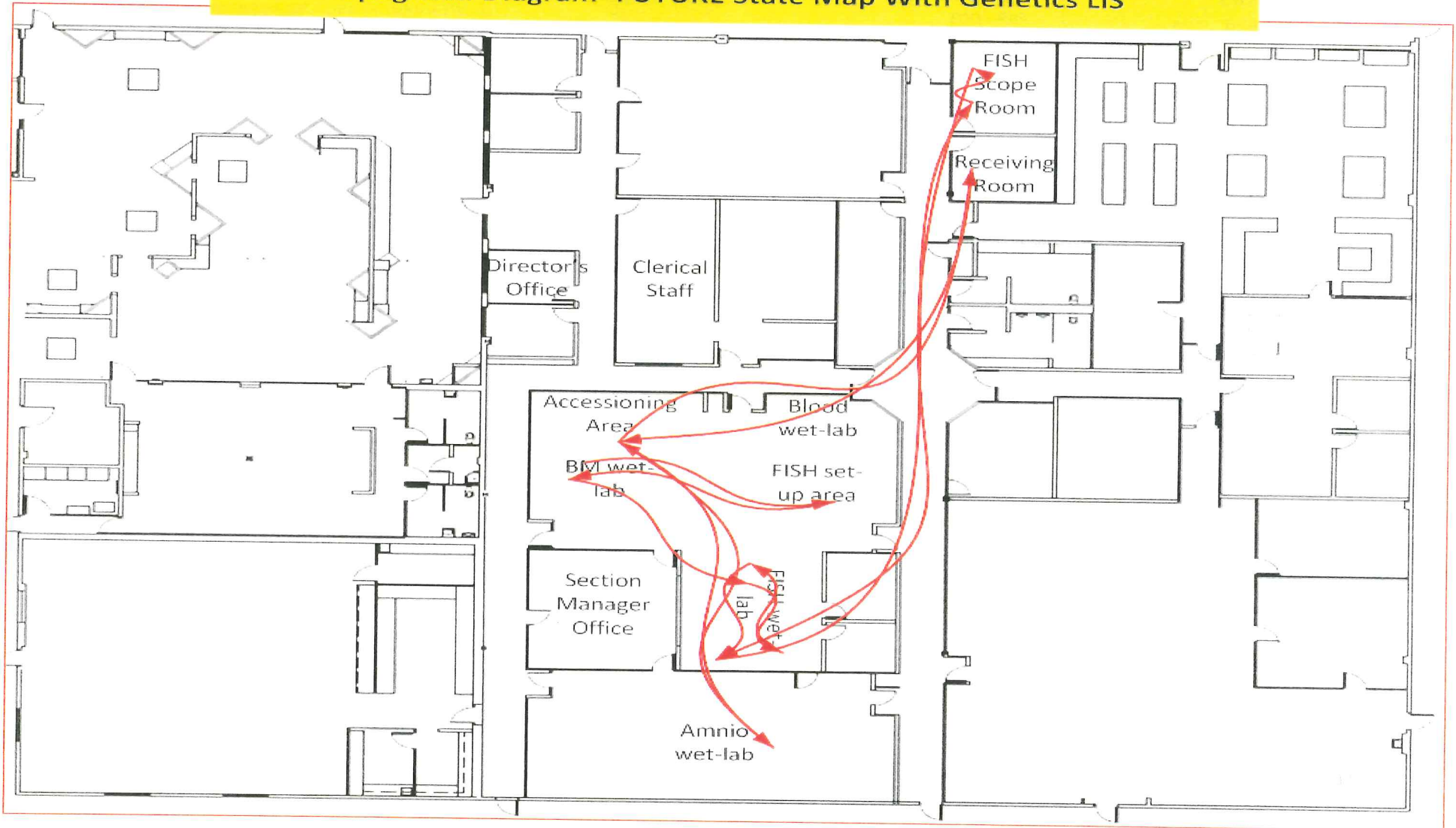


**ANALYTICAL FUTURE STATE With Genetics LIS**





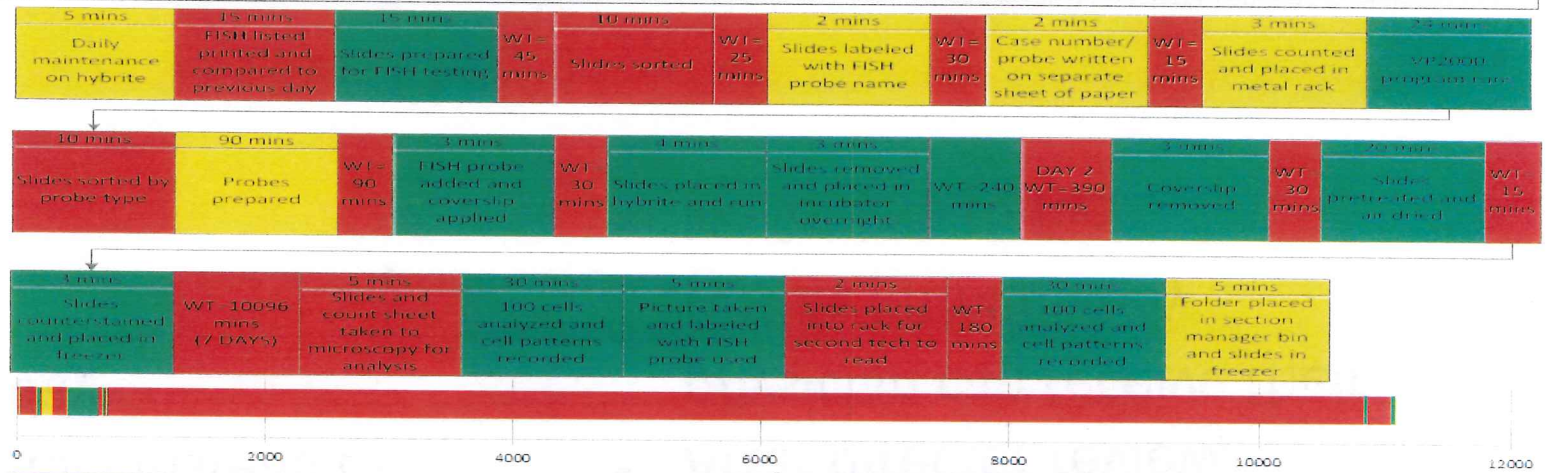
### Spaghetti Diagram- FUTURE State Map With Genetics LIS



# COMPARISON of ANALYTICAL STATE MAPS

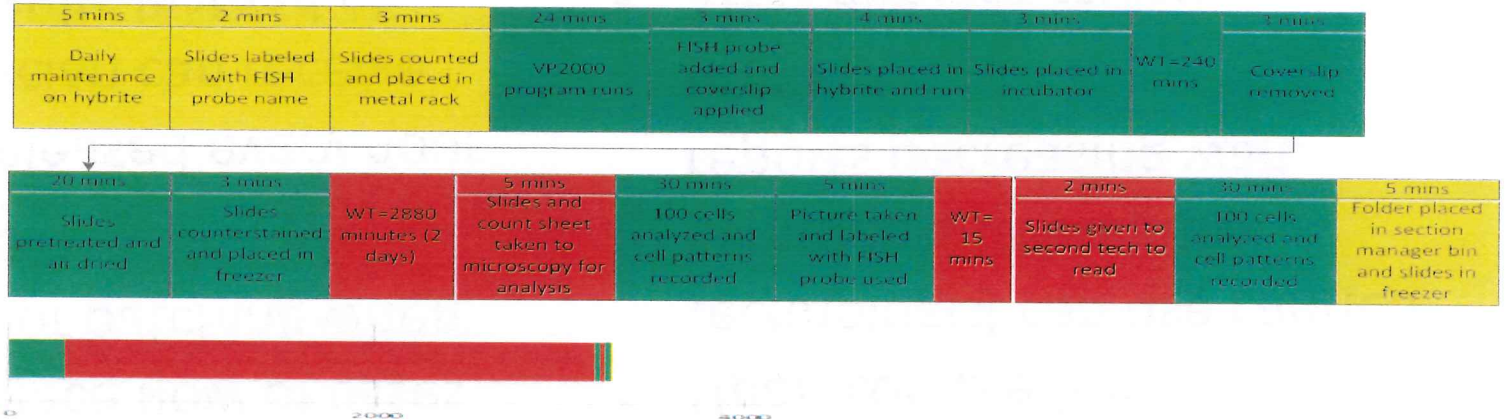
Current  
State Map  
Total Time:  
11475 minutes

~8 days

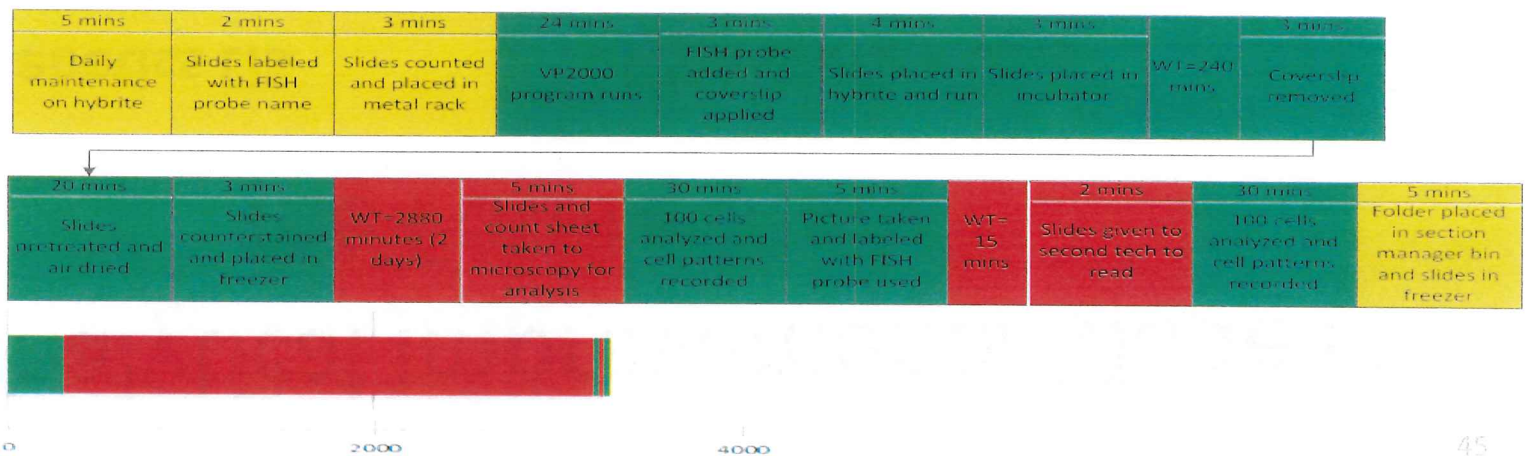


Future State  
Map without  
Genetics LIS  
Total Time: 3282  
minutes

2.28 days



Future State  
Map with  
Genetics LIS  
Total Time: 3282  
minutes 2.28 days



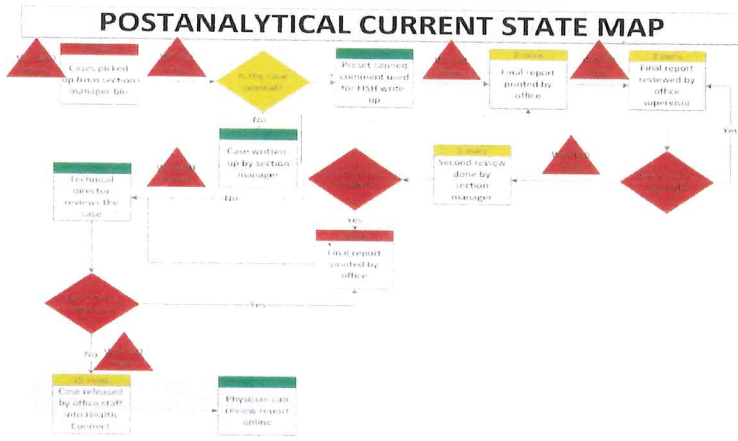
# Postanalytical Improvements Made in the Future State

## Without Genetics LIS

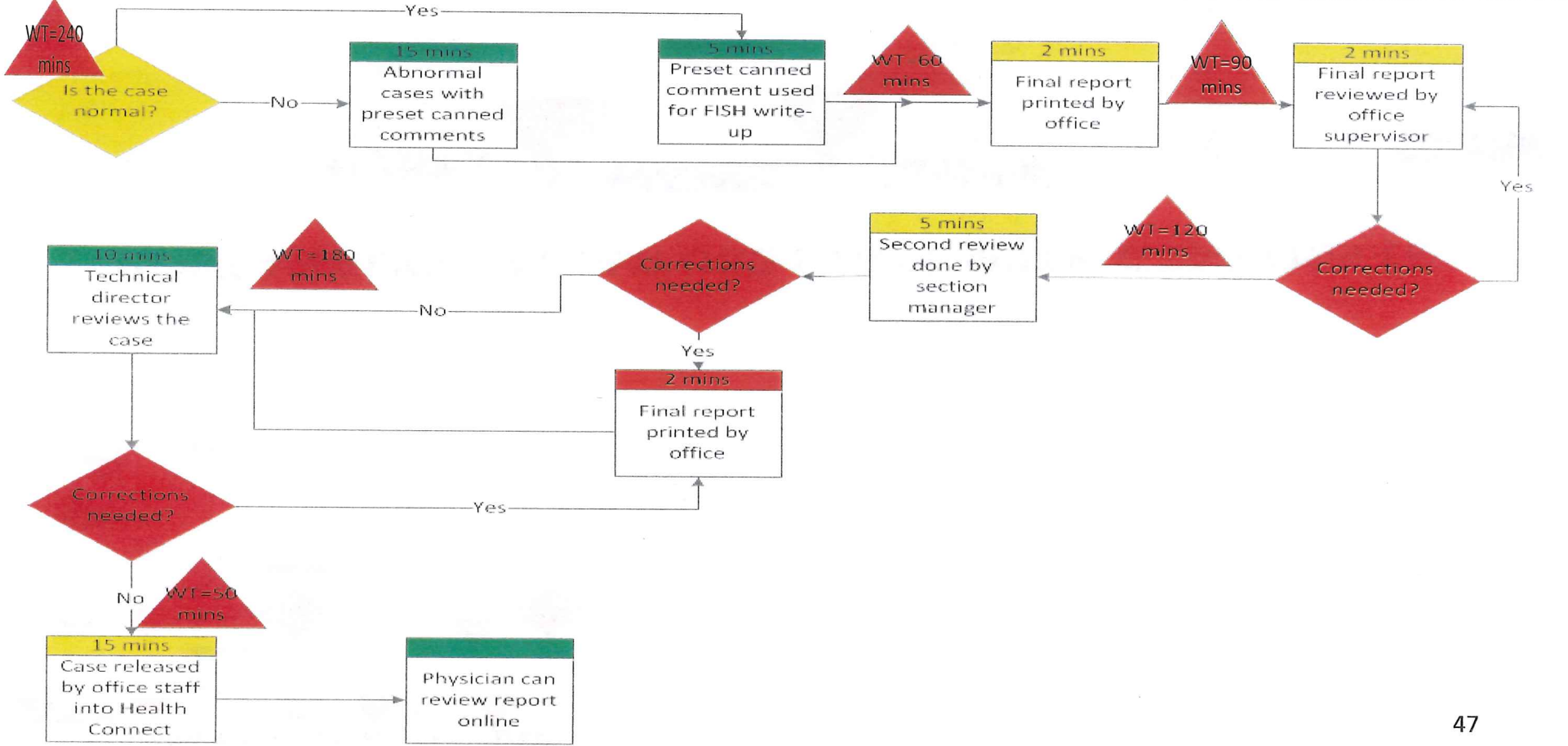
- Single piece flow of cases instead of batching when possible
- Cases released every hour so physician can receive their results instead of twice a day

## With Genetics LIS

- Upon completion, technologist can use canned comments to prepare reports decreasing wait times
- After director review, physician can receive their results immediately
- No folders to file

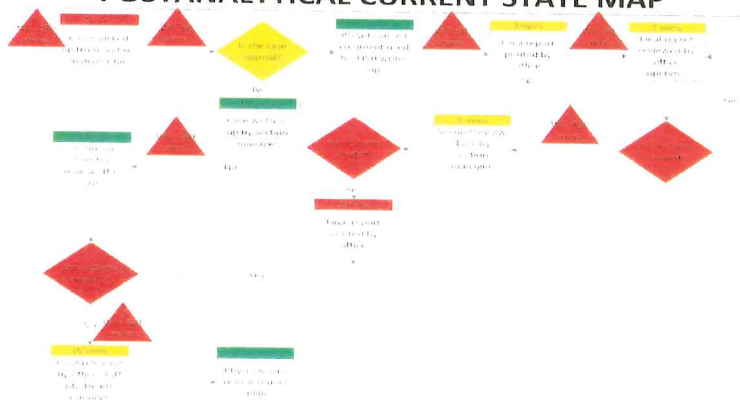


## POSTANALYTICAL FUTURE STATE MAP WITHOUT Genetics LIS

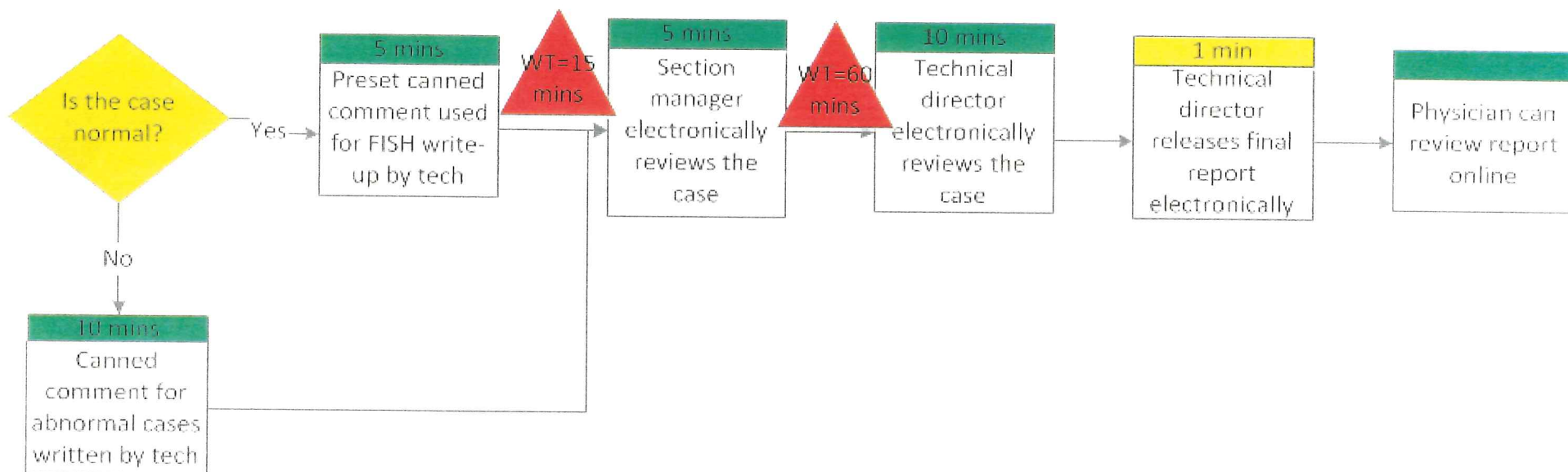




### POSTANALYTICAL CURRENT STATE MAP



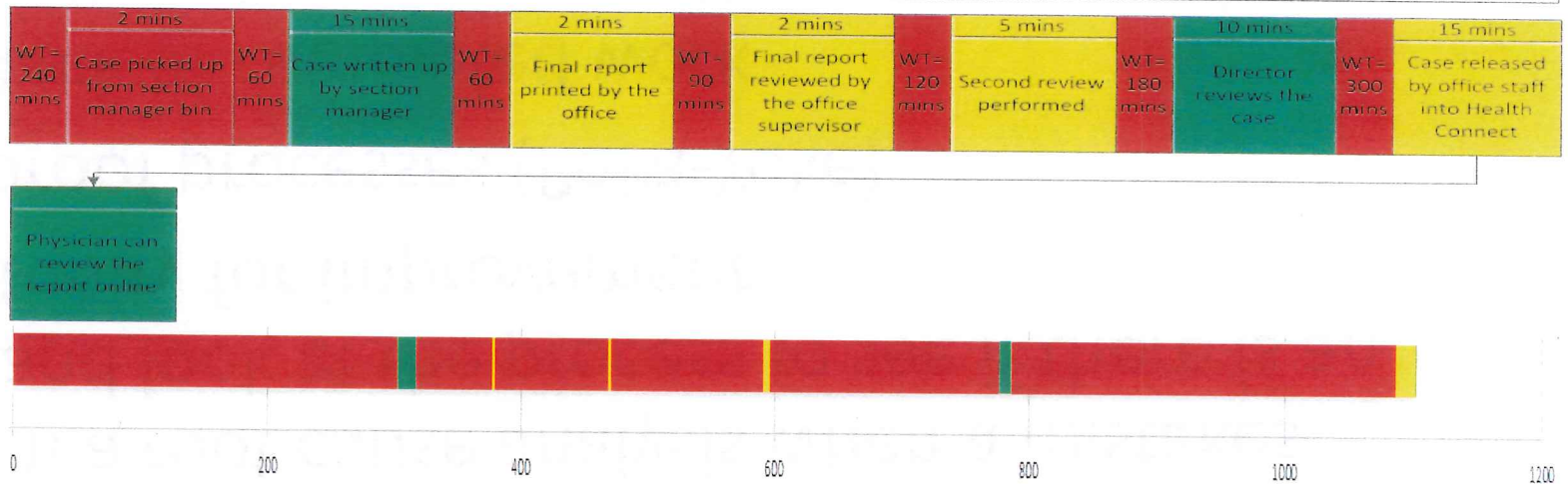
### POSTANALYTICAL FUTURE STATE WITH GENETICS LIS



## COMPARISON of POST-ANALYTICAL STATE MAP WITHOUT and WITH GENETICS LIS

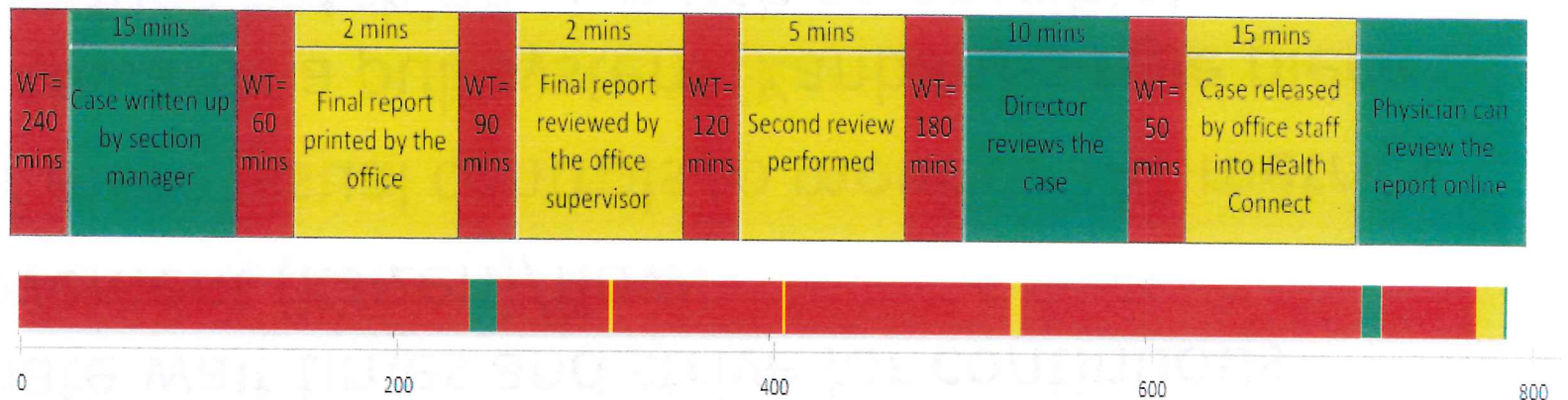
### Current State Map

Total Time:  
1101 minutes



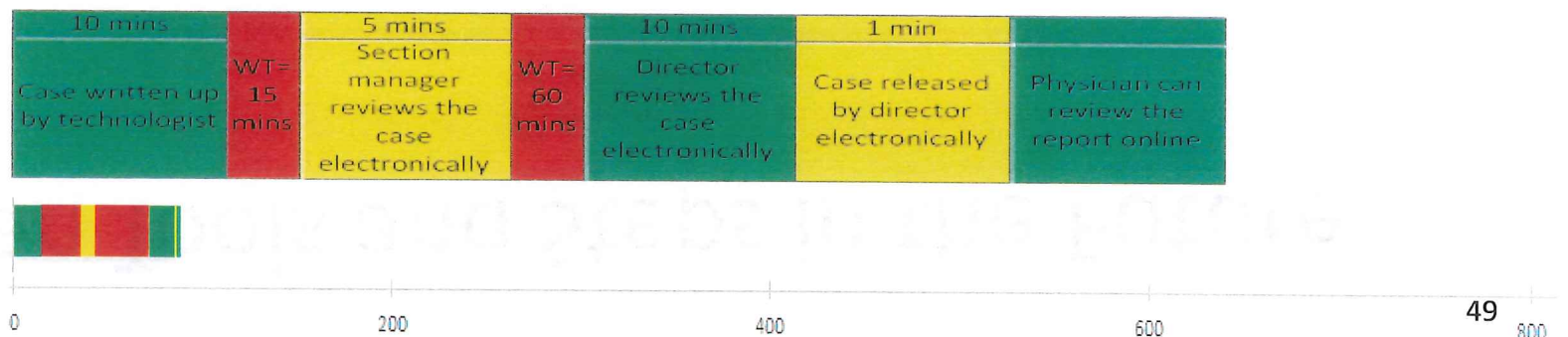
### Future State Map without Genetics LIS

Total Time:  
789 minutes



### Future State Map with Genetics LIS

Total Time:  
101 minutes



# Lean Tools and Steps in the Future State

- Eliminate wait times and strive for continuous improvement (kaizen)/flow
- Use of more visual controls to monitor TAT metrics
- Move towards a pull system (Kanban)-single piece flow (reduce batching as much as possible)
- Perform a root cause analysis when a mistakes occur and look at the process to see if there is an opportunity for improvement
- Error proof processes (Poka-Yoke)
- Self-check of completed work

# Implementation of the Future State with Genetics LIS

- Need the Genetics LIS completely funded
- Managers to lead staff to embrace the migration towards single piece flow and Lean principles
- Cross-training of employees across different work groups to ensure FISH scope room populated on both shifts
- Standardization of work flow processes

# Benefits of a Genetics LIS

- Move from a paper system to a electronic (paperless) system-significant reduction in rework and labor
- More efficient system providing staff with the tools they need to provide the best patient care possible
- Allows processing of cases following laboratory's SOPs including tracking of specimens (real-time) and auto-generation of reports with canned comments
- Rules based system (RBS) that can assist in processing and reporting which in turn can help reduce TAT's
- Track reflex testing
- Reagent inventory monitoring
- QA efforts and trending
- Billing simplified

# Ideal State Improvements

- Manual processes completely replaced with automation freeing up staff to work on other cytogenetic cases
- Entire process can be completed in a matter of hours

# IDEAL STATE (eFISHiency)

Preanalytical  
Total Time=102  
minutes

2 mins	5 mins	1 min	5 mins	3 mins	4 mins	3 mins	75 mins	5 mins
Specimens picked up from Receiving Room	Specimens sorted	Specimen bar code scanned	Tech enters set-up info into GLIS	Specimen and culture tubes labeled	BM inoculated into test tube	Section mgr reviews set-up info in GLIS	Specimen harvested directly	Slides prepared

Analytical

Total time=100  
minutes

30 mins	10 minutes	60 mins
Put slides in BioGenex Xmatrix machine and press start	Machine loaded	Slides are placed in BioGenoMX Vision



Postanalytical

Total time=40 minutes

30 mins	10 mins	
Results are interfaced with Genetics LIS	Technical director reviews the case	Physician can review report online

# Flow and Pull

- Move towards single piece flow to reduce wait times and eliminate non-value added steps where possible
- Introduce Poka-Yoke devices to eliminate rework due to data entry corrections e.g. spelling errors



# Perfection

- Eliminate backlog through better scheduling and cross-training of laboratory staff
- Imperfections will be made more transparent through more frequent communication with staff regarding weekly and monthly bone marrow FISH TAT
- Non-value added steps will be eliminated and emphasis geared towards continuously improving related processes

# Respect for People

- Encourage staff to provide feedback and offer suggestions on ways to continually increase efficiency and solve problems in current work flow processes
- Eliminate the “Shame and Blame” culture

# Summary of Improvements Before and After

	Current State Map	Future State Map without Genetics LIS	Future State Map with Genetics LIS	Ideal State Map
<b>Throughput time</b>	10 days	4 days (60% reduction)	2.5 days (75% reduction)	1 day (90% reduction)
<b>Quality</b>	Moderate	Moderate	High	High
<b>Frustration of lab staff</b>	High	Moderate	Low	Low
<b>Frustration of MD &amp; patient</b>	High	Moderate	Low	Low



# Reflections

- Lean uncovered and made transparent productivity reserves in processes
- Use and application of different Lean tools to increase throughput time was learned
- Principles learned can be applied to other work flow processes for increased efficiency
- THANK YOU to Kaiser Permanente and LMU for the opportunity

QUESTIONS?

